The Case for Abandoning Induction Chemotherapy

DANIEL A. POLLEY, MD, MS
Associate Professor of Medicine, Division of Hematology, University of Colorado School of Medicine, Aurora, CO

If the definition of insanity is doing the same thing over and over again and expecting a different result (just as the definition of a bad review article may be one that leads off with a questionable cliché), hematologists treating acute myeloid leukemia (AML) with intensive induction chemotherapy should reconsider the logic of their approach. To be fair, there are subsets of patients, such as those with core binding factor chromosomal rearrangements, or NPM1 or CEBPA mutations, for whom intensive chemotherapy is effective and potentially curative. For everyone else, the longstanding argument in favor of induction chemotherapy is that it beats the alternative, which in the absence of any U.S. Food and Drug Administration (FDA)–approved therapies is... nothing. Generations of hematologists who spent careers banging their heads against the chemotherapy wall would certainly have traded their miserable analogs for a sleek new targeted therapy. Colleagues, the time is now upon us: I am excited to announce that the field has officially entered the postchemotherapy era. Allow me to explain. First, we must make the case as to why there is a need to abandon intensive induction chemotherapy. For patients younger than 60 years, the complete remission (CR) rate with induction is around 70 percent, but the treatment-related mortality (TRM) rate may be as high as 13 percent; five-year overall survival (OS), the surrogate endpoint for cure, is only around 30 percent. Not surprisingly, given that the basic recipe for intensive chemotherapy has not substantially changed in more than 40 years, no meaningful improvements in outcomes have occurred for decades that are not attributable to advancements in supportive care or transplant.

However, the problems with induction chemotherapy are more pernicious than simply its lack of efficacy. Physicians live by the credo primum non nocere; as the frightening biological impact of induction chemotherapy on AML is becoming clear, we must question whether it violates this code to “first, do no harm.” Induction chemotherapy does not appear to eliminate preleukemic hematopoietic stem cells, and clonal evolution of this population after exposure to chemotherapy during remission is a likely contributor to relapse. Induction chemotherapy provokes clonal hematopoiesis from nonleukemic progenitor cells, the consequences of which are unknown and possibly deleterious. Gene expression profiling studies performed on AML patients pre- and post-treatment with cytarabine revealed the activation of resistance pathways that occurred as the direct result of chemotherapy. Most ominous is the recent discovery of the increased number and heterogeneity of leukemia stem cells (LSCs) after induction fails and patients relapse. Like a zombie movie where cutting one monster in half leads to a temporary halt in the aggression, with treatment, there can be an initial decrease in the quantity and diversity of leukemia stem cells (LSCs) after induction fails and patients relapse. With the definition of insanity being repeated so often, we must consider the reality that very often, when treating AML with intensive chemotherapy, we are not simply passive users of a therapy that doesn’t work very well, but instead, we are responsible for making this disease worse. Call relapsed AML after induction what it is: iatrogenic AML (Figure).

(Cont. on page 13)
Precision Medicine at Work

The presence of RAS pathway mutations was associated with shorter survival than the absence of RAS pathway mutations (median, 0.9 vs. 2.2 years; p=0.004), owing to a higher risk of relapse. This higher risk of relapse was restricted to those who received a reduced-intensity conditioning regimen. Patients older than 40 years with JAK2 mutations had a shorter median survival than those without JAK2 mutations (0.5 vs. 2.3 years; p=0.001), which was associated with a higher non-relapse mortality, regardless of the intensity of the conditioning regimen. These data suggest that among older MDS patients undergoing HSCT, high-intensity conditioning regimens may benefit patients with RAS pathway mutations but not those with TP53 or JAK2 mutations.

The study also yielded important insights into the biology of MDS in specific subsets of patients. When comparing younger (<40 years) and older patients with MDS, mutations in TET2, DNMT3A, SRSF2, SF3B1, and PPM1D were more common in older patients, and mutations in GATA2, PIGA, and compound heterozygous mutations in the Shwachman-Diamond syndrome–associated SBDS gene were more common in younger patients, suggesting a difference in disease pathophysiolog. Indeed, in young adults, 4 percent of the patients had compound heterozygous mutations in SBDS that were purported to be germline, indicating an underlying inherited predisposition to MDS. Of note, all seven of the patients with biallelic SBDS mutations had somatic TP53 mutations, which may provide insight into mechanisms of clonal evolution in Shwachman-Diamond syndrome. Mutations in the TP53 regulator PPM1D were more common among patients with therapy-related MDS than those with primary MDS (15% vs. 3%; p<0.001).

This exciting work offers a clinical guide to begin to optimize transplant candidate selection and transplant planning for MDS based on the genetic profile of the disease and certain clinical factors. By improving our ability to identify patients who are most likely to relapse or experience significant transplant-related complications, this precision medicine approach benefits the individual patient and additionally, may lead to better pre-transplant therapies or strategies for preventing relapse more broadly. The diagnosis of previously unrecognized Shwachman-Diamond syndrome among younger MDS patients highlights the limitations of diagnosing this disorder based on clinical acumen alone. Additional studies aimed at deciphering the biology underlying the somatic acquisition of TP53 mutations and how this should inform patient management in this disease are warranted.

New Opportunities for International Members to Get Involved

ASH Global Research Award

ASH provides numerous pathways for its growing international membership to learn, develop, and engage with the Society. The recently launched ASH Global Research Award supports future international scientific leaders and encourages global collaboration. Hematologists will receive support between completion of training and the establishment of their independent careers. The award also promises to be accessible to individuals across geographical regions by ensuring applicants only compete with those in their classification.

Applicants must be ASH International Associate Members (postdoctoral fellows who reside outside of Canada and the United States with an MD or equivalent medical degree in an approved hematology program, a related training program, or who are medical school), Early Career ASH International Members (a scientist holding an MD or PhD who has concluded their fellowship and is engaged in basic, translational, or clinical research in hematology), or ASH Active and Associate Members who reside in Mexico.

The letter of intent submission deadline for this award is August 31, 2017, and the full application must be completed by May 1, 2018. Applicants must submit proposals to complete research in the following categories: basic research, translational research, patient-oriented clinical research, and outcomes-based research. For additional eligibility and application details, visit www.hematology.org/awards/career-training/7160.aspx.

Global Capacity-Building Showcase

ASH will showcase capacity-building programs in lower- or middle-income countries at the 59th ASH Annual Meeting in Atlanta. Participants in such programs are invited to prepare a digital poster that shines a spotlight on the details and results of their program. Please note that these are not scientific abstracts and will not be considered alongside regular oral or poster abstracts, but selected posters will be displayed digitally at the meeting. The call for digital posters for the Global Capacity-Building Showcase and further instructions will be posted in the annual meeting section of the ASH website in May; the submission deadline for these posters is July 18.

Submit a Nomination for the 2017 ASH Honorific Awards by July 15

The Honorific Awards are ASH’s highest distinctions, recognizing significant contributions made by hematologists to the field. Each year, the Society presents outstanding hematologists with the Wallace H. Coulter Award for Lifetime Achievement in Hematology, the Henry M. Straus Jr. Medal, the William Dameshek Prize, the E. Donnell Thomas Lecture and Prize, the Ernest Beutler Lecture and Prize, the ASH Mentor Award, and the recently announced ASH Award for Leadership in Promoting Diversity.

