A Step Forward in the Treatment of Adolescent and Young Adult B-cell Acute Lymphoblastic Leukemia


Acute lymphoblastic leukemia (ALL) occurring in the adolescent and young adult (AYA) patient population (defined as 15-39 years of age) has a disease biology and clinical course that is distinct from childhood and adult ALL. Thus, research efforts during the past decade have focused on discovery of the ALL “genomic landscape” in AYA patients, as well as on optimizing the therapeutic regimens for these patients. 

Intensive multiagent chemotherapy remains the standard of care in newly diagnosed patients with this disease, but pediatric and adult ALL therapeutic regimens differ in important ways. Pediatric protocols for ALL include higher cumulative doses of nonmyeloablative chemotherapy (glucocorticoids, vincristine, and L-asparaginase), early and more intensive central nervous system therapy, a longer period of maintenance therapy, and restricted indications for hematopoietic stem cell transplantation (HSCT) in first remission (CR1). Adult chemotherapy protocols include higher doses of myeloablative chemotherapy (daunorubicin, cytarabine, and cyclophosphamide) and broader indications for HSCT in CR1. Importantly, retrospective analyses and a meta-analysis demonstrate that AYA patients with ALL have superior outcomes when treated with pediatric protocols and by pediatric treatment teams. Whether the adult treatment teams could implement a pediatric-like protocol with the same rigor as pediatric teams and achieve comparable outcomes for young adult patients has not been studied.

Dr. Wendy Stock and colleagues conducted a prospective, multicenter, phase II, single-arm trial (Cancer Leukemia Group B [CALGB] 10403) to test the efficacy and feasibility of a pediatric regimen for AYA patients with newly diagnosed B- or T-lineage Philadelphia chromosome-negative ALL. The three U.S. adult cooperative groups, CALGB, Eastern Cooperative Oncology Group, and Southwest Oncology Group, enrolled 318 young adult patients with a median age of 24 years (range, 17-39 years) in the study between November 2007 and September 2012. The treatment regimen of CALGB 10403 was a replica of the high-risk arm of the Children’s Oncology Group trial, ALL02P3, which comprised a four-drug induction followed by consolidation, interim maintenance, delayed intensification, and long-term maintenance therapy.

Two hundred ninety-five patients were eligible for treatment and evaluation. The complete marrow response rate was 89 percent (n=263), with most responses (90%) occurring at the end of induction (n=227), although additional responses occurred after the extended induction therapy (n=26). Minimal residual disease (MRD) assessment using quantitative polymerase chain reaction was performed on a subset of patients (n=80) following induction therapy. The MRD-negative remission rate was 44 percent (n=35). Detection of MRD following induction therapy was associated with an inferior three-year disease-free survival (DFS; 54% for patients with detectable MRD >10-3 vs. 85% for undetectable MRD; p=0.001). The median follow-up for the cohort was 64 months; 190 patients (64%) were alive and 105 (36%) have died. The median event-free survival (EFS) was 78.1 months (95% CI, 41.9–not reached), three-year EFS was 59 percent (95% CI, 54-65%), and the estimated three-year overall survival (OS) was 79 percent (95% CI, 68-78%). Twenty patients (4%) underwent allogeneic HSCT in first remission (CR1), and the DFS for the transplant cohort was 26 months. These data indicate a significant improvement in outcomes compared with historical controls, among whom the three-year OS was 58 percent (95% CI, 52-64%) and median EFS was 30 months (95% CI, 22-38).

Treatment-related mortality was 3 percent (n=8), and most treatment-related deaths occurred during induction therapy (n=6). More than 10 percent of patients experienced grade 3 to 4 nonhematologic toxicities. These adverse effects included hyperbilirubinemia (42%), hyperglycemia (30%), elevated transaminases (28%), hyperlipidemia (18%), febrile neutropenia (23%), and infection (18%).

The Hazards of Hazardous Drug Labeling: Time to Revisit Hydroxyurea?

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Despite benefits in reducing pain crises, transfusions, hospitalizations, and mortality in sickle cell disease (SCD),1 hydroxyurea (HU) is underutilized.1,2 A recent Cochrane meta-analysis found no significant increase in adverse events among HU-treated patients with SCD, yet fears of possible adverse effects have been identified as a key barrier to HU acceptance.3,4 In light of the poor uptake of HU among the SCD population, hematologists need to fully understand patient and provider reluctance about this disease-modifying therapy.

Fears relating to the carcinogenic and teratogenic potential of HU, along with concerns over the potential effect of HU on reproductive health, are pervasive among patients with SCD.1,5 Yet, is there basis for these anxieties? These potential toxicities serve as the basis for HU’s classification as a hazardous drug by the National Institute for Occupational Safety and Health (NIOSH), though support for this has not been well-established in the literature.1,6 The primary purpose of NIOSH drug labeling is to protect workers from potential adverse effects when coming into direct contact with hazardous drugs.1 Based on HU’s classification as a hazardous drug, health care workers are advised to wear double gloves, a protective gown, and sometimes eye and face protection when administering liquid HU and when dealing with HU-contaminated waste.1,6 Moreover, hospitals adhering to cytotoxic drug-handling guidelines may mandate that a cytotoxic drug warning be posted outside the patient’s hospital room door.1 The implications of the “hazardous drug” listing on patient acceptance of HU should not be underestimated.

NIOSH labels a hazardous drug any agent with carcinogenicity, teratogenicity, reproductive toxicity, organ toxicity at low doses, genotoxicity, and/or structure that mimics existing hazardous drugs.1 Drug package inserts serve as the primary source of information used by the NIOSH Hazardous Drug Committee.1 All drugs identified as hazardous by manufacturer package inserts are automatically added to the list. It is our understanding that HU’s classification has never undergone an independent formal review. Moreover, it is concerning that this
**Hematologist**

ASH NEWS AND REPORTS  
ISSN 1528-1779  
PUBLISHED BIMONTHLY

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Dr. Michaels has no relevant conflicts of interest to disclose.

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**President’s Column**

“Teachers and Preachers” of Quality Improvement

In 1999, the Institute of Medicine, now known as the National Academy of Medicine (NAM), issued a thought-provoking report titled “To Err is Human: Building a Safer Health Care System.” The report illuminated the toll on patient morbidity and mortality that could be attributed to preventable errors and care gaps in American hospitals. This was followed in 2001 by another report, “Crossing the Quality Chasm,” which identified six foundational aims that should be the basis of re-engineering the health care system to foster quality. They stated that health care should be safe, effective, patient-centered, timely, efficient, and equitable. These reports were a call to arms for health systems and professional societies, and ASH, always at the forefront, responded with a re-commitment to high-quality care and continuous quality improvement as central tenets of our mission. In the ensuing 20 years, ASH created a standing Committee on Quality and with support from a talented group of ASH staff with training and expertise in quality improvement (QI), made substantial investments in providing care and continuous improvement, and created educational materials addressing specific training and knowledge gaps such as sickle cell disease, and enhanced popular features in our publications, such as “How I Treat” and “Ask the Hematologist.” Most recently, we began developing a series of evidence-based clinical practice guidelines on the topics of venous thromboembolism (VTE; 10 guidelines), sickle cell disease (SCD; 5 guidelines), von Willebrand Disease (2 guidelines), immune thrombocytopenia, and acute myeloid leukemia in older adults. The aim of these and SCD guidelines have been to make sure that we are effective teachers and preachers of continuous QI and adding both QI and implementation science to our repertoire of research efforts further enriches the Society. We should celebrate these efforts and take great pride in the cutting-edge approaches ASH is taking to advance quality clinical care.

The ASH clinical practice guidelines project is an outstanding example of the commitment of our Society to the core mission of helping hematologists conquer blood diseases worldwide. Importantly, in addition to QI, the project touches our global outreach, education, training, and research efforts. Helping hematologists become teachers and preachers of continuous QI and adding both QI and implementation science to our repertoire of research efforts further enriches the Society. We should celebrate these efforts and take great pride in the cutting-edge approaches ASH is taking to advance quality clinical care.


Roy L. Silverstein, MD

**DIFFUSION**

AYA B-Cell Acute Lymphoblastic Leukemia

(Cont. from page 1)

In univariate models, the initial white blood count was greater than 30 x 10⁹/L in B-lineage patients; obesity, the Ph-like signature, and aberrant CRLF2 expression were associated with inferior EFS, DFS, and OS. There was no significant difference in outcome between patients with a B-cell versus T-cell phenotype, or in CD20 expression. Historically, both T-cell phenotype and CD20 expression have been associated with a poor outcome. Multivariate analysis of pretreatment characteristics on treatment outcomes revealed that obesity (hazard ratio [HR], 1.82; p=0.04) and aberrant CRLF2 expression (HR, 2.84; p<0.001) were associated with inferior DFS.

The study results are important for several reasons. Outcomes were improved significantly in both B- and T-cell-lineage ALL subtypes by using a pediatric therapeutic regimen. The regimen was safe in adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols and young adults with acute lymphoblastic leukemia treated on cooperative group studies. Blood. 2008;112:1646-1654.

In a successor trial for B-lineage ALL (A041501; ClinicalTrials.gov Identifier: NCT01350693) is studying the addition of the antibody drug conjugate, inotuzumab ozogamicin, to examine whether it will increase the MRD-negative remission rate and further improve survival. Finally, despite the recognition of the superiority of a pediatric regimen, many AYA patients are treated in adult community cancer facilities and are more likely to receive an adult ALL regimen. Adult oncologists should consider applying the CALGB 10403 therapeutic approach to newly diagnosed AYA patients with ALL to centers with experience treating these patients.

Save the Date for the ASH Meeting on Hematologic Malignancies

Register to attend the ASH Meeting on Hematologic Malignancies, taking place September 6-7, 2019, at the Fairmont Chicago, Millennium Park. Attendees will have the opportunity to gain knowledge from top experts in the field and interact with colleagues in an intimate, small-group setting. Through “How I Treat” presentations covering each of the core malignancies, including leukemia, lymphoma, myelodysplastic syndromes, myeloma, and myeloproliferative neoplasms, speakers will provide evidence-based treatment approaches, present cutting-edge scientific data that can be translated into new strategies for diagnosis and treatment, and address what to do when data are unavailable. Visit www.hematology.org/malignancies for additional information and to register.