The ASH Award for Leadership in Promoting Diversity will recognize hematologists who have demonstrated extraordinary commitment to diversity and inclusion of those who face barriers to success because of societal disadvantages. Individuals may be nominated for significant leadership or mentorship benefitting the career development of trainees from underrepresented groups, contributions that have led to a more diverse and inclusive hematology workforce, and commitment to diversity and inclusiveness within ASH.

The deadline to submit nominations for the 2017-2018 Honorific Awards cycle is July 15, 2017. For eligibility information of each award as well as past awardees, visit www.hematology.org/Awards/Honorific.

Visit www.hematology.org/TheHematologist/Multimedia for a podcast featuring Awards Committee members Drs. Linda Burns and Mohandas Narla discussing the significance of these awards for hematologists worldwide.

NHLBI Division of Blood Diseases and Resources Funding Opportunities

The Division of Blood Diseases and Resources (DBDR) of the National Heart, Lung, and Blood Institute (NHLBI) provides several award opportunities that ASH members may take advantage of to further their research efforts. Pointing to the success of these opportunities are the following grant award rate data. (Data were derived from a DBDR analysis of grants awarded by their division and based on four rounds of NHLBI council approval in accordance with fiscal year 2016 and 2017 NHLBI Funding and Operating Guidelines.) From October 2015 to October 2016, DBDR funded 50 percent of applicants for Research Career Development Awards, 48 percent for Individual Research Awards, 24 percent for Institutional Training Grants, 27 percent for R01 Awards, and 35 percent for R01 – Early Stage Investigators. Additionally, they funded 75 percent of blood science investigators eligible for the NHLBI R03 Bridge Award. Given NHLBI’s impressive success rate, ASH encourages its members to apply to one of the many new DBDR Funding Opportunity Announcements (FOAs).

A recently published FOA, “Sex Hormone Induced Thromboembolism in Pre-menopausal Women (R61/R33)” explores exploratory/developmental–phased awards to evaluate the effects of sex hormones and sex hormone-based therapies on thrombus formation in pre-menopausal women. The application due date is June 20, 2017.

Soon-to-be-published FOAs include: “Consortium Linking Oncology with Thrombosis (CLOT) (U01),” “Centers for the Investigation of Factor VIII (FVIII) Immune Response in Patients with Hemophilia A (U54),” “Catalyzing Innovation in Late Phase Clinical Trial Design and Statistical Analysis Plans (U54 & X01),” and “Early Phase Clinical Trials for Therapeutics and/or Diagnostics (R61/R33).” These will be available in spring/summer 2017.

For additional information, visit www.nhlbi.nih.gov/about/org/dbdr, or visit www.nhlbi.nih.gov/research/funding/opportunities for more on specific FOAs.

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New Podcast for The Hematologist Available: Beat AML Update

A new podcast for The Hematologist is now available. The “Beat AML Trial Update” features a conversation between Contributing Editor for The Hematologist, Dr. Elizabeth Raetz, and AML experts, Drs. John Byrd and Eytan Stein. They discuss the Beat AML Trial’s design, rationale, and its significance in developing a precision medicine approach for the treatment of acute myeloid leukemia. The podcast complements the March/April 2017 Clinical Trials Corner article by Drs. Raetz and Tibor Kovacsovics (available at www.hematology.org/thehematologist/clinical-trials/7134.aspx). ASH has partnered with the Leukemia & Lymphoma Society to help spread the word about this pivotal trial.

Visit www.hematology.org/Multimedia for a full list of all podcasts and videos for The Hematologist. Follow us on SoundCloud and iTunes to stay up to date with new installments.

Attend the 2017 ASH Meeting on Hematologic Malignancies

The ASH Meeting on Hematologic Malignancies will take place September 9-9, 2017, at Chicago’s Fairmont Chicago, Millennium Park. The meeting will feature the top experts in hematology showcasing their evidence-based treatment approaches to hematologic malignancies through “How I Treat” sessions. The core malignancies discussed at the meeting include leukemia, lymphoma, myelodysplastic syndromes, myeloma, and myeloproliferative neoplasms. The intimate, small-group setting of this meeting will provide attendees with the opportunity to discuss challenging patient care questions during topic-based panel discussions, as well as allowing for closer networking opportunities.

For additional information, including a list of confirmed program topics and speakers, visit www.hematology.org/malignancies. Get full access to recordings of all sessions and panel discussions from last year’s meeting via www.ashondemand.org/meeting/109612279. You can also visit www.soundcloud.com/ash_hematology to listen to The Hematologist’s August 2016 podcast, featuring 2016 meeting co-chairs Drs. Martin Tallman and Kenneth Anderson discussing the significance of this meeting for hematologists.

Early-bird registration is now open. To register, go to www.hematology.org/malignancies/registration.aspx.

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The Case
A 37-year-old woman 28 weeks into her first pregnancy was referred to hematology clinic given a history of von Willebrand disease (vWD) diagnosed during her teenage years, after presenting with excessive menstrual bleeding requiring oral iron supplementation. She had taken oral contraceptives until six months prior to this pregnancy due to diagnosis of anemia. While pregnant, she had oral surgery, and had no history of bleeding complications during pregnancy. She was on aspirin and had used oral contraceptives until six months prior to this pregnancy. Her platelet count was 135 × 10⁹/L, and baseline vWF:Ag 99 IU/dL (normal, 43-176 IU/dL), and FVIII activity 84 percent (normal, 50%-150%).

The Question
What is your approach to the diagnosis and management of vWD during pregnancy?

Our Response
vWD is the most common inherited bleeding disorder, affecting up to 1 percent of the general population. vWD is a heterogeneous disorder characterized by two crucial roles in hemostasis. First, it serves as a bridging molecule between platelets and subendothelial collagen exposed during vascular injury. Second, it acts as a chaperone protein for factor VIII, preventing premature degradation and increasing availability at sites of active thrombus formation. Quantitative (type 1 and 3) and qualitative (type 2, with 4 different subtypes) abnormalities in vWF protein may result in bleeding diatheses. The vast majority of cases are type 1, resulting in mild to moderate reduction of functionally normal vWF. Bleeding severity, however, is variable, and only a fraction of individuals with the disorder present with symptoms of bleeding. The gene encoding vWF is located on chromosome 12, spanning 178 kb over 52 coding exons. The qualitative mutations observed in type 2 vWD can result in 1) a defect in the intracellular assembly and transport of normal vWF multimers (type 2A); 2) an abnormal cleavage site in vWF multimers using gel electrophoresis, and ristocetin-induced platelet aggregation (RIPA). In type 1 vWD, multimers are normal or mildly decreased with normal distribution.

Consequences of vWD During Pregnancy
During pregnancy, hormonal influences lead to an increase in vWF and clotting factors VII, VIII, and X while anticoagulant factors (such as protein S) decrease, shifting hemostasis to a procoagulant state to compensate for anticipated hemorrhage during parturition. Although vWF and FVIII levels rise and peak during the third trimester, women with vWD remain at risk of early pregnancy bleeding, as well as postpartum hemorrhage (PPH), immediate and delayed. This can be explained by the rapid fall of vWF after delivery. Other screening considerations include the need to address anemia options, mode of delivery, and management of obstetric bleeding. This is best conducted with a multidisciplinary team for safer care of the mother and baby.