The Abstract Submission Site for the 2019 ASH Annual Meeting Opens May 30

The abstract submission site for the 61st ASH Annual Meeting and Exposition will open from May 30 until August 1, 2019. This year’s meeting, taking place December 7-10, at the Orange County Convention Center in Orlando, will feature the latest breakthroughs in hematology while connecting and convening the global hematology community. Registration and housing for ASH members will open July 24, at 11:00 a.m. Eastern Time. Visit www.hematology.org/annual-meeting for updated information on abstract submission, program sessions, and new events and activities.

Browse the 2018 ASH Annual Report

Opens May 30 for the 2019 ASH Annual Meeting

The 2018 ASH Annual Report is now available for updated information on annual achievements and commitments; annual statistics demonstrating the breadth and reach of ASH in 2018 both in the United States and worldwide; select highlights from Capitol Hill showing how ASH is shaping policy using its Grassroots Network to inform Congress of ASH in 2018 both in the United States and worldwide; and much more. Visit annual-report.hematology.org to browse online. Readers will find a message from 2018 ASH President Dr. Alexis Thompson, an overview of ASH’s key accomplishments and commitments; annual statistics demonstrating the breadth and reach of ASH in 2018 both in the United States and worldwide; select highlights from Capitol Hill showing how ASH is shaping policy using its Grassroots Network to inform Congress of ASH in 2018 both in the United States and worldwide; and much more. Visit annual-report.hematology.org to view the 2018 ASH Annual Report and learn how you can get involved in advancing ASH’s mission to conquer blood diseases worldwide.

New Conversations With Innovators Video

Contributing Editor for The Hematologist Dr. Amy DeZern talks about the MEDALIST Trial. Dr. DeZern and colleagues carried out a study of luspatercept to treat anemia in lower-risk patients with myelodysplastic syndromes, presented at the 2018 ASH Annual Meeting. Visit www.hematology.org/Thehematologist/Multimedia/ to watch this video and others from the Conversations With Innovators series on YouTube.

The Hematologist Has a New Home on the ASH Publications App

Thanks to everyone who downloaded The Hematologist mobile app in the past year. To keep readers up to date with The Hematologist and all ASH content, the Society has launched the new ASH Publications app, featuring content from The Hematologist, Blood, Blood Advances, and, coming soon, ASH Clinical News, in one convenient, free app. Readers of the ASH publications app can now view content from various ASH publications in a single app on the go and even offline, save your favorite articles to your smartphone or tablet, browse, download, take notes, listen to podcasts, and more. To learn more about this transition and the new ASH Publications app, visit www.hematology.org/Thehematologist/app.

CONVERSATION STARTER

Featured content from Blood Advances, Volume 3, Issue 7

Functional analysis of clinical response to low-dose IL-2 in patients with refractory chronic graft-versus-host disease

Patients with chronic graft-versus-host disease (cGVHD) have a paucity of regulatory CD4 T cells (CD4Tregs) that mediate peripheral tolerance. In clinical trials, daily low-dose interleukin-2 (IL-2) has been administered safely for prolonged periods in patients with steroid-refractory cGVHD. Peripheral CD4Tregs expand dramatically in all patients during IL-2 therapy but clinical improvement was observed in ∼50% of patients. Here, we examined the impact of low-dose IL-2 therapy on functional T-cell markers and the T-cell repertoire within CD4Tregs, conventional CD4 T cells (CD4Tcons), and CD8+ T cells. IL-2 had profound effects on CD4Tregs homeostasis in both response groups including selective expansion of the naive subset, improved thymic output, and increased expression of Ki67, FOXP3, and B-cell lymphoma 2 within CD4Tregs. Similar changes in vitro, CD4Treg-suppressive activity in both response groups, and all patient CD4Tcons were similarly suppressed by healthy donor CD4Tregs... From Whangbo JS, et al. Blood Advances. 2019;3: 984-994. More available at www.bloodadvances.org.
The Case
A 55-year-old man presented with persistent shortness of breath and cough. A chest x-ray showed a mediastinal mass that was confirmed on computed tomography, along with evidence of lymph node enlargement and splenomegaly. Although physical examination revealed no adenopathy or organomegaly, biopsy of the mediastinal mass demonstrated a diffuse large B-cell lymphoma (DLBCL) non-Hodgkin lymphoma (NHL). Complete blood count was normal as were liver function tests, except for moderate elevation in lactate dehydrogenase. The patient was started on rituximab plus doxorubicin, vincristine, and prednisone (R-CHOP). He was found to have severe neutropenia (absolute neutrophil count, 100 cells/μL) after one cycle of chemotherapy. Owing to the risk of future febrile neutropenia or sepsis, the treating hematologist recommended the addition of prophylactic granulocyte colony-stimulating factor with future cycles of chemotherapy. A new biosimilar pegfilgrastim was added to the formulary and was ordered with the next cycle of chemotherapy. The patient went on to tolerate the treatment regimen well with improvement in his symptoms of cough and mild peripheral neuropathy. Repeat imaging after two cycles of treatment revealed a greater than 50 percent reduction of the mediastinal mass and complete resolution of adenopathy and splenomegaly. Following his second treatment, the patient and his wife decided to continue treatment during the winter months at an institution in Florida. The institution has recently added biosimilar rituximab to the formulary.

The Question
Are there concerns about safety or efficacy of biosimilar pegfilgrastim for reducing the risk of febrile neutropenia in this setting? Furthermore, are there concerns about the safety and efficacy of biosimilar rituximab as part of the patient’s continuing treatment regimen for DLBCL NHL?

The Response
Following an initial slow start, 18 biosimilars have been approved by the U.S. Food and Drug Administration (FDA) including 10 with immediate relevance to hematologists and oncologists. Approved biosimilars include supportive care agents represented by two filgrastim and two pegfilgrastim biosimilars, and more recently, cancer treatments including a biosimilar rituximab, with several more anticipated in the near future (Figure 1). While biosimilars have been on the market for more than a decade in Europe, the regulatory process, approval, and availability of these agents is a relatively recent addition to clinical practice in the United States. It is essential that providers familiarize themselves with the rationale for biosimilars, available evidence on safety and efficacy, terminology such as interchangeability, in vivo and in vitro, and interconvertibility; as well as the novel drug nomenclature adopted to differentiate from the originator and other biosimilars. Several professional organizations and institutions have undertaken education initiatives to further inform providers, patients, administrators, and policy makers about biosimilars in hematology/oncology. The primary motivating driver of interest in the development and integration of biosimilars in clinical practice relates to the extraordinary increase in health care costs throughout the past decade. This is highlighted by rapid increases in cancer drug prices and most notably by the introduction of biologic therapies often associated with dramatically increased costs and simultaneously accompanied by high and escalating prices. While biologic therapies have unquestionably revolutionized treatment for cancer patients, this has been achieved at an extraordinarily high cost. The median price for newly approved biologic cancer therapies now well exceeds $10,000 per month, which is severalfold greater than the median monthly household income in the United States. Patients and their families are facing an ever-increasing financial burden potentially limiting access to optimal effective treatment with many health plans passing on a greater share of the cost of health care through coverage restrictions and high deductibles.

Biosimilars are large, complicated molecules produced in living organisms that cannot be fully characterized, may vary from lot to lot, and can induce antibodies that may block their drug efficacy. The FDA defines a biosimilar as “a biological product that is highly similar to a U.S.-licensed reference biological product for which there are no clinically meaningful differences in safety, purity, or potency of the product.” While differences will exist between the biosimilar and reference product, the amino acid sequence and the presumed mechanism of action will be the same. Although not identical to the reference product and requiring less clinical evidence than originators in order to reduce the cost of drug development, highly sophisticated molecular characterization, preclinical and human pharmacokinetic/pharmacodynamic testing, as well as immunogenicity testing are required (Figure 2). Additionally, there is considerable emphasis on postmarketing surveillance for any rare or delayed toxicities to assure high similarity with the reference agent. As with originator biologics, the molecular characteristics and behavior of biosimilars have the potential to drift over time, with relatively minor changes in manufacturing and ingredients requiring regular monitoring. Once approved for one indication, the FDA has the authority to grant approval based on extrapolation to other indications approved for the originator, without requiring additional clinical evidence for those indications. Although regulations granting a designation of interchangeability between biosimilar and originator have been put forward requiring additional costly clinical trials, no biosimilar company has yet sought or been granted such designation.

While biosimilars that support patients receiving cancer chemotherapy have been integrated into clinical guidelines and routine clinical practice, access to confirmatory research evidence by clinical professionals appears to be essential for guideline development and practice integration. With careful regulatory oversight, transparent reporting, and postapproval vigilance, the adoption and use of biosimilars in oncology will likely increase progressively in the United States, leading to greater price competition and improved patient access to these important and potentially curative agents. Evidence for interchangeability may be modest but important influence on price associated with the introduction of the first biosimilar rituximab into oncology practice has been reported. While patent challenges persist and no data are yet available, the greater convenience of pegfilgrastim for supporting patients receiving cancer chemotherapy would suggest that increasing use of these biosimilars is likely to follow suit.

Figure 1. FDA-Approved Biosimilars

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Figure 2. Approval Pathway for Biosimilars in the US

Analytic Studies (molecular characterization: protein structure and function)

Preclinical Studies (in vivo animal: pharmacokinetic and pharmacodynamic modeling, immunoactivity, toxicity)

Clinical Pharmacologic Studies (human: pharmacokinetic and pharmacodynamic modeling, immunoactivity, toxicity)

Comparative Clinical Trials (dose ranging, efficacy, safety)

Adapted with permission from Lyman G, et al. NEJM. 2018;378:2036-2044.
The Hematologist

classification may be based on data from outdated in vitro and animal models that have since been replaced by long-term follow-up studies in patients with SCD demonstrating safety and efficacy of HU in clinical practice.