Laboratory Diagnosis of vWD in Pregnancy
Given the hormonal changes that occur during pregnancy, the diagnosis can be obscured and is ideally made prior to conception. For patients without a previous diagnosis, a history of excessive menstrual or mucocutaneous bleeding, prior PPH, bleeding after prior surgical/dental procedures, or family history may prompt diagnostic testing. In addition to a complete blood count to evaluate platelet count and standard coagulation studies (PT and PTT), recommended screening tests include plasma vWF:Ag, vWF activity (with ristocetin cofactor activity being most commonly performed, and the collagen binding assay less readily available), and FVIII activity. vWF:Ag informs the total amount of vWF in the plasma, but the assay does not distinguish between active or inactive protein. vWF:RCo is a functional assay, testing the ability of patient vWF to bind to GPIb in the presence of ristocetin (an antibiotic that binds both vWF and GPIb), causing agglutination. In patients with type 2A, 2B, and 2M vWD, the qualitative protein defect causes greater decline in activity over time than antigen concentration, resulting in a vWF:RCo:vWF:Ag ratio less than 0.5 to 0.7 (Table 1).

Table 1. Laboratory Diagnosis of von Willebrand Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>vWF:RCo (IU/dL)</th>
<th>vWF:Ag (IU/dL)</th>
<th>FVIII Activity</th>
<th>vWF:RCo:vWF:Ag Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Normal quantitive vWF deficiency</td>
<td>&lt;30**</td>
<td>&lt;30**</td>
<td>Low or normal</td>
<td>&gt;0.5-0.7</td>
</tr>
<tr>
<td>Type 2A</td>
<td>Decreased vWF-dependent platelet aggregation with selective deficiency of high-molecular weight multimers</td>
<td>&lt;30**</td>
<td>&lt;30-200**</td>
<td>Low or normal</td>
<td>&lt;0.5-0.7</td>
</tr>
<tr>
<td>Type 2B</td>
<td>Increased affinity for platelet GPIb; decreased platelets</td>
<td>&lt;30**</td>
<td>&lt;30-200**</td>
<td>Low or normal</td>
<td>&lt;0.5-0.7</td>
</tr>
<tr>
<td>Type 2M</td>
<td>Decreased vWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers</td>
<td>&lt;30**</td>
<td>&lt;30-200**</td>
<td>Low or normal</td>
<td>&lt;0.5-0.7</td>
</tr>
<tr>
<td>Type 2N</td>
<td>Markedly decreased binding affinity for GPIb</td>
<td>30-200</td>
<td>30-200</td>
<td>Very low</td>
<td>&lt;0.5-0.7</td>
</tr>
<tr>
<td>Type 3</td>
<td>Virtual complete deficiency of vWF</td>
<td>&lt;3</td>
<td>3</td>
<td>Extremely low (&lt;10 IU/dL)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Abbreviations: vWF, von Willebrand factor; vWF:RCo, vWF ristocetin cofactor activity; vWF:Ag, vWF antigen. **<30 IU/dL is designated as the level for a definitive diagnosis of vWD, some patients with type 1 or type 2 vWD have levels of vWF:RCo and/or vWF:Ag of 30-50 IU/dL.

Treatment of vWD During Pregnancy
Antepartum hemorrhage is uncommon, but PPH has been observed in up to 37.5 percent of women with type 2 vWD who do not receive adequate prophylaxis. It is therefore recommended that women have their vWF/FVIII levels monitored during the third trimester to facilitate planning for delivery. The need for therapeutic intervention depends on level of vWF and FVIII, thrombocytopenia, and type of vWD. With the rise of FVIII and vWF during pregnancy, women with mild type 1 vWD rarely need treatment, while type 3 disease (where vWF and FVIII do not increase in pregnancy) will require factor replacement. When FVIII or vWF:RCo levels are less than 50 IU/dL, prophylaxis is recommended prior to vaginal or surgical delivery.® DDAVP, a synthetic analogue of vasopressin that increases vWF and FVIII, is an option for certain patients; however, there is the potential risk of tamponade at the time of delivery. In a 2011 Argentinean cohort of 54 pregnant women with vWF levels lower than 50 IU/dL, none treated with DDAVP preprocedurally or prior to epidural developed complications, suggesting it may be a safe option in pregnancy.® In type 2 vWD, less benefit is seen with DDAVP because of the qualitative defect. Furthermore, in type 2B, use of DDAVP can exacerbate thrombocytopenia, leading to an additional risk of bleeding; this agent is contraindicated if a persistent decrease in platelet count has been documented. Replacement products are needed for type 2B and 3 vWD. Plasma-derived vWF containing concentrates licensed in the United States for the treatment of vWD include Humate P (CSL Behring), Wilate (Octapharma), and Alphanate (Grifols). More recently, recombinant vWF (NovoSeven, Shire) has become commercially available. In phase III studies, use of recombinant vWF was highly effective in restoring hemostasis, with hemostatic levels achieved within six hours and sustained for up to 72 hours following infusion.® Platelet transfusions may be needed for type 2B, with transfusion thresholds of 50 × 10⁹/L, frequently used. Other adjunctive options include antifibrinolytic agents.
such as tranylcypromine and ampicarolac acid in the
postpartum setting. Although they have not been studied
specifically in the management of PPH, retrospective
studies have shown reduction in rates of PPH when used
for up to three weeks following delivery.13 Finally, while
there is no consensus on factor levels needed for safe
regional anesthesia during labor and delivery, it can be
considered if FVIII and vWF:RCo are above 50 IU/dL.14

Patient Follow-Up

This patient’s baseline vWF activity at 28 weeks was lower
than would be expected for the stage of pregnancy. Type
2 WD was considered in this case given the discrepancy
between vWF:RCo and vWF:Ag, with a ratio of 0.47 and
relatively low vWF:RCo levels. Later in the third trimester,
she developed worsening thrombocytopenia with a
platelet count of 70 × 10^9/L. vWF activity improved during
the latter part of the pregnancy (vWF Activity 55 IU/dL, vWF:Ag 145 IU/dL, vWF:RCo 130 IU/dL). This was expected to
be related to her delivery. Multimer analysis showed loss of
high-molecular weight multimers. RIPA testing was performed (Table 2), showing typical aggregation findings in
patients with type 2B vWD, including the hyper-responsiveness to a low ristocetin concentration (see Table 2 results in
type for patient PPR aggregation percentage with ristocetin
concentrations of 0.5-0.7 mg/mL).

Sequence analysis of exon 28 showed a R57Q mutation in
the GPIb binding site of the vWF protein, confirming
the diagnosis of type 2B vWD. Given the type 2B
variant and persistent thrombocytopenia, DDAVP is
contraindicated. The delivery plan includes administration of
vWF concentrates at time of delivery, possible platelet
transfusion, and oral tranexamic acid after discharge.

In 1955, Dr. Emil Freireich had the privilege of serving in the U.S. Public Health Service as a commissioned officer when he was assigned to take over the chemotherapy
arm of the American Army in Korea. In this capacity, he
finished his work on a new drug, vincristine, which had
been developed as an antitumor agent by Dr. Irving
Johnson of Eli Lilly. Vincristine is a naturally occurring
desquamative alkaloid isolated from the roots of the
tropical lily, Catharanthus roseus, and produces its
effect through microtubule disruption. Its mechanism of
action is thought to be related to its effect on the mitotic
spindle, leading to cell death by apoptosis. Vincristine
was approved by the U.S. Food and Drug Administration
for the treatment of childhood acute lymphoblastic leukemia
in 1969.

Dr. James Holland from Columbia University preceded Dr. Freireich by approximately one year. He had been
to attract referrals of children with ALL to study treatment with the three then-known active agents —
methotrexate, 6-mercaptopurine, and prednisone — each of which could induce a small percentage of complete remissions that lasted for a few weeks. Back then, about 10 percent of children with ALL
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them was Dr. Kenneth B. McCredie who heard Dr. Freireich give a talk about curing ALL in Australia. He was so inspired that he packed his family and showed up one night at the door of Dr. Freireich's home, asking for a job. He had the dream and vision to cure leukemia. Dr. McCredie was hired as the first leader of the adult leukemia program from 1969 until 1980. Dr. Keating joined MD Anderson as a fellow in 1974, and Dr. Elihu Estey joined in 1979. They became the third and fourth long-term faculty in the Leukemia Section. In 1979, Dr. Charles LeMaistre became the second MD Anderson Cancer Center president with the vision of creating tumor-specific programs. This resulted in the creation of the Division of Cancer Medicine within the Department of Hematologic Malignancies. Drs. Freireich led the Department, and Dr. McCredie ran the Leukemia Section.

Dr. Hagop Kantarjian visited MD Anderson as a medical student for four months in 1978, joined MD Anderson as a fellow in 1981 and was recruited to be part of the leukemia faculty in 1983. In rapid succession, the Leukemia Section recruited several visionary leukemia specialists who were interested in the dream of curing leukemia. Most of them remained as leukemia experts in the subsequent Department for most of their careers. These included Drs. Ronald Walters, Susan O'Brien, Michael Andreeff, Miloslav Beran, Elihu Estey, William Plunkett, Zeev Estrov, Borje Anderson, Moshe Talpaz, Razelle Kurzrock, Alessandra Ferrajoli, Varsha Gandhi, Jorge Cortes, Guillermo Garcia-Manero, William Wierda, Srdan Verstovsek, Gautam Borthakur, Elias Jabbour, Marina Konopleva, Francis Giles, Farhad Ravandi, and numerous others. The Leukemia Section later expanded into the Leukemia Department in 1994, under the Division of Cancer Medicine. The Leukemia Department started with seven faculty and 10 leukemia research staff. In 2016, the Department was home to 40 leukemia faculty, 80 mid-levels, 10 PharmDs, and 300 research staff. In 2016, more than 2,000 new patients with leukemia (including myelodysplastic syndromes [MDS] and myeloproliferative neoplasms [MPN]) were referred to MD Anderson, and the leukemia research staff. In 2016, more than 2,000 new patients with leukemia (including myelodysplastic syndromes [MDS] and myeloproliferative neoplasms [MPN]) were referred to MD Anderson, and the leukemia faculty oversaw an inpatient service of 120 beds. The Leukemia Department would continue its mission of research-focused leukemia discoveries for the next three to four decades.

The leukemia research program created multiple research initiatives that resulted in important discoveries, many of which became standards of care and improved survival in leukemia subsets. Prominent among these discoveries are the following:

1. **Hairy cell leukemia:** The discovery of the activity of interferon. Later confirmatory studies of the efficacy of cladribine, and the discovery of the efficacy of rituximab. This led to the development of the cladribine - rituximab regimen, associated with a 10-year disease-free survival of 80 percent.

2. **Acute myeloid leukemia:** The development of cytarabine, cytarabine - anthracycline combinations, and high-dose cytarabine regimens in 1983. The expansion of the discovery of the activity of ATRA and arsenic trioxide in acute promyelocytic leukemia, and the development of the ATRA - arsenic trioxide regimen. The development of nucleoside combinations with cytarabine and anticyclines (e.g., FLAIDA). The development of epigenetic therapy with decitabine.

3. **Chronic myeloid leukemia (CML):** The creation of the definitions of accelerated phase and of cytogenetic response criteria. The discovery of the activity of interferon. Later numerous developmental programs with tyrosine kinase inhibitors (TKIs) including imatinib, high-dose imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. These endeavors in long-term historical studies demonstrated the survival benefit with TKIs. The development of omacetaxine for the treatment of CML.

4. **ALL:** The development of the hyper-CVAD regimen in 1992. Subsequent follow-up regimens including hyper-CVAD plus TKIs in Ph+ ALL, hyper-CVAD - rituximab in Burkitt Leukemia and pre-B-ALL. The development of cladribine and liposomal vincristine. Replacement of CNS radiation prophylaxis with intrathecal chemotherapy prophylaxis. The discovery of the activity of imatinib in 2001. The US development of imatinib monotherapy. The discovery of the efficacy of imatinib. This led to the development of TKIs and chemotherapy in ALL. These studies have established new standards of care and have improved long-term survival in adult ALL. Several of the discoveries were then incorporated also into the pediatric regimens (CNS intrathecal prophylaxis, cladribine, combination of TKIs and chemotherapy in Ph+ ALL, monoclonal antibodies).

5. **MDS and MPNs:** The development of decitabine in MDS. The development of decitabine in myelofibrosis.

6. **Chronic lymphocytic leukemia:** The discovery of the activity of fludarabine (F). Later development of F - cyclophosphamide (FC), and FC - rituximab (FCR, Keating regimen). Original studies with the new B-cell receptor inhibitors including ibrutinib, idelalisib, and with the Bcl-2 inhibitor venetoclax.

Authors' Note: This historical account of the MD Anderson Cancer Center Leukemia genealogy relies on historical documents and the recollections of the three authors. Thus, any inaccuracies and incomplete information are the sole responsibility of the authors.
ASH Advocates Visit Congress and NIH in Support of Hematology Research

Following its March 27, 2017, meeting in Washington, DC, the ASH Committee on Government Affairs visited nearly 40 congressional offices on March 28 to advocate for funding for the National Institutes of Health (NIH) and a sickle cell disease (SCD) surveillance program within the Centers for Disease Control and Prevention (CDC). ASH advocates encouraged House and Senate offices to recognize the value of biomedical research by finalizing fiscal year (FY) 2017 NIH funding and opposing the administration’s proposed cuts in funding to NIH for FY 2018. Members of the Committee on Government Affairs also pressed legislators to provide dedicated funding for SCD surveillance, outreach, and education programs at the CDC in FY 2018.

The ASH Committee on Scientific Affairs also met with leadership at the National Cancer Institute (NCI) as well as the National Heart Lung and Blood Institute (NHLBI) on March 24 to advocate for continuous support of ASH’s research priorities and to highlight precision medicine needs for the field of hematology. ASH was pleased to learn of significant alignment of mutual priorities and looks forward to continuing to work with the various institutes at NIH to support hematology research.

Congressional meetings and visits with the NIH are important components of ASH’s advocacy efforts, providing an opportunity for members of Congress and their staff to gain insight on issues of concern to hematologists, including hematology research and SCD. However, the Society needs the help of all of its members in bringing these important issues to the attention of Congress and other governmental agencies. ASH strongly encourages members to let the ASH Government Relations and Practice Department know when you are in Washington, DC, and are available to meet with your congressional delegation. ASH staff can assist by arranging appointments so that your voice is heard when you are in Washington, DC, and are available to meet with your congressional delegation. ASH staff can assist by arranging appointments so that your voice is heard when you are in Washington, DC, and are available to meet with your congressional delegation.

ASH Continues Advocacy to Ensure Patient Access to Hematologic Drugs

While oral and patient self-administered forms of chemotherapy have become more prevalent and represent the standard of care for many forms of cancers, they are covered differently from intravenous drugs, leaving many patients responsible for unsustainable, high monthly co-payments.