How does HU fit within NIOSH’s definition of hazardous? While leukopenia has been ascribed to HU since reports of secondary leukemia in patients using this medication for management of myeloproliferative neoplasms (MPNs), it is well established that MPNs harbor an inherent propensity toward development of leukemia. A nationwide cohort analysis of MPN patients followed for upwards of 10 years did not identify HU as an independent risk factor for transformation to acute leukemia.11 Similarly, follow-up studies of patients with SCD taking HU have not identified a clear relationship between HU and leukemia.9

Overall, female patients with SCD are advised to avoid HU during pregnancy due to concern for birth defects, based on initial reports of fetal malformations in rodent studies.4 However, congenital anomalies in these studies were seen at doses 10 to 100 times the maximum recommended dose for humans.12 Although prospective studies evaluating the safety of HU in pregnancy do not exist, available case series of female individuals exposed to HU do not provide clear evidence of adverse outcomes.13,14 Decreased sperm production is another potential short-term complication of HU that may be transient and reversible; yet it contributes to the hazardous classification by NIOSH. Several studies have been published demonstrating impaired sperm parameters in patients with SCD taking HU; however, a proportion of these defects were present in patients prior to initiating the drug,20 making it difficult to differentiate the relative impact of HU and SCD on sperm production. Further research on the potential impact of HU on reproductive health in SCD is strongly warranted to properly address this key barrier to HU acceptance in the SCD population.

Although NIOSH drug classification processes are assigned with the optimal occupational safety of health care workers in mind, they have also had to influence the labeling of medications dispensed in outpatient and inpatient pharmacies. There is obvious concern that by mandating health care professionals to purchase expensive personal protective equipment and medication bottles and patient hospital rooms to bear “cytotoxic drug” warnings, HU’s hazardous drug classification may contribute to patient and health care provider misconceptions about HU. It is unknown whether NIOSH’s hazardous labeling of HU has implications for the poor utilization rates to the only pharmacologic disease-modifying therapy that currently exists reported among patients with SCD, and warrants further study.

Chronic Graft-Versus-Host Disease: Therapeutics at Last?

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Chronic graft-versus-host disease (cGVHD) is a leading cause of late nonrelapse mortality and morbidity following allogeneic hematopoietic stem cell transplantation, and its incidence is rising as recipient age and use of peripheral blood stem cell grafts increase. The cardinal feature of cGVHD is tissue injury, which leads to the characteristic clinical manifestations of cutaneous scleroderma and bronchiolitis obliterans syndrome that typically have limited reversibility in their late stages. For decades, systemic corticosteroids, with or without calcineurin inhibitors, have been the mainstay of treatment for moderate-to-severe cGVHD, beyond which there have been no established second-line agents available. Thus, patients usually receive multiple lines of treatment, typically in an ad hoc fashion based on physician experience and biases. This lack of logical therapeutic paradigms for steroid refractory disease has in large part reflected our lack of understanding of the pathophysiology of cGVHD. Fortunately, this situation has dramatically changed in the past five years such that we now have a flourishing pipeline of potentially active agents undergoing analysis in both early- and late-phase clinical trials.

The factors initiating acute GVHD and cGVHD are linked: Both have their genesis in the expansion and differentiation of naïve alloreactive T cells along Th1/Th17/Tc1 and T follicular helper (Tfh) paradigms, driven by high levels of IL-12 and IL-6. Th17 cells are central to cGVHD pathophysiology. They traffic to GVHD target organs and secrete multiple cytokines including IL-17, IL-21, IL-22, interleukin (IL)-6, tumor necrosis factor, colony-stimulating factor (CSF)-1, and granulocyte-macrophage CSF (GM-CSF) stem cell mobilization with G-CSF promotes Th1/Th17 differentiation and scleroderma-like cGVHD. Recently, IL-22 and IL-6 have been shown to be co-requisite in the pathogenesis of cGVHD. Th17 cells secrete IL-6, which can induce Tfh cells to secrete IL-17 and IL-21 by T cells. This complex interaction between the key players (Th17/Tc17 and Th1, germinal center B cells, and tissue macrophages) is modulated by an array of immune regulatory populations. Of these, CD4+CD25+Foxp3+ regulatory T cells (Tregs) are the best-studied entity and are both quantitatively and qualitatively abnormal in cGVHD, but type 1 regulatory cells (Tr1), myeloid-derived suppressor cells (MDSC), and other cell types can also contribute.

The arrival of a range of kinase inhibitors has provided new opportunities for targeting both the innate and adaptive arms of GVHD pathogenesis. The Bruton tyrosine kinase (BTK) inhibitor ibrutinib blocks in B-cell activation and the secretion of auto- and alloreactive antibodies. Antibodies have been shown to be pathogenic in preclinical models of bronchiolitis obliterans and scleroderma. This complex interaction between the key players (Th17/Tc17 and Th1, germinal center B cells, and tissue macrophages) is modulated by an array of immune regulatory populations. Of these, CD4+CD25+Foxp3+ regulatory T cells (Tregs) are the best-studied entity and are both quantitatively and qualitatively abnormal in cGVHD, but type 1 regulatory cells (Tr1), myeloid-derived suppressor cells (MDSC), and other cell types can also contribute. This latter difficulty. Likewise, new IL-2 mutesins are now being studied that have more favorable pharmacokinetic profiles (NCT03422627).

Chronic GVHD has been the scourge of transplantation, but a confluence of factors, including advances in our understanding of cGVHD biology, availability of a range of small molecules, biologics, and cellular therapies; and the development of a system for clinical classification, staging, and response assessment has paved the way for a range of highly promising therapies that are now on the horizon. The next challenge will be in selecting the right (expensive) drug for an individual at the right time to effectively interrupt the disease process.


The lack of logical therapeutic paradigms for steroid refractory disease has in large part reflected our lack of understanding of the pathophysiology of cGVHD. Fortunately, we now have a flourishing pipeline of potentially active agents undergoing analysis...
Committee on Practice Chair Talks to DC Policy Makers About Issues Facing Practitioners

Today’s practicing hematologist faces many issues, including a reimbursement system that fails to adequately recognize the value of care services and growing administrative burdens from routine practices such as prior authorization and new federal initiatives such as the Quality Payment Program. Because these issues are often affected by the happenings in Washington, DC, it is important for physicians to have their voices heard by policymakers; the ASH Committee on Practice represents practicing hematologists in this regard.

To learn more about how ASH advocates on behalf of practicing hematologists, The Hematologist spoke with the Chair of the ASH Committee on Practice, Joseph Alvarnas, MD. Dr. Alvarnas was first introduced to hematology advocacy after being selected to attend the ASH Advocacy Leadership Institute in 2012, and he has served as the Chair of the Committee on Practice since 2016. “This experience gave me a great opportunity to get a sense of the full breadth of the activities of the Society in advocating for essential issues in our field,” said Dr. Alvarnas.

On April 30, the ASH Committee on Practice visited more than 45 congressional offices to talk to lawmakers about two issues affecting patient access to care. The first was the need to pass oral chemotherapy parity legislation, which aims to end the out-of-pocket cost disparity that some patients face when prescribed an oral or self-injectable anticancer regimen versus receiving chemotherapy intravenously. Intravenous chemotherapy treatments are typically covered under a health plan’s medical benefit with a small office-visit copay; however, oral or patient-administered anticancer therapies are often only covered as part of a plan’s prescription benefit and typically at a lower rate, resulting in many patients being responsible for high and unsustainable copays and co-insurance.

The second issue the committee advocated for was adequate reimbursement for practicing hematologists.

Hematologists face longstanding challenges, such as misvalued and outdated evaluation and management codes, as well as new challenges such as finding a sustainable reimbursement model for cell and gene therapies such as chimeric antigen receptor (CAR) T-cell therapy.

The committee works on an extremely diverse range of issues. Dr. Alvarnas explained, “It would be very difficult to distill the broad and complex work of the committee — some of the current initiatives include ensuring patient access to life-saving technologies and helping to ensure the human and economic sustainability of practicing hematologists.” Recently, the committee has focused on sustainable access to cell and gene therapies, adequate reimbursement for cognitive care services; how to leverage new telemedicine opportunities; and how to appropriately capture what a modern hematologist looks like.

The committee uses various additional tactics in its advocacy efforts, including hosting congressional briefings, establishing working groups to focus on specific policy issues, and drafting comment letters to various federal agencies on rules, policies, and coverage decisions.

Meeting with legislators either in Washington or back home in the district is one of the most effective ways that ASH advocates for the issues that affect the Society’s members. Speaking about the Committee’s most recent trip to Capitol Hill in April, Dr. Alvarnas noted, “The best illustration of the impact of the committee’s work comes when we go into a congressional office for the second time. We are welcomed. The staff or member is actively engaged. They note the prior work of the Society and the committee in engaging with them on a prior issue.”

All ASH members can participate in the Society’s advocacy efforts by joining the Grassroots Network to receive regular updates and information about how to contact their members of Congress. “The impact [of advocacy] is real and best manifested by the relationships that we foster and through which we provide valued input to congressional and administrative leaders,” said Dr. Alvarnas.

Additionally, physicians interested in practice-related issues can join the ASH Practice Partnership (APP). The APP is composed of practicing hematologists across the United States with interests in hematology care issues, quality of care, new health care delivery systems, and practice management issues. Members serve in a geographically diverse panel that provides feedback to ASH committees or staff about matters affecting the practice of hematologist. The group also advises ASH about the Society’s practice-related policies, resources, and programs. Interested members can submit a nomination by visiting www.hematology.org/Clinicians/Practice-Partnership.

ASH members can also participate in the ASH Advocacy Leadership Institute (see below), a two-day workshop to learn how to advocate for hematology in Washington, or they can visit the ASH Advocacy Center (www.hematology.org/advocacy) to quickly write your legislators about issues affecting your research or practice.

“Working with the Society to become an advocate is a meaningful path toward amplifying your voice and ensuring that the issues faced by you, your colleagues, and your patients are understood by legislators,” said Dr. Alvarnas.

NOMINATE YOURSELF OR A COLLEAGUE FOR THE 2019 ASH ADVOCACY LEADERSHIP INSTITUTE

ASH is now accepting nominations for the ninth annual Advocacy Leadership Institute, an intensive two-day program for ASH members to learn about advocacy, health policy, the legislative process, and how to become engaged in the Society’s activities. This year’s Advocacy Leadership Institute will be held on October 21 and 22, 2019, at the Society’s headquarters in Washington, DC. The first day will focus on learning about the legislative process and health policy. Participants learn about the major issues facing the field of hematology and see first-hand how Congress can affect research and practice. On the second day, participants meet with their congressional delegation on Capitol Hill to turn their knowledge into action in support of hematology.

Nominations are due no later than June 28, 2019.

For more information, email ASH Government Relations Coordinator Foster Curry at fcurry@hematology.org or visit www.hematology.org/ALI.

Dr. Toy indicated no relevant conflicts of interest. Dr. Hill has received funding from Pharmacyclics for immune analysis within a clinical trial of rituximab for the treatment of chronic GVHD.
Checkpoint blockade therapy has revolutionized the therapeutic management of cancer and given rise to the burgeoning field of immuno-oncology. Checkpoint–ligand pairs (e.g., programmed cell death protein 1 [PD-1] and its ligands PD-L1, PD-L2) play critical roles in the regulation of T-cell responses, particularly in the setting of exhaustion by chronic antigenic challenge, such as in cancer. Both activating (e.g., OX40, 4-1-BBL, indoleamine 2,3-dioxygenase [IDO]), and inhibitory (e.g., PD-1, cytotoxic T-lymphocyte antigen 4 [CTLA4], lymphocyte-activation gene 3 [LAG3], T-cell immunoglobulin mucin domain-containing protein 3 [TIM3]), checkpoint molecules provide positive or negative signals that fine tune CD4+ and CD8+ T effector cells (Teffs; Figure 1A). T regulatory cells (Tregs), marked by co-expression of CD4, CD25, and FoxP3, maintain self-tolerance. Certain tumor types have co-opted these checkpoint mechanisms to evade antitumor T-cell responses. One of the best examples of this immune evasion strategy is through genetic alteration (i.e., polyomavirus, amplification, or rearrangement) of the 9p24.1 locus, which contains the genes encoding Jak2, PD-L1, and PD-L2, by classic Hodgkin lymphoma (HL) and several subtypes of non-Hodgkin lymphoma.1

Checkpoint blockade strategies have enjoyed early clinical success in both hematolymphoid neoplasms and many solid tumors. Although objective response rates (ORR) vary widely based on tumor subtype (e.g., 15-25% in genitourinary, renal, and lung malignancies vs. 87% in HL),1 many of these patient cohorts are in the relapse/refractory setting where therapeutic options are limited, emphasizing its clinical impact. Although much of the previous work has focused on tumors of lymphoid origin, within the past two to three years investigations into the role of immune checkpoint blockade in non-Hodgkin lymphoma (NHL) has begun. Robust immunomodulatory approaches, such as mass cytometry, have characterized the bulk cellular makeup of the tumor microenvironment in individual samples of AML but do not analyze T-cell subsets at the subset level.2 Others have investigated the functional heterogeneity of T-cell subsets and expression of specific checkpoint markers in this setting, but also only in small patient cohorts.3 These early efforts have led to the initiation of several clinical trials to evaluate checkpoint blockade therapy in AML, including in the post-transplant setting4 in combination with hypomethylating agents in the relapse/refractory AML5 and in a cohort of elderly AML patients6, among others. Despite the initiation of these trials, a paucity of data exists in the evaluation of checkpoint markers and T-cell subsets in large cohorts of patients with AML.

Accordingly, Dr. Patrick Williams and colleagues of The University of Texas MD Anderson Cancer Center undertook a broad examination of T-cell frequencies, subset distribution, and checkpoint receptor expression patterns in 107 patients with AML (n=39 newly diagnosed, n=68 relapsed) and healthy donors (HD). Briefly, the study analyzed bone marrow and peripheral blood specimens by multiparameter flow cytometry for CD4+ and CD8+ Teffs and Treg frequencies and expression of both activating and inhibitory checkpoint receptor and ligand expression on these T-cell subsets and AML blasts. Additionally, these data were correlated with conventional cytogenic and mutational characteristics of the patients’ tumors.

Although the authors found no difference in absolute number or percentage of infiltrating CD3+ T-cells between AML patients and HD, they found a significant enrichment of Tregs (p=0.02) in both newly diagnosed and relapsed AML patients versus HD with an increase in the number of Tregs with the number of relapses (Figure 1B). Additionally, Teffs are increased in AML compared to HDs with an upward trend with an increasing number of relapses, as measured by the frequency of PD-1+/CD4+ T-cells, CD40+/CD4+ T-cells, and ICOS+/CD4+ T-cells (p values: <0.01, <0.05, and 0.04, respectively). Importantly, the frequency of “highly exhausted” PD-1+/LAG3+/CD4+ or PD-1+/TIM3+/CD8+ Teffs, but not Tregs, tended to be increased in AML (p=0.05 and p=0.16, respectively) and particularly in the setting of relapse. The accumulation of these highly exhausted T cells has been associated with earlier relapse after allogeneic stem cell transplantation (ASTCT) in AML patients and provides therapeutic rationale for anti–PD-1, anti-TIM3, and/or anti-LAG3 checkpoint inhibition in this setting.

The authors also sought to assess how particular genetic profiles of AML influence T-cell subset distribution and checkpoint ligand expression on AML blasts. Although most parameters tested were not impacted by specific genetics, in patients with TP53-mutated AML, there was an increased frequency of PD-L1 (p=0.05) and 4-1-BBL (p=0.01), that is hypothesized to be mediated by the TP53/miR-34/CD8 pathway (Figure 1C). A similar trend was observed for PD-L1+ blasts in patients with adverse cytogenetics (p=0.09). They also observed increased Teffs but not Tregs in patients harboring mutations in DNA methylation pathways (DNMT3A, IDH1/2, TET2, which seemed to be independent of bone marrow blast burden. Taken together, these data suggest that AMLs harboring TP53 mutations or adverse cytogenetics may be more amenable to PD-1/PD-L1 inhibition, whereas those with DNA methylation pathway alteration may respond better to interventions that preferentially affect CD4+ Teffs.

In summary, Dr. Williams and colleagues have examined T-cell subset distribution and activating/inhibitory checkpoint receptor-ligand expression in the bone marrow microenvironment of AML using the largest cohort yet studied. The authors show increased frequencies of highly exhausted Teff cells and non-exhausted Tregs in AML. These findings point to the mechanism of leukemic blast evasion from the immune system and provide a rationale for harnessing checkpoint-directed therapies as well as potentially other therapeutic approaches, including in the relapse/refractory setting.

4. Scherfer MI, Lohrenger FG, Enmeyer K, et al. T cells are functionally not impaired in AML; increased PD-1 expression is only seen at time of relapse and correlates with a shift towards the memory T cell compartments. J Hematol Oncol. 2019;12:89.
Hematopoietic Stem Cell Transplantation: Not Always a Panacea for Leukemia Patients With Unfavorable Outcome


Most children and young adults with acute lymphoblastic leukemia (ALL) are cured. Nevertheless, the outcome remains poor for patients with relapsed and refractory disease, as well as for patients with certain high-risk biologic features. Infants with KMT2A-rearranged ALL for example, do very poorly with current therapies, as cure rates have not improved past the past 30 years.1 Patients with t(17;19) and hypodiploid ALL also have poor survival.2 Most children with ALL do not require hematopoietic stem cell transplantation (HSCT) for cure. Historically, decisions to transplant or not transplant in children with ALL have been based on arbitrary lines in the sand with most centers and expert groups advocating for transplantation in first complete remission (CR1) if event-free survival (EFS) is predicted to be approximately 50 percent or less with chemotherapy alone or to use HSCT prophylactically such as HSCT in patients who fare poorly with chemotherapy alone, the decision to transplant should be based on whether or not has HSCT can improve cure rates.

Dr. Jennifer L. McNeer and colleagues report data on 131 children with hypodiploid B-ALL who were treated on Children’s Oncology Group (COG) protocols, AALL0301, AALL0331, or AALL0323 between 2003 and 2001. Patients treated on AALL0331 received a “three-drug” four-week remission induction regimen with vincristine, daunorubicin, and asparaginase, as well as intrathecal chemotherapy. Patients on AALL0331 and AALL0323 received a “four-drug” induction regimen that also included an anthraccline. All patients were enrolled on a companion biology study, AALL0381. After induction, patients underwent flow-cytometry-based minimal-residual disease (MRD) testing at one of two centralized laboratories.

Of 8,522 patients enrolled on AALL0381, 131 (1.5%) had hypodiploid ALL, defined as having less than 44 chromosomes or a DNA index less than 0.81. Fifty-five, 47, and three patients had 25 to 29, 30 to 39, and 40 to 43 chromosomes, respectively. Twenty-six patients had masked hypodiploidy. Patients with hypodiploid ALL are often subdivided into different groups because the degree of aneuploidy is associated with prognosis and disease biology. In 2013, Dr. Linda Hofmildt and colleagues published seminal work performing genomic profiling of 131 patients with hypodiploid ALL and found that patients with 22 to 29 chromosomes frequently have alterations in RB1 (41%), IKZF2 (53%), or TP53 (91%).3,4 Importantly, TP53 alterations were germline in approximately 50 percent of cases. In contrast, patients with 24-31 chromosomes frequently have alterations in receptor tyrosine kinase and RAS signaling (71%) and IKZF2 (13%).