As part of the Patients Equal Access Coalition (PEAC), ASH has advocated for legislation at the Federal level and applauded the recent introduction of the Cancer Drug Parity Act (H.R. 1409) by Representatives Leonard Lance (R-NJ) and Brian Higgins (D-NY) in the U.S. House of Representatives. This legislation aims to ensure that cancer patients have equality of access (and equality of insurance coverage) to all approved anticancer regimens including, but not limited to, oral and intravenous drugs.

Although only federal legislation will ensure coverage for all cancer patients, 43 states plus the District of Columbia have enacted laws to limit patient out-of-pocket costs for oral anticancer medications. ASH has supported legislative efforts in many of these states and continues to work with stakeholders and advocacy groups on legislative efforts in numerous additional states. In the first half of 2017, there has been significant action on bills in several states, as noted below:

- **Arkansas**: The Arkansas governor recently signed into law legislation granting oral chemotherapy parity to patients, making the state the 43rd to enact such legislation.

- **Michigan**: As with efforts in other states, ASH continues to work as part of a larger coalition of patient and provider organizations to seek passage of oral parity legislation in Michigan. The 2017 legislative session will mark the fourth attempt to pass oral chemotherapy legislation in Michigan. The bill’s previous sponsor has agreed to reintroduce the legislation and is committed to seeing it enacted.

- **Tennessee**: ASH has been working as part of the Tennessee Fair Access to Cancer Treatment Coalition. Currently the legislation has been reintroduced by the bill’s previous sponsors and is being debated in committee in both the state house and senate.

- **North Carolina**: Legislation was reintroduced on March 1 in the North Carolina assembly and is currently waiting for a hearing by committee. The outlook for North Carolina looks positive since the retirement of the previous committee chairman who had been blocking the legislation from advancing during last year’s session.

ASH remains committed to working with leaders in Congress and in State legislatures to remove barriers to access to care and the heavy cost burdens on patients with blood disorders. If you live in one of these states and are interested in working with ASH to help ensure that your patients have affordable access to oral chemotherapy drugs, please contact ASH Government Relations Coordinator Foster Curry at fcurry@hematology.org.

Last Chance to Register for the 2017 ASH Advocacy Leadership Institute

ASH’s Advocacy Leadership Institute (ALI), which was created in 2011, is an intensive two-day program for ASH members to learn about advocacy, health policy, and the legislative process, and to become engaged with the Society’s activities. The first day of the Institute focuses on learning about the legislative process and health policy. On the second day, participants will be divided into groups for a full day of meetings with their respective Congressional delegation on Capitol Hill, to turn their knowledge into action in support of hematology. Participants learn about the major issues facing the field of hematology today, including budget cuts to NIH. ASH members call on their representatives to reverse the damaging impact that cuts to NIH have on their research and their patients. For more information on ALI and to apply to attend, please visit www.hematology.org/ALI.

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**HEADLINES FROM Washington**

ASH Advocates Visit Congress and NIH in Support of Hematology Research

ASH Continues Advocacy to Ensure Patient Access to Hematologic Drugs

Last Chance to Register for the 2017 ASH Advocacy Leadership Institute
Utility of Flow Cytometry in Amyloid Light-Chain Amyloidosis


Primary amyloidosis is a plasma cell dyscrasia with tissue deposition of abnormally folded (β-pleated) immunoglobulin light chains, or rarely, heavy chains. The resultant organ dysfunction leads to significant morbidity and mortality. Cardiac disease is the leading cause of death in amyloidosis. Indicators of poor prognosis include hepatomegaly, elevated serum creatinine, significant weight loss, urinary light-chain excretion, and elevated β-2 microglobulin. A commonly used hematologic prognostic factor is the difference between the involved and uninvolved free light-chain level (dFLC), with a cutoff of 180 mg/dL. The plasma cell burden in marrow biopsies from patients with amyloid light-chain (AL) amyloidosis is highly variable ranging from no overt increase in plasma cells, to frank myeloma.

Drs. Eli Muchtar and colleagues evaluated the utility of multiparametric flow cytometry in patients with AL amyloidosis at diagnosis (N=173) and at the end of the first line of treatment (N=82). They evaluated two flow cytometry generated parameters: the percentage of monotypic plasma cells and the ratio of polytypic plasma cells to total plasma cells.

At diagnosis, those with higher numbers of monotypic plasma cells had inferior progression-free survival (PFS) as well as overall survival (OS), using a cutoff of ≥ 2.5 percent for monotypic plasma cells. Interestingly, morphologic enumeration of plasma cells did not demonstrate a similar difference in PFS or OS, using a cutoff of 10 percent or greater (two-year PFS of 50% vs. 48% in those with plasma cells <10%; p=0.9; 2-year OS of 65% vs. 60% in those with <10% plasma cells; p=0.8). On the other hand, patients with reduced proportion of polytypic plasma cells by flow cytometry (i.e., polytypic plasma cells/total plasma cell ratio of ≤ 5%) had shorter PFS, but no significant difference in OS. These findings held true in both univariate and multivariate analyses (Figure 1).

When the authors stratified those who underwent autologous stem cell transplantation (ASCT; N=108) from those who did not (N=65), higher monotypic plasma cells (≥0.5%) and a lower proportion of polytypic plasma cells (≤5%) were associated with a worse PFS and OS only in the non-ASCT group.

Of the 82 patients analyzed at the end of the first line of treatment, 69 (84%) had undergone ASCT, 10 (12%) received bortezomib-based therapy, and three (4%) received melphalan-based therapy. Patients with ≥0.1 percent monotypic plasma cells had a shorter PFS (2-year PFS 31% vs. 87%, p<0.0001), and OS (2-year OS 87% vs. 98%; p=0.02) compared to those with <0.1 percent monoclonal plasma cells. They also conducted a subgroup analysis of patients who had a very good partial response or better, by standard hematologic criteria (dFLC <40 mg/L). In this subgroup, flow cytometric quantification of monotypic plasma cells had added predicted value; those with ≥0.1 percent monotypic plasma cells had a higher rate of progression versus those with <0.1 percent monotypic plasma cells (54% vs. 17%, p=0.1; Figure 2).

This study demonstrates the value of using multiparametric flow cytometry in patients with AL amyloidosis, both at diagnosis and at the end of treatment. Increased percentage of monotypic plasma cells and decreased proportion of polytypic plasma cells are indicative of a worse prognosis and of shortened overall survival in patients who do not undergo ASCT. After therapy, flow cytometric enumeration of monotypic plasma cells may help further risk stratify those with an apparent, very good hematologic response.

Taking a Bite Out of Relapsed or Refractory Acute Lymphocytic Leukemia


Chemotherapy has revolutionized the treatment of acute lymphocytic leukemia (ALL), but despite progress of 50 years of progression, the aspiration of achieving cure for all patients remains stubbornly out of reach. The outlook is particularly poor for adults, for whom, despite a complete remission rate approaching 80 percent, only around 40 percent achieve long-term survival. As such, there is a need to develop new approaches for the management of relapsing disease, where salvage chemotherapy achieves remission in only 18 to 44 percent of cases. Moreover, refractory or relapsed disease has a median overall survival of between two to six months and a five-year survival that remains below 10 percent.

It is against this sobering backdrop that the immunotherapy agent blinatumomab has been compared directly with chemotherapy. Blinatumomab is a “bispecific T-cell engager” (BiTE) antibody construct that binds simultaneously to CD19 on B cells and CD3 on T cells, thereby bringing effector T cells into close contact with ALL tumor cells, which are then killed.

Relatively small clinical studies had identified the potential of blinatumomab in ALL but this phase III randomized trial sought to define the magnitude of this effect. The TOWER trial was an impressive multinational study involving 101 centers from 21 countries. Investigators randomly assigned 405 patients to receive either blinatumomab or investigator’s choice of chemotherapy in a 2:1 randomization. The most popular chemotherapy was FLAG, chosen in 46 percent of cases, with additional regimens based on clofarabine, high-dose cytarabine, or high-dose methotrexate. A key feature of the study was that patients were heavily pretreated. Entry criteria included patients refractory to primary induction or salvage, first relapse within 12 months, second or greater relapse, or relapse after allogeneic stem-cell transplantation. Indeed, 35 percent of patients had undergone previous transplantation, and 25 percent of patients received blinatumomab as third or later salvage therapy.

Blinatumomab was administered as a continuous infusion every six weeks with “four weeks on” and “two weeks off.” The protocol included two cycles of induction therapy, after which patients could proceed to consolidation treatment if they achieved morphologic remission. In reality, the tyrosines in the blinatumomab arm and one in the chemotherapy arm. Only 3 percent of chemotherapy patients proceeded to consolidation, whereas this was achieved by 52 percent of blinatumomab-treated patients. Both treatments were used as a bridge to allogeneic stem-cell transplantation; ultimately 24 percent of patients in both arms proceeded to this high-intensity treatment modality.

The primary outcome was overall survival, and the headline result was that this was increased from four months in the chemotherapy group to 7.7 months in the blinatumomab arm (HR: 0.71; p<0.001). Complete remission with full hematologic recovery within 12 weeks was seen in 34 percent of blinatumomab patients compared with only 16 percent of chemotherapy patients (p<0.001). Moreover, event-free survival (defined as time from randomization until relapse after achieving a complete remission, or death) at six months was 31 percent for blinatumomab patients compared with 12 percent for the chemotherapy arm. Quality of life was also improved in the blinatumomab cohort.

Blinatumomab has previously been associated with characteristic adverse effects that include cytokine release syndrome (CRS) and neurotoxicity. These are becoming less of a concern with experience in the current study. Dexamethasone was given prior to infusion, and CRS did not usually require treatment discontinuation. Intrahepatic prophylaxis was also given according to local guidelines. The rate of neurologic grade 3 or adverse events was 9 percent in both arms of the study.

The independent data and safety monitoring committee recommended that the trial be stopped early on the basis of the increase in survival seen with blinatumomab. An increase in median survival from four to 7.7 months may be viewed as either a relatively modest 3.7-month increase in survival or as a “near doubling” of overall survival. Health economists may perhaps focus on the former statement, and clinical enthusiasts on the latter. However, either interpretation represents a substantial improvement for patients. Certainly we should focus on how much still remains to be achieved within this area. Combination therapy, new immunotherapy agents in different antigen targets, and the expansion of CD19-directed chimeric antigen receptor (CAR) T-cell treatment out of academic centers and into routine clinical practice may yet prove disruptive. Nevertheless, this trial is the first study to show that an immunotherapeutic agent improves survival over chemotherapy in relapsed or refractory ALL patients, and as such, represents a genuine landmark.

Stopping Imatinib in CML: Safe in the Long Term for Deep Molecular Responders As the Immune System Steps Up


Targeted therapies have delivered great efficacy benefits for patients with some hematologic cancers. However, with treatment paradigms typically based on ongoing therapy until loss of response, these benefits can be accompanied by clinical and financial toxicities. Imatinib and later-generation tyrosine kinase inhibitors (TKIs) have revolutionized outcomes for patients with chronic myeloid leukemia (CML), and their use has shaped our thinking about how to deploy truly targeted therapies for greatest benefit. Increasingly, attention has turned to whether imatinib can be ceased indefinitely in patients who have achieved a durable deep remission where BCR-ABL1 transcripts are undetectable. The pioneering Stop Imatinib (STIM1) trial by a group of French investigators revealed that approximately 40 percent of deep responders with undetectable BCR-ABL1 transcripts could maintain remission for more than one year after cessation of imatinib. 1 Although these data were independently confirmed by other groups, doubts about the long-term safety of this approach have delayed its introduction into routine clinical practice.

Now, Dr. Gabriel Etienne and colleagues have reported the long-term follow-up of the 100 patients who discontinued imatinib in the STIM1 trial. After a median follow-up of more than six years after imatinib discontinuation, molecular recurrence-free survival was 38 percent at five years. Molecular recurrence was defined as at least two positive reverse transcriptase-polymerase chain reaction results showing a significant increase (>10-fold) on consecutive assessments, or loss of a major molecular response (MMR; BCR-ABL1 ≤0.1%). Molecular recurrence was observed in 61 patients and occurred within one to seven months of discontinuation in 58 of these patients (95%). No patient had molecular recurrences beyond two years, and 55 of 57 patients who resumed imatinib re-achieved an undetectable BCR-ABL1 state. Of the 39 patients with randomization to imatinib re-escalation, 80% of the patients were progression-free at four years on study, none were related to CML. Intriguingly, three of four patients who refused retreatment with imatinib have maintained very low levels of BCR-ABL1 transcript (i.e., maintained MMR) without interruption. Long-term follow-up of patients without molecular recurrence revealed that intermittently positive tests for BCR-ABL1 transcripts at very low levels occurred in some patients.

Dr. Amy Hughes and colleagues have begun to address the question of whether restoration of immune function may help explain maintenance of treatment-free molecular responses. They conducted a cross-sectional survey of imatinib and adaptive immune cell numbers and function in small cohorts of patients at diagnosis, on TKIs before achieving MMR, on TKIs at MMR or deeper response (BCR-ABL1 ≤0.0032%), and in treatment-free sustained transcript-negative remission. At diagnosis, immune-inhibitory cells (such as myeloid-derived suppressor cells, and CD163+ and CD33+ macrophages) and immunostimulatory T cells (such as CD8+ T cells) have been found to secrete factors that inhibit blood from healthy donors whereas immune natural killer (NK) cells and cytotoxic T-lymphocyte responses to leukemia-associated antigens were reduced. Therapy with imatinib was associated with normalization of immune function, whereas this was only seen in patients with deep molecular responses. Restoration of effector NK cell and T-cell immune responses was also only seen in patients with deep molecular responses. Longitudinal sampling was reported for 53 patients and confirmed the observations in the cross-sectional survey. For patients with treatment-free molecular response, the same pattern of immune restoration was observed as seen in deep molecular responders receiving ongoing TKIs. The authors hypothesize that in the setting of chronic myeloid cell load at diagnosis, imatinib reduces the leukemic cell burden and suppressor cell activity, and PD-1 expression, there is consequent reactivation of the immune effector response. Normalization of immune effector responses seem to be most consistently observed when leukemic burden has fallen more than 4 logs or is undetectable.