Of the 131 patients with hypodiploid ALL, HSCT data were available for 113: 61 patients underwent HSCT in CR1, and 52 did not. The investigators found no statistically significant differences in EFS or overall survival (OS) comparing those who underwent transplant with those who did not (5-year EFS, 56.4% +/- 7.3% vs. 48.8% +/- 7.8% [p = 0.62] and 5-year OS, 65.6% +/- 6.9% vs. 53.8% +/- 7.6% [p = 0.32], respectively). Unlike patients without hypodiploid ALL, where the National Cancer Institute (NCI) risk group predicts outcomes, the outcomes for NCI-high-risk (HR; WBC 50,000/mm3 or age 10 years) and NCI standard-risk (SR; WBC < 50,000/mm3 and age < 10 years) patients were different. Patients with end-of-induction MRD lower than 0.01 percent had outcomes superior to those with MRD 0.01 percent or greater. Strikingly, subanalyses demonstrated no statistically significant impact in improvement with outcome (HSCT vs EFS or OS in patients with MRD lower than 0.01 percent [5-year EFS, 66.3% +/- 9.9% [HSCT] vs. 60.3% +/- 9.2% [no HSCT]; p=0.7) or MRD 0.01 percent or greater (5-year EFS, 29.4% +/- 14.3% [HSCT] vs. 16.7% +/- 10.8% [no HSCT]; p=0.7). Figure). HSCT did not affect outcome in the NCI HR or NCI SR groups. The overall sample size was small, and subgroup analyses only included a few patients in each group. Yet, no group was identified that benefited from HSCT.

Similar results were also published recently by the Ponte di Legno Group. Dr. Ching-Hon Pui and colleagues reported outcomes from 306 patients with hypodiploid ALL from 12 cooperative groups who were treated between 1997 and 2013. They also found that patients with 22-29 chromosomes had worse outcomes compared to patients with 24-31 chromosomes.

Outcomes for matched-sibling donor, unrelated donor, and haploidentical transplantation for children with leukemia are similar using modern protocols and supportive care.5 Thus, the decision to transplant in 2019 is often agnostic to donor status and is typically based on whether or not a child with ALL is expected to have poor outcomes with chemotherapy alone. The benefit of transplantation primarily derives from the graft-versus-leukemia (GVL) effect, where donor T and NK cells eliminate leukemic blasts.6,7 Arguably, not all types of ALL will derive the same benefit from GVL as some biologic ALL subtypes are likely more sensitive to immune surveillance than others. In theory, there are patients with ALL with good prognosis with chemotherapy alone who might have even better prognosis with HSCT. In contrast, as demonstrated by Dr. McNeer and colleagues and by Dr. Pui and colleagues, poor response to chemotherapy does not equate to benefit from transplantation. As HSCT has significant risks and long-term morbidities, it is crucial to determine which patients with ALL have the potential to benefit from transplantation and to not make transplant decisions based entirely on poor response to chemotherapy. For patients with hypodiploid ALL and positive MRD at en induction, new therapies such as immunotherapies, or biologically based therapies such as BCL-2 inhibitors are needed.


Unravelling the Loops of Drug Resistance in ALL


The phenomenon of resistance achieved in the treatment of pediatric acute lymphoblastic leukemia (ALL) stands out as one of the great achievements in cancer medicine. Unfortunately, a small minority of patients will still have disease that is refractory to initial chemotherapy, or disease that relapses after chemotherapy, and these patients continue to have poor long-term outcomes. Glucocorticoids are an essential component of chemotherapy in lymphoid malignancies (ALL, lymphoma, and myeloma) but have limited efficacy in myeloid, or indeed in many other cancers. This discrepancy suggests a conserved mechanism of tissue-specific response to glucocorticoids. It follows therefore that if such a mechanism exists, and this is independent of the genomic factors giving rise to leukemia, there may also be a common, non-genomic process that regulates acquired glucocorticoid resistance in ALL. These intriguing observations linking tissue specificity of glucocorticoid response and acquired glucocorticoid resistance were examined in a recent article by Dr. Duhua Jing and colleagues.

Chromatin conformation mediates many biologic functions, including cellular differentiation, by facilitating DNA accessibility of key lineage-specific transcription factors and regulators. Each cell type has 70 to 100,000 accessible chromatin domains that interact with transcriptional regulators to generate a complex interactive network that is highly correlated with cellular identity, a kind of three-dimensional cellular fingerprint. Using a bioinformatics approach and in silico data, the authors identified a specific chromatin conformation pattern found in lymphocytes. Interestingly, although some of the open, transcriptionally active sites correlated with lymphoid transcription factors, many were related to other cellular processes including hematopoietic development and the induction of apoptosis. When the authors examined glucocorticoid receptor binding sites specifically, they observed that these were highly correlated with open chromatin in lymphocytes, and closed chromatin in myeloid cells. Additionally, CTCF, a chromatin architectural protein that maintains DNA loops, was specifically enriched at the areas of open chromatin that also had glucocorticoid receptor binding, suggesting that this genomic architecture was a prerequisite for glucocorticoid receptor-mediated transcriptional changes and consequent downstream signaling. In particular, they identified chromatin accessibility at regulatory regions associated with the proapoptotic factor, BIM.

Next, to determine whether these changes were associated with resistance to glucocorticoid therapy in ALL, the authors examined a number of human ALL patient-derived xenografts (PDX) that had been extensively characterized for glucocorticoid response and annotated as sensitive or resistant. They integrated the findings from chromatin immunoprecipitation, accessibility, and gene expression by RNA sequencing to identify gene expression changes that were associated with open chromatin and glucocorticoid receptor binding. A relatively small number of genes were identified that showed increased expression in sensitive ALL PDX, and these correlated with open chromatin and higher H3K27Ac marks (an epigenetic marker for active gene enhancers). The converse was also true, as downregulated genes had fewer H3K27Ac marks and higher levels of DNA methylation. Gene expression analysis linked these genes with apoptotic signaling, but also with B-cell receptor signaling, an integral component of glucocorticoid efficacy in ALL. Again, there was a striking association of induced chromatin accessibility at the proapoptotic BIM locus, and sensitivity to glucocorticoids. These observations were validated functionally using a luciferase reporter assay. Moreover, chromatin confirmation capture was used in the PDX models to directly link CTCF-mediated DNA looping between the BIM promoter and this putative enhancer region. Ablation of this CTCF-binding motif was sufficient to prevent BIM induction after corticosteroids.

This article demonstrates that lymphocytes are pre-programmed for glucocorticoid binding that is mediated through a lineage specific chromatin architecture, and that the structural protein CTCF may be involved in manipulating or maintaining this architecture. This work helps explain a recurring clinical observation that we often take for granted if such a mechanism exists, and this is independent of the genomic factors giving rise to leukemia, there may also be a common, non-genomic process that regulates acquired glucocorticoid resistance in ALL. These intriguing observations linking tissue specificity of glucocorticoid response and acquired glucocorticoid resistance were examined in a recent article by Dr. Duhua Jing and colleagues.

Thrombolysis for Acute Pulmonary Embolism Is Not One-Size-Fits-All


Patients are often confused about the difference between thrombolytics and anticoagulants for treatment of pulmonary embolism (PE). If anticoagulants don’t break down clots and thrombolitics do, why don’t we give thrombolitics to more patients with acute PE? This is an excellent question with a rather complex answer.

Dr. Qiuka Hao and colleagues recently published an update of a 2015 systematic review of thrombolytic therapy for acute PE. They included 18 randomized trials enrolling 2,197 patients, comparing thrombolytic therapy followed by heparin with heparin alone or heparin plus placebo. Eleven of the 18 randomized controlled trials (RCTs) explicitly included submassive PE (PE with right heart dysfunction or elevated troponin but without systolic blood pressure < 90 mmHg). Outcome measures varied but the majority of trials reported overall mortality, recurrence of PE, and major bleeding. Thrombolysis used included alteplase, urokinase, streptokinase, recombinant tissue plasminogen activator, and tenecteplase. Risk of bias was high due to concerns about randomization, blinding, small sample sizes (range, 8 to 1,006 patients), and potential influence of pharmaceutical companies.

A meta-analysis of the studies with a lower risk of bias (n=2054) showed no mortality benefit for thrombolysis over heparin (OR, 0.66; 95% CI, 0.40-1.06; p=0.08). Furthermore, the risk of major bleeding was significantly higher in the thrombolytic group (OR, 2.96; 95% CI, 1.95-4.31; p<0.001, low quality of evidence). The results were not significantly different according to subgroup (massive PE/submassive PE/unknown types).

It is important to note that the mean age of participants in the meta-analysis was 60 years. Only one RCT (n=1,006) included a subgroup of participants older than 75 years. This subgroup showed a much higher risk of major extracranial bleeding with thrombolysis compared with heparin (OR, 0.04; 95% CI, 2.69-154.53) and an excessive number of intracranial bleeds (7 tenecteplase vs. 1 placebo).

The most current version of the American College of Chest Physicians Versus Thrombembolism Treatment guidelines (2016) recommends against thrombolysis in acute PE not associated with hypotension (Grade 1B). The guidelines addressing the same topic are awaited in 2019.

Most clinicians agree that thrombolysis is indicated in patients who present with PE and hemodynamic compromise. Within this context, the prognosis is poor that the risk of major bleeding, including intracranial bleeding, is justified. The more challenging clinical scenario is when patients present with submassive PE without clear evidence of hemodynamic instability. The Cochrane Review article summarized here suggests there is no clear mortality benefit, though the upper limit of the 95 percent CI comes close to reaching significance.

My approach to symptomatic patients with submassive PE is to evaluate them on a case-by-case basis. If after 24 to 48 hours of anticoagulation therapy, there is no improvement in oxygen requirements, heart rate, and/or dyspnea with minimal exertion, I consider thrombolysis. I am much more reluctant to offer thrombolysis if the patient is 75 years or older, due to the increased risk of intracranial bleeding. For patients who do well with thrombolysis, the immediate improvement in vital signs and/or symptoms is very rewarding; however, when they experience intracranial bleeding, it is equally devastating.

Investigators are considering using lower doses of thrombolysis to offset the bleeding risk, especially in patients who are 75 years or older. Studies are needed to show whether this approach would be effective in terms of clinical outcomes.

Could Lullabies and Bedtime Stories Help Youth With Sickle Cell Have Less Pain?


P

arents recognize the importance of sleep for newborns, infants, and toddlers. When well rested, infants are less cranky, preschoolers are happier, and kindergartners are less disruptive. Somewhere between early grade school and high school, life gets easier, and days become packed full of activities making sleep take a back seat. Bedtime shifts from 7:00 p.m. in elementary school to 11:00 p.m. or later for high schoolers. School-based educators alike recognize the importance of sleep for young adolescents and young adults, less, as they struggle with waking up early for that 7:15 a.m. school start. Factor in after-school sports and part-time jobs, and the average adolescent clocks in less than five hours of sleep per day.

In his commentary “Sleep and the Developing Brain,” Dr. Ronald Dahl cited that sleep was one of the three most fundamental requirements for healthy growth and development in young children, in addition to loving support and protection, and adequate nutrition.1 Research suggests that when the growing brain is sleep deprived, children and adolescents present with symptoms of irritability, attention deficit hyperactivity disorder, and various other behavioral problems.2 The pr...
Clonal Selection and Mutation-Therapy Interaction in the Development of Therapy-Related Myeloid Neoplasms


The development of a secondary hematologic malignancy is one of the most serious risks of therapeutic cancer chemotherapies. Therapy-related myeloid neoplasms (t-MN) including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are associated with a particularly poor prognosis. Broadly, there are two main mechanisms by which cytotoxic therapies are proposed to cause t-MN. First, cytotoxic therapy-induced DNA damage might directly lead to cancer-driving mutations through inappropriate DNA repair. Alternatively, chemotherapy exposure may apply selective pressure on specific subpopulations of pre-existing abnormal hematopoietic stem cells (HSCs), which then gain a survival advantage, thus promoting subsequent clonal evolution. Clonal hematopoiesis (CH) takes place when mutant stem cells occur in healthy individuals and contribute disproportionately to the production of blood; it is increasingly recognized that individuals with CH are at markedly increased risk of subsequent development of hematologic malignancies, including t-MN.

PPM1D (protein phosphatase Mn2+ Mg2+ dependent 1D) is involved in the DNA-damage response pathway and is a regulator of p38 activity. Recurrent truncating mutations of PPM1D with gain-of-function activity have been detected in CH in normal populations, but also following chemotherapy and in patients with solid organ cancers. This association prompted Drs. Hsu and colleagues to investigate the PPM1D gene in patients with MDS/AML in a study led by the Goodell Laboratory. Using targeted-capture sequencing of 295 cancer genes on bone marrow samples of 156 t-MDS/AML patients, investigators found PPM1D mutations in 20 percent of patients (31 of 156) with only 3% of 156 patients. Strikingly, mutated PPM1D occurred in only one of 228 patients in a matched de novo MDS/AML cohort. Perhaps surprisingly, for two mutations proposed to act through the same pathway, presence of TP53 and of PPM1D mutations were not mutually exclusive, suggesting a distinct mechanism of action.

A significant association was observed with prior exposure to platinum agents and etoposide and topoisomerase inhibitors but not with other cytotoxic agents such as 5-fluorouracil. To investigate the mechanism by which platinum agents might promote t-MN associated with mutant PPM1D, in an elegant series of experiments the authors created PPM1D-mutant cell lines using a CRISPR-Cas9 system and showed mutant cells selected in vitro with relative frequency of 100 percent after exposure to a mixture of wild-type (WT) and mutant cells to cisplatin. This expansion was tempered by treating the cells with a combination of a PPM1D inhibitor and cisplatin, demonstrating the potential role of increased PPM1D expression in mutant cell fitness advantage during cytotoxic therapy. This chemoresistance was specific to cisplatin, doxorubicin, etoposide and topoisomerase inhibitors but not with other cytotoxic agents such as 5-fluorouracil.

In this impressive work, Dr. Hsu and colleagues have clearly delineated that hematopoietic clones carrying PPM1D mutations are selected for following exposure to certain cytotoxic therapies, clearly implicating an important role for PPM1D in therapy-related leukemogenesis. Presence of PPM1D mutations in healthy individuals would suggest that this mutation alone is insufficient to drive leukemogenesis but is nevertheless enough to drive a degree of clonal expansion. This is somewhat at odds with the findings from the mouse model in this study, raising the possibility that certain environmental exposures or other factors might influence the impact of PPM1D mutations on hematopoiesis. Furthermore, the observation that t-MN patients typically had PPM1D mutations with a low variant allele frequency implies that the mutation is only present in a subclass of t-MN cells in most patients. Consequently, the exact role of this mutation in disease pathogenesis remains uncertain. Nonetheless, this study clearly advances our understanding of mechanisms of t-MN development and highlights the importance of specific mutation-therapy interactions during the development of secondary hematologic cancers.

Reprogramming the Repurposed Drug, a Structural Study of Thalidomide Analogs


Advances in technology and understanding the molecular profile of tumors have resulted in the identification of new therapeutic targets in cancer. However, the process of drug discovery and development usually takes 10 to 15 years and is costly and risky. Given the huge demand for new treatments and the lengthy process for novel drug development, some scientists turn to drug repurposing – namely, the identification of new uses for U.S. Food and Drug Administration (FDA) –approved or investigational drugs. Thalidomide is a poster child for drug repurposing in cancer, as it was developed in the 1950s as a sedative for pregnant women, subsequently used as a therapy for leprosy, and approved by the FDA in 2006 for treatment of multiple myeloma (MM).

MM is a genetically complex and heterogeneous malignancy of plasma cells that is characterized by progression of disease from distinct precursor states: monoclonal gammapathy of undetermined significance and smoldering MM.2,4 MM is the second most common hematologic malignancy in the United States and remains an incurable disease. Frontline therapy for MM differs across countries depending on drug availability; the most common regimens are either double-agent therapy with lenalidomide and dexamethasone or triple-agent therapies with bortezomib, lenalidomide, and dexamethasone; bortezomib, thalidomide, and dexamethasone; and bortezomib, cyclophosphamide, and dexamethasone.4

The immunomodulatory drug (IMiD) thalidomide and its structural analogs lenalidomide and pomalidomide induce the ubiquitin–proteasome degradation of key MM transcription factors IkB kinase (IKZF1) and IκBζ (IKZF3) via binding to Cereblon (CRBN). CRBN is the substrate receptor for the E3 ubiquitin ligase, and binding of those drugs to CRBN alters its ability to substrates such as IKZF1 and IKZF3, and subsequently leads to their degradation through proteolysis.2,4 IKZF1 and IKZF3 are members of the largest family of C3H2 zinc finger (ZF) proteins in the human proteome, which includes many putative transcription factors – usually challenging targets for drug development due to the lack of targetable active sites.

In a recent functional and computational study, Dr. Quinlan S. Siveers and colleagues defined novel protein targets of thalidomide analogs, drawing from approximately 800 C3H2 ZF-containing proteins. Screening 6,572 C3H2 ZF motifs, they discovered 11 ZFs that were degraded in the presence of thalidomide, lenalidomide, and pomalidomide, while six of those were able to mediate the degradation of their corresponding full-length protein, comprising known targets IKZF1/IκBζ as well as five novel targets, ZNF690, ZFp91, ZFp276, ZNF653, and ZFp827.

Although the 11 ZF motifs discovered in the screen did not show major similarities in their amino acid sequences, those that could mediate the degradation of their full-length protein had an additional ZF protein motif that was associated with high-affinity binding to the drug-CRBN complex. A structural study further suggested that it is the overall shape of the C3H2 ZF domain, rather than its amino acid sequence, that determines whether a ZF motif will bind and the complementary groove on the drug-CRBN complex surface. Supporting this notion, Dr. Siveers and colleagues performed an analysis on structurally similar ZFs and showed that approximately 50 to 150 additional C3H2 ZFs were capable of binding to the drug-CRB-N complex with similar or better scores than the 11 ZFs discovered in the screen.

Functionally validated of biologically relevant ZFs in vitro further proved that the drug-CRBN interface is prone to interacting with higher numbers of ZF proteomes than discovered in the screen and introduced novel target ZF proteomes for therapeutic intervention, such as the lymphoma oncoprotein E2A, the transcription factor ESR1 that regulates multiple tumor suppressor genes, and the oncophallic SOX2. Importantly, chemical modification of thalidomide analogs and drug-ZF interface resulted in the degradation of particular groups of ZFs, suggesting that thalidomide analogs can be modified to selectively target different proteins, including transcriptional factors that are traditionally considered to be “undruggable.”

Although those promising in vitro results might not fully translate into in vivo due to potential competition for CRBN occupancy and the modulation of affinity and binding kinetics of ZF motifs to CRBN by the drug, this comprehensive study by Dr. Siveers and colleagues significantly enhanced our understanding of thalidomide-CRBN-mediated protein degradation and introduced novel target proteomes for thalidomide therapy. These results pave the way for the expansion of both, IMiD indications across different cancers or diseases, and IMiD utility in the treatment of MM itself, while they offer the possibility to target undruggable transcription factors, which can expand the list of existing drug targets and pathways and improve patient outcomes.
Apixaban Versus Rivaroxaban: Which One to Use in VTE Treatment?


There are numerous anticoagulant options for the treatment of acute venous thromboembolism (VTE), with four direct oral anticoagulants (DOACs) approved by the U.S. Food and Drug Administration (FDA) in addition to traditional anticoagulants. Draft recommendations from ASH on the treatment of VTE do not recommend one over another. Two recent observational studies have directly compared apixaban to rivaroxaban for the initial treatment of VTE.