These long-term safety data from Dr. Etienne and colleagues confirm that molecular progression is rare if it is not observed within the first two years off imatinib. Further, molecular recurrence can be effectively treated by resumption of TKI therapy, without significant risk of later failure. Together with less mature, but highly consistent data from other trials, these findings mean that cessation of imatinib should be considered in patients with long-standing deep molecular responses. Regular monitoring of BCR-ABL1 transcripts as outlined in the article is necessary, especially in the first year. For patients with chronic low-grade toxicity from imatinib, the ability to safely attempt cessation without compromise of long-term outcomes will be a substantial relief. Many pragmatic questions remain unanswered however, and are the subject of ongoing investigations. How low does the transcript level need to be before a trial of cessation should occur, and for how long should that depth of response be maintained? Do the results apply similarly to patients receiving other TKIs? What distinguishes those patients who have molecular recurrence from those who do not? What role does the immune system play in maintaining remissions? The data from Dr. Hughes and colleagues at least establish that patients who achieve a deep molecular response to imatinib (and other TKIs) have a normalization of key aspects of their innate and adaptive immune systems that can be maintained without ongoing TKI therapy. But whether re-establishment of immunity is central to the ability to stop imatinib successfully is unknown. Hence, the spotlight will stay on the treatment of CML. But how best to use the wealth of information gained for diagnosis, treatment of blast crisis, and how to augment responses to enable successful discontinuation in a larger proportion of patients with deep molecular recurrences.

Identification of Recurrent Mutations in **NFKBIE** in Chemotherapy-Resistant Primary Mediastinal B-Cell Lymphoma


**Primary mediastinal B-cell lymphoma (PMBL)** is a rare B-cell lymphoma (BCL) that presents in the large mediastinal mass, often in young women in their 20s and 30s. It has a distinct gene expression profile from diffuse large B-cell lymphoma (DLBCL) involving the mediastinum, and it is more genetically similar to nodular sclerosis Hodgkin lymphoma (HL). Similarities include variable CD30 and PD1/PDL2 expression, the latter through the same amplification of the common receptor CR1 that has been described in HL. Since its recognition as a distinct entity with distinct histopathologic findings, prognosis following anthracycline-containing chemotherapy in PMBL is appreciably better than in other lymphomas, with five-year progression-free and overall survival rates of approximately 80 percent and 90 percent, respectively. Phase II data of dose-adjusted R-EPOCH (etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisolone, and rituximab) from the National Cancer Institute yielded even better results, with five-year event-free and overall survival rates of 93 percent and 97 percent, respectively. The role of radiotherapy for patients with bulgy disease and a negative positron emission tomography scan at the end of treatment is uncertain. Despite these very good outcomes in a vast majority of patients, there is also a subset of patients for whom refractory or relapsed disease is quite poor. Response rate to salvage chemotherapy is only 20 to 30 percent, and five-year overall survival for those patients drop to 15 percent (11% CR rate) and 1 percent (11% CR rate), respectively. These patients represent an unmet medical need.

**Dr. Larry Mansouri and colleagues previously identified a recurrent 4-pan base pair truncating deletion in the NFKBIE gene that codes for IkBa in clinically aggressive chronic lymphocytic leukemia (CLL). IkBa is a negative regulator of the NFkB pathway, and mutations in NFKBIE are associated with decreased IkBa levels, decreased p65 phosphorylation, and increased phosphorylation and nuclear translocation of p65.** They went on to screen nearly 1,500 lymphoid malignancies for mutations in **NFKBIE** and found them to be highly enriched in HL (in four of 11) and PMBL (in 46 of 203). In contrast, mutation frequency was less than 5 percent in other B-cell lymphomas, such as T-cell lymphoma, T-cell acute lymphoblastic leukemia, DLBCL, mantle cell lymphoma, primary central nervous system lymphoma, and small lymphocytic lymphoma. Among the 203 patients with PMBL, mutations were associated with chromoresistance (25% vs. 6%; p=0.022) and poor prognosis (5-year overall survival, 59% vs. 78%; p=0.034) compared with wild-type tumors. Whole-exome sequencing of 14 PMBL tumors (seven of which harbored the NFKBIE deletion) demonstrated overlapping mutations in other NFKB factors like TNFAIP3 in up to 50 percent of cases; mutations in BCL6, however, which occur in up to 36 percent of PMBL cases, were mutually exclusive with alterations in NFKBIE.

Finally, gene expression profiling was performed with NanoString PanCancer Pathways to evaluate both canonical cancer pathways, as well as 30 non-cancer pathways known to be important in cancer. NFKBIE expression was associated with the NFkB pathway.

These findings highlight the role of deregulated NFKB signaling in a subset of chemoresistant PMBL and offer potential new therapeutic targets for these patients with known poor outcomes. Although this study offers important insight into the pathobiology of a disease with a poor prognosis, there are several limitations to this series. First, patients were treated with variable chemotherapy regimens, with or without rituximab, and it is therefore not known if these results would apply to the most current regimens used clinically, such as R-EPOCH. However, only one quarter of patients received dose-intensive regimens, and that did not seem to improve outcomes in the NFKBIE-deleted patients. Similarly, gene expression in NFKBIE deletions were not predictive of a poor response to radiotherapy; therefore, these mutations may not identify the most vulnerable PMBL patients refractory to both chemotherapy and radiation therapy. They may, however, help identify patients for whom adjuvant radiation therapy may be beneficial. Finally, the overlap of NFKBIE mutations and other mutations in the NFKB pathway raises questions as to whether such molecular abnormalities are markers of chemoresistance, and therefore a good therapeutic target. Nevertheless, the abundance of mutations in genes involved in the NFKB pathway suggests that drugs like the proteasome inhibitors or drugs that promote apoptosis, such as venetoclax, alone or in combination with chemotherapy or immunotherapy, may result in improved outcomes and survival. Certainly, further identification and development of novel NFKB inhibitors is a strategic approach worth pursuing in these patients.

**SAMHD1 is a Targetable Enzyme That Regulates Cytarabine Efficacy**


Dr. Abdel-Wahab indicted no relevant conflicts of interest.

**Dr. Abdel-Wahab indicted no relevant conflicts of interest.**

The role of SAMHD1 in cytarabine (ara-C) metabolism. Upon entering cells, ara-C is converted into its active metabolite ara-CTP. Ara-C, in turn, results in lethal misincorporation into genomic DNA. The enzyme SAMHD1 limits ara-C cytotoxicity by hydrolyzing ara-CTP, interestingly, an accessory protein, transmembrane viral protein X (Vpx), encoded by several viruses recruits SAMHD1 to a cullin4A-RING E3 ubiquitin ligase, targeting SAMHD1 for proteasomal degradation. Depletion of SAMHD1 in this method promotes sensitivity of cells to ara-C. The expression level of other proteins responsible for ara-C transport metabolism as shown in this figure do not correlate with response to ara-C mediated cell death. Abbreviations: cytidine deaminase (CDA), deoxyadenylate deaminase (DCTD), deoxycytidine kinase (DCK), 5’ nucleotidase II (NT5C2).

**The Hematologist: ASH NEWS AND REPORTS**

OMAR ABDEL-WAHAB, MD

Dr. Abdel-Wahab indicted no relevant conflicts of interest.

CARRON JACOBSON, MD

Dr. Jacobson indicated no relevant conflicts of interest.
Another Therapeutic Agent in the Pipeline for Preventing Acute Vaso-Occlusive Events in Sickle Cell Disease


Anticoagulation Failure in Venous Thromboembolism: Should We Test for JAK2 V617F or CALR Mutations?