The first study by Ghaeder Dawgs and colleagues is a retrospective cohort study using claims databases from the United States between 2014 and 2016. Propensity score matching was used to compare 3,091 apixaban users with 12,163 rivaroxaban users for initial treatment of acute VTE (initiated drug within 30 days of VTE diagnosis). Outcomes of recurrent VTE [positive predictive value of International Classification of Diseases (ICD) 9/10 codes for VTE, 73-83%] and major or minor bleeding were defined by ICD-9/10 codes (positive predictive value of ICD 9/10 codes for major or minor bleeding, to our knowledge, do not exist). Recurrent VTE (adjusted hazard ratio [aHR], 0.37; 95% CI, 0.24-0.55), major bleeding (aHR, 0.54; 95% CI, 0.37-0.82), and minor bleeding (aHR, 0.57; 95% CI, 0.49-0.67) were all lower with apixaban than with rivaroxaban.

The second study by Dr. Ghaeder Dawgs and colleagues is a single-center prospective observational study from the Mayo Clinic comparing 302 apixaban-treated patients to 298 rivaroxaban-treated patients from 2013 to 2018. Patients were included if they had started the medication within 14 days of a diagnosis of acute VTE. Outcomes of VTE recurrence, major bleeding (MB), clinically relevant nonmajor bleeding (CRMB), and composite of CRMB and MB were adjudicated by independent investigators using standard International Society on Thrombosis and Hemostasis (ISTH) definitions. Outcomes were analyzed at three months by total person-time of exposure for patients receiving longer treatment. At three months, recurrent VTE occurred in three apixaban-treated patients (1%) and in two rivaroxaban-treated patients (0.7%; p=0.66). Major bleeding occurred in six apixaban-treated patients (2%) and six rivaroxaban-treated patients (2%; p=0.98). A propensity score was generated and used in a Cox proportional hazard model evaluating total follow-up duration; after adjustment no differences were observed between apixaban and rivaroxaban in VTE recurrence (aHR, 1.4; 95% CI, 0.5-3.8) or MB (aHR, 1.7; 95% CI, 0.2-13.3). A lower rate of CRMB was demonstrated with apixaban (aHR, 0.4; 95% CI, 0.2-0.8), but the composite (CRMB and MB) safety outcome was not different (aHR, 0.6; 95% CI, 0.3-1.2). The authors concluded that the safety and efficacy of apixaban and rivaroxaban were similar in clinical practice.

Patient populations and methodologies differed between studies; both are limited by their observational, nonrandomized design (Table). Interestingly, active cancer was more prevalent in the second study but did not seem to increase overall adverse event rates. Weight was not addressed in the study by Dr. Dawgs and colleagues but was similar in the two groups from the Mayo study by Dr. Ghaeder Dawgs and colleagues. Concerns about the efficacy of DOACs in the morbidly obese remain, and it is unknown whether one drug is better than another. The first study has a very large sample size that allows for identification of small differences in outcomes between the two drugs but is limited by potentially imprecise outcome definitions based on ICD 9/10 codes, whereas the second study had prospective follow up and adjudicated outcomes based on standard ISTH definitions of bleeding. These two new studies with conflicting conclusions do not provide enough evidence to suggest the superiority of one medication over another for the treatment of acute VTE. Data directly comparing other DOACs are also needed.

Additional observational data will continue to be useful to assess the real-world efficacy of these drugs.


Table. Comparison Between Studies of Baseline Characteristics and Crude Adverse Events for Apixaban and Rivaroxaban in the Treatment of Acute Venous Thromboembolism

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dawgs GK et al</td>
<td>Bott-Kitslaar DM et al</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61.5</td>
<td>62.4</td>
</tr>
<tr>
<td>Indication for anticoagulation: PE (%)</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>Indication for anticoagulation: Provoked VTE (%)</td>
<td>51</td>
<td>83</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>Not reported</td>
<td>88</td>
</tr>
<tr>
<td>Active cancer (%)</td>
<td>14</td>
<td>47</td>
</tr>
<tr>
<td>ASA or NSAI (%)</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>17a</td>
<td>2.3b</td>
</tr>
<tr>
<td>Adverse Outcomes (No. of events/100 person-years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE events</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Nonmajor bleeding events</td>
<td>20a</td>
<td>4.0b</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, aspirin; NSAI, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolism; VTE, venous thromboembolism.

* Unknown definition of CKD. + Creatinine clearance < 30 mL/min. - Minor bleeding. • Clinically relevant nonmajor bleeding (CRMB).

Dr. Usmani indicated no relevant conflicts of interest.

In “Empires of the Indus: The Story of a River,” the riveting account of Alice Albinia’s own journey from the delta of the mighty Indus river up to the northern regions of Pakistan, the author describes the intricate fabric that weaves the region’s culture with finesse. She traverses millennia, from the accounts of the Mesopotamian merchants and Alexander the Great’s historians, to the Persian emperors and the Buddhist civilizations of old, the Greek kings, Afghan Sultans, Moghuls, and of course, the colonizers. The Indus (a.k.a., Sindhu, Sher Darya) river has witnessed thousands of years of human history as though it were on a loop—repeating the same mistakes, then repeatedly forgetting the lessons learned. The Indus has seen borders drawn and erased around it time and again and has witnessed many Southeast Asian civilizations emerge and disappear. The characters change over time, but the themes remain the same: When diverse people come together for a common purpose, they thrive. Whenever the Indus witnessed a conflict based on race, religion, caste, creed, or nationalism, the people always lost. The Indus has witnessed the wonders of the human spirit and ingenuity, as well the cruelty and follies of mankind. The further into the book I read, the more it occurred to me that this could very well be the story of the Mississippi River a few hundred years from now.

As I approach the 16th anniversary of my life in the United States, I can’t help but reflect on experiences that have helped shape my own journey as a physician—this book being one of them. My wife and I are Pakistani-Muslim immigrants who followed our dreams after medical school and made a life for ourselves in a land of opportunity. We persevered to be part of the story of the United States of America. Although the age of information technology has made the world a “smaller” place, it appears counterintuitive that there is a sort of selective amnesia for the lessons etched in the annals of human history. What makes the United States great is us as a collective; being different is okay and, if anything, makes us stronger as a whole. Even in the current political environment, I find great comfort in being part of a profession and research community that works in sync toward the common goal of alleviating human suffering.

A Story About a River Named Indus

SAAD USMANI, MD
Director of Clinical Research in Hematologic Malignancies, Atrium Health, Charlotte, NC

As I approach the 16th anniversary of my life in the United States, I can’t help but reflect on experiences that have helped shape my own journey as a physician—this book being one of them. My wife and I are Pakistani-Muslim immigrants who followed our dreams after medical school and made a life for ourselves in a land of opportunity. We persevered to be part of the story of the United States of America. Although the age of information technology has made the world a “smaller” place, it appears counterintuitive that there is a sort of selective amnesia for the lessons etched in the annals of human history. What makes the United States great is us as a collective; being different is okay and, if anything, makes us stronger as a whole. Even in the current political environment, I find great comfort in being part of a profession and research community that works in sync toward the common goal of alleviating human suffering.
Can We Use MRD Status to Personalize Therapy in Mantle Cell Lymphoma?  

**STUDY TITLE:** A Randomized Phase III Trial of Consolidation with Autologous Hematopoietic Cell Transplantation vs Maintenance Rituximab for Patients with Mantle Cell Lymphoma in Minimal Residual Disease-Negative First Complete Remission (ECOG-ACRIN 4151)  

**IRSCN NUMBER:** NCT03267433  

**SPONSOR:** ECOG-ACRIN Cancer Research Group; National Cancer Institute (NCI)  

**ACCRUAL GOAL:** 412 patients randomized to arms A and B (206 patients to each arm)  

**PARTICIPATING CENTERS:** All ECOG-ACRIN sites (lead organization) and Cancer Trials Support Unit sites (including Alliance and Southwest Oncology Group). The study also is endorsed by the Blood and Marrow Transplant Clinical Trials Network. The study is open at both academic centers as well as at some larger community oncology practices.  

**STUDY DESIGN:** This trial is enrolling adult patients with mantle cell lymphoma (MCL) aged 18 to 70 years, who are complete responders after four to six cycles of induction chemotherapy and have undergone autologous stem-cell transplantation (auto-HCT). Patients are enrolled at any time during first-line therapy. The study will allow any induction regimens (per their treating physician’s preference), and patients have the option to receive their induction regimens by their community oncologist. After completion of induction therapy, patients will undergo restaging with a PET/CT scan, bone marrow biopsy, and minimal residual disease (MRD) analysis using an immunoglobulin high-throughput sequencing (next-generation sequencing) circulating tumor DNA (ctDNA) assay. The MRD assay is highly sensitive, being able to detect approximately one in 1,000,000 ctDNA sequences in the peripheral blood. Patients who are in an MRD-negative complete remission (CR) are then randomized to either auto-HCT followed by three years of maintenance rituximab (arm A) or three years of maintenance rituximab with deltaritux (auto-HCT) (arm B). Patients who remain MRD positive or who are in a partial remission will proceed to auto-HCT followed by three years of maintenance rituximab (arm B). The primary objective of the study is to compare six-year overall survival (OS) of arm A versus arm B. The secondary objectives include four-year progression-free survival (PFS) for MRD-negative patients, as well as PFS and OS for MRD-positive patients (or patients in partial remission) who undergo auto-HCT followed by maintenance rituximab, and MRD status at day 100 in MRD-positive patients prior to auto-HCT.  

**RATIONALE:** The OS benefit of auto-HCT in first-line therapy for MCL following modern induction regimens is unproven. The only prospective randomized trial comparing autologous hematopoietic cell transplantation (auto-HCT) followed by maintenance rituximab (arm A) versus maintenance rituximab alone (arm B) in patients in MRD-negative first CR. The secondary objectives include four-year progression-free survival (PFS) for MRD-negative patients, as well as PFS and OS for MRD-positive patients (or patients in partial remission) who undergo auto-HCT followed by maintenance rituximab, and MRD status at day 100 in MRD-positive patients prior to auto-HCT.  

**RATIONAL:** The benefit of auto-HCT in first-line therapy for MCL following modern induction regimens is unproven. The only prospective randomized trial comparing autologous hematopoietic cell transplantation (auto-HCT) followed by maintenance rituximab (arm A) versus maintenance rituximab alone (arm B) in patients in MRD-negative first CR. The secondary objectives include four-year progression-free survival (PFS) for MRD-negative patients, as well as PFS and OS for MRD-positive patients (or patients in partial remission) who undergo auto-HCT followed by maintenance rituximab, and MRD status at day 100 in MRD-positive patients prior to auto-HCT.  

**COMMENT:** This is a bold and important study, randomizing young patients with MCL in first CR (must be MRD-negative to auto-HCT or no auto-HCT). All patients received three years of maintenance rituximab as it has shown survival benefit in patients receiving transplant as well as non-transplant-based first-line therapy.  

**REFERENCES:**  


— Timothy S. Fenske, MD, MS, and Brad Kahl, MD  

**Giving the Axe to R-CHOP?**  

**STUDY TITLE:** A Phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with rituximab and CHOP (R-CHOP) versus rituximab and CHOP (R-CHOP) in previously untreated patients with diffuse large B-cell lymphoma (POLARIX)  

**ClinicalTrials.gov Identifier:** NCT03274492  

**SPONSOR:** Hoffman-La Roche  

**PARTICIPATING CENTERS:** More than 250 centers in the United States, Australia, Europe, Canada, New Zealand, and Asia  

**STUDY DESIGN:** This is a randomized, placebo-controlled, double-blind phase III study investigating the safety and efficacy of polatuzumab vedotin in combination with rituximab and CHOP (R-CHOP), polatuzumab vedotin and CHOP (R-CHOP) in previously untreated patients with diffuse large B-cell lymphoma (POLARIX). The primary objective of this study is to determine the efficacy of polatuzumab plus R-CHOP compared with R-CHOP with respect to progression-free survival. Secondary objectives include additional measures of efficacy and safety of polatuzumab and CHOP. Exploratory objectives include biomarker and pharmacokinetics.  

**RATIONALE:** R-CHOP has been the standard of care for the treatment of DLBCL since the results of the MInT trial and on results in durable remissions in approximately 65 percent of patients. Patients with high IPI, double- and triple-hit cytogenetics, and activation of B-cell subtypes have inferior outcomes with this regimen. Several attempts to improve R-CHOP, including the addition of drugs such as ibrutinib and bortezomib as well as with regimens such as dose-adjusted R-EPOCH (rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), have been unsuccessful when tested in a randomized, controlled setting. Standard R-CHOP or R-EPOCH have been met with disappointment, as have randomized studies of alternative regimens such as dose-adjusted R-EPOCH. Although the activity of polatuzumab, both as a single-agent and in combination with chemotherapy, makes it the next culprit in combination with R-CHOP-like backbone, one could argue that history is likely to repeat itself and the results of the POLARIX study will once again disappoint. However, there are reasons to be more hopeful this time around. The activity of this drug in the relapsed/refractory setting is higher than any of the agents that have come before it and its target (CD79b) is more ubiquitous in this heterogeneous group of lymphomas. Furthermore, the addition of antibody-drug conjugates to upfront chemotherapy regimens has already demonstrated a significant advantage and POLARIX. It may be naive, but the field once again awaits the results of this important study to hopefully confirm the activity of this drug in this disease and to establish a new standard for the upfront treatment of the most common lymphoma.  

**REFERENCES:**  


— Carol Jacobson, MD  

Dr. Jacobson has no relevant conflicts of interest.
Dr. Bob Löwenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) have combined efforts to identify some of the most outstanding Blood articles that have appeared either in print or online during the two-month interval between issues of The Hematologist. The goal is to underscore the remarkable research that is published in Blood and to highlight the exciting progress that is being made in the field.

MARCH 21, 2019

In a Plenary Paper, Dr. Antonio Piga and colleagues report improved hemoglobin levels in thalassemia patients treated with luspatercept, a recombinant protein that acts as a ligand trap for transforming growth factor β ligands that suppress late erythropoiesis.

MARCH 28, 2019

In a Plenary Paper, the authors examine activation and effector functions of normal and FcγRIIIA-negative neutrophils. Their work reveals that normal neutrophils also express FcgRIIB (CD16a) and that the two receptors on neutrophils mediate distinctly different effector functions for processing antibody-opsonized substrates.


The investigators present positive results from a randomized study (HOVON-97) showing that disease-free survival (DFS) in older patients with acute myeloid leukemia (AML) is improved by azacitidine compared with postremission observation.

APRIL 4, 2019

In this Plenary Paper, the investigators report a significant advance in our understanding of von Willebrand factor (vWF) structure and the interaction of vWF with factor VIII. They describe the first high-resolution crystal structure of the monomeric D9D3 assembly of human vWF and the additional structural implications for hundreds more proteins that contain von Willebrand disease domains.


Using a mouse model, the investigators address the critical question of the vascular and cardiac toxicity of the BCR- ABL1 tyrosine kinase inhibitor ponatinib. Their experiments reveal that ponatinib vascular toxicity is due von Willebrand factor-mediated platelet adhesion.


This article reports the results of a large multicenter phase II study evaluating an intensified pediatric chemotherapy regimen to treat older adolescents and young adults with Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia.

Francesco Lo Coco, MD

It has been said that you don’t always know what you have until it’s gone. This admonition certainly does not apply to our friend and colleague Dr. Francesco Lo Coco whose sudden death on March 3, 2019, has stunned the hematology community. We all know exactly what we had. He was a warm, inspiring, clear thinking, collaborative academic clinician focused on advancing our understanding of the biology, pathogenesis, and treatment of acute promyelocytic leukemia (APL).

Dr. Lo Coco was Professor of Medicine at the University of Rome Tor Vergata where he was Head of the Integrated Diagnostic Laboratory. Such a position reflected his particular interest in deciphering the molecular and genetic features of a variety of hematologic malignancies. However, his name is most closely associated with APL. He was completely immersed in the study and treatment of this rare yet fascinating subtype of acute myeloid leukemia. His insights and contributions were many. He was the co-chair of a series of international symposiums on APL held every four years in Rome starting in 1993. He was a founding member of the International Consortium on APL (IC-APL), an initiative supported by ASH, which began in 2004 as an endeavor to improve the care and outcome for patients with APL in less developed countries. He published hundreds of manuscripts addressing a wide range of topics in APL, both in the form of original research and reviews, which demonstrated the breadth of his interests and achievements. Perhaps his most important accomplishment is the introduction of chemotherapy-free treatment for low-risk APL, with al-trans retinoic acid (ATRA) and arsenic. This approach changed the standard of care and resulted in a cure rate of 98 percent of patients. Such a strategy serves as a model for the targeted treatment of other hematologic malignancies.

Dr. Lo Coco was an active member of ASH, serving on the International Members Committee as well as contributing a significant amount of time as Editor-in-Chief of the Italian edition of Blood. He served on the editorial boards of several other prestigious journals including the Journal of Clinical Oncology and Leukemia. He chaired the Education Committee of the European Hematology Association and was president of the Italian Society of Hematology. Dr. Lo Coco was a frequent and skilled educator, lecturing at numerous important meetings on acute leukemias around the world. He always discussed APL in a clear and authoritative way as he conveyed his wealth of experience in the disease. As focused as he was in APL, Dr. Lo Coco made many contributions in other hematologic malignancies as well. He leaves an important legacy of scholarly contributions from which both clinicians and patients will benefit for many years to come.

Nothing endowed Dr. Lo Coco more than talking about APL, except one person: his son Gaetano. He was exceptionally proud of Gaetano, a gifted, young orchestra conductor. No surprise. The apple never falls far from the tree.

-Martin S. Tallman, MD, Chief, Leukemia Service, Memorial Sloan Kettering Cancer Center; Professor of Medicine, Weill Cornell Medical College, New York, NY
An Older Man With Cytopenias and Seemingly Normal-Looking Marrow

BENJAMIN KAUMEYER, MD; DANIEL ARBER, MD; AND GIRISH VENKATARAMAN, MD
1. Fellow, Department of Pathology, The University of Chicago, Chicago, IL
2. Donald West and Mary Elizabeth King Professor and Chair of Pathology, The University of Chicago, Chicago, IL
3. Editor in Chief, ASH Image Bank; Medical Director, Immunohistochemistry; Associate Professor, Department of Pathology, The University of Chicago, Chicago, IL

A 71-year-old man was diagnosed seven years ago with a hematologic malignancy that was successfully treated with chemotherapy and determined to be in complete remission. He later presented in clinic with mild fatigue. A complete blood count with differential is performed.

White blood cell count was 2.2 × 10^3/μL; hemoglobin, 14.5 g/dL; and platelet count, 77 × 10^3/μL. Differential test revealed a neutrophil count of 52 percent; lymphocytes, 43 percent; monocytes, 2 percent; eosinophils, 2 percent; and basophils, 0 percent.

A bone marrow biopsy was performed to further evaluate the patient. The images shown here are the bone marrow core biopsy with hematoxylin and eosin (H&E; Figures 1 and 2) staining, CD20 (Figure 3) and CD11c (Figure 4) immunohistochemistry on core biopsy, and representative flow cytometry plots (Figures 5 and 6). Additionally, next-generation sequencing was performed on the bone marrow biopsy and detected a BRAFV600E mutation.

What is the diagnosis?
A. Myelodysplastic syndrome
B. Splenic marginal zone lymphoma
C. Hairy cell leukemia
D. Hairy cell leukemia-variant

Figure 1. Bone marrow core biopsy with H&E staining.
Figure 2. Bone marrow core biopsy with H&E staining.
Figure 3. CD20 immunohistochemistry on core biopsy.
Figure 4. CD11c immunohistochemistry on core biopsy.
Figure 5. Representative flow cytometry plots.
Figure 6. Representative flow cytometry plots.

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

Dr. Kaumeyer, Dr. Arber, and Dr. Venkataraman indicated no relevant conflicts of interest.