Anticoagulation for general venous thromboembolism (VTE) is quite effective in preventing recurrent VTE. However, recurrent VTE on warfarin or a direct oral anticoagulant occurs in approximately 2 percent of general VTE patients.1

Prior to diagnosing “anticoagulation failure,” one must determine whether the anticoagulated VTE patient who presents with new extremity or respiratory symptoms truly has a recurrent VTE. Doppler ultrasound and chest computed tomography angiography results may have to be reviewed with the radiologist and compared with prior studies to better determine if the thrombosis is acute or chronic. A D-dimer assay also can be helpful, as a positive result is supportive evidence for a recurrent clot, while a negative D-dimer makes new thrombosis less likely. A common cause of subtherapeutic anticoagulation is suboptimal medication adherence, occurring in 63 percent, 62 percent, and 51 percent of patients on warfarin at three, six, and 12 months, respectively.2 Unsurprisingly, subtherapeutic anticoagulation increases risk for recurrent VTE while “on” anticoagulation.3,4 It can be difficult to determine suboptimal adherence.

The Table lists the causes of anticoagulation failure that clinicians should consider. Thrombophilies, other than antiphospholipid syndrome (APS), are not associated with a higher risk of recurrent VTE during warfarin therapy.5 Patients with antiphospholipid syndrome (APS), have a high prevalence of myeloproliferative neoplasms (MPNs) who may have a high risk for anticoagulation failure.6 Failure of vitamin K antagonist therapy is seen in 4.2 percent of patients with an established MPN per year.7 With regard to which patients with anticoagulation failure should be screened for JAK2 V617F or CALR mutations, no previous study has reported the prevalence of JAK2 V617F mutations in unselected patients with anticoagulation failure. Therefore, the present exploratory study was undertaken.

The article by Dr. Jean-Christophe Ianotto and colleagues reports the results of a single-center observational prospective cohort of 878 patients with untreated VTE enrolled between the years 2000 and 2013. JAK2 V617F and CALR mutation analyses were performed retrospectively on stored blood samples. The present analysis is from the first half (n=372) of these 878 patients. Of 372 patients, 138 (37.1%) had isolated deep vein thrombosis (DVT), and 234 (62.9%) had multiple venous thrombosis with or without DVT.

The main findings of this study include prevalence of the JAK2 V617F and CALR mutations, rates of recurrent VTE on warfarin and off anticoagulation, and presence of an overt MPN. In the overall cohort, 10 patients (2.7%) were carrying the JAK2 V617F mutation, none had a CALR mutation, and 19 patients (5.1%) had a recurrent VTE on therapeutic anticoagulation. The key finding is that four (21%) of those patients who had the JAK2 V617F mutation, compared to six (1.7%) of 353 patients who did not have VTE recurrent on anticoagulation (p<0.001). In the first four JAK2 V617F-positive patients with anticoagulation failure, an MPN was diagnosed within six months of the recurrence, but the remaining three did not develop an overt MPN during the follow-up period (length of follow-up in these 3 patients was not reported). Four (54.5%) of these patients (4 of 7) in the overall cohort developed a VTE recurrence within four weeks of having stopped anticoagulation. None of them carried the JAK2 V617F mutation.

The authors concluded that screening for the JAK2 V617F mutation in VTE patients with anticoagulation failure may be warranted, as the prevalence is high, reaching 21 percent; that the prevalence of CALR mutations in patients with anticoagulation failure is low (0%); and that systematic screening for JAK2 V617F and CALR mutations cannot be recommended for patients with recurrent VTE off anticoagulation.

How do these study findings impact our practice? In patients with recurrent VTE on anticoagulation but without established MPN, we consider JAK2 V617F testing, but not CALR testing. However, we acknowledge that it is not known whether mutation testing in this situation is beneficial, nor whether an overt MPN will develop.8 It may be necessary to serially monitor CBCs, as only elevations in hematocrit or platelet count would merit cytoreduction in the present treatment paradigms for MPN.

High Prevalence of Ph-Like ALL Across the Age Spectrum

Philadelphia chromosome-like (Ph-like) acute lymphoblastic leukemia (ALL), first described in 2009, is a gene expression profile similar to Ph-positive ALL that lacks BCR-ABL1 and has been independently associated with a poor prognosis.1,2 Notably, the majority of patients with Ph-like ALL have underlying genetic alterations in kinase or cytokine receptor signaling pathways that can be targeted with available tyrosine kinase inhibitors (TKIs) – an approach supported by preclinical studies and individual case reports. While the prevalence of Ph-like ALL has been shown to increase with age ranging from 10 to 15 percent in children up to 24 percent in older adults, the prevalence of this high-risk subtype in older patients was not previously established.

To address this question, Dr. Kathryn G. Roberts and colleagues completed an international study analyzing 798 patients with B-ALL, aged 21 to 86 years. Comprehensive genomic analyses were completed using banked leukemia samples to determine the frequency of Ph-like ALL in adults. Another aim of this study was to identify the underlying kinase-activating alterations and to compare the findings to those observed in children and adolescents.

For the analyses, the patient population was subdivided into three age groups: young adults (21-39 years of age), adults (40-59 years of age), and older adults (60-86 years of age). The expression of 15 genes by either microarray or a quantitative reverse-transcriptase polymerase chain reaction low density array (LDA) screening card was assessed and patients with an LDA coefficient of 0.5 to 1 were designated positive for Ph-like ALL. Additional confirmatory testing, including fluorescence in situ hybridization (FISH) and transcriptome sequencing, was completed in LDA screen positive patients to identify specific underlying genetic alterations (Figure).

The authors found a high frequency of Ph-like ALL across the adult age spectrum, occurring in 194 patients (24.3%) overall. When examining adult age subtypes, Ph-like ALL was identified in 27.9 percent, 20.4 percent and 24 percent of the young adults, adults and older adults, respectively. As demonstrated in previous studies, the Ph-like subtype conferred a poor prognosis. Five-year survival for adults with Ph-like ALL was 23.8 percent compared with 52.4 percent for adults with non-Ph-like ALL, excluding BCR-ABL1 and PKC723-rearranged ALL. The outcome differences were most significant in young adults where five-year survival for Ph-like ALL was 25.4 percent compared to 64.2 percent for non-Ph-like ALL. Eighty-eight percent of the Ph-like ALL patient population was confirmed to have an underlying alteration activating kinase signaling. The most common alterations were cytokine-receptor-like factor 2 (CRLF2) rearrangements, which occurred at the highest frequency in older adults (58.4%). Additional findings included ABL1 class fusions (9.8%) along with mutations and rearrangements in the JAK-STAT and Ras pathways. Overall, approximately 70 percent of the patient population had an underlying genetic fusion targetable with a JAK inhibitor.

The investigators identified several fusions that were previously unreported in Ph-like ALL. Aside from EPOR rearrangements, which were more common in older adults, the frequency of specific underlying alterations did not differ across age groups and kinase-activating alteration profiles identified in adults with Ph-like ALL were similar to those previously reported in children.

This report demonstrates that Ph-like ALL is common across the age spectrum. The translational implications are significant because the vast majority of patients with Ph-like ALL have alterations that are treatable with existing therapies. Trials evaluating TKI therapy with either dasatinib for ABL1 class fusions or ruxolitinib for CRLF2 rearrangements or JAK-STAT pathway alterations, in combination with chemotherapy, are presently underway in both children (NCT02885049, NCT02723994) and adults (NCT02420717) with Ph-like ALL. These studies will provide essential information about the optimal treatment approach for this high-risk disease subtype.

In addition to defining the optimal treatment strategies for Ph-like ALL, there are additional challenges for the future surrounding the efficiency and accessibility of testing. Eleven new targetable fusions were identified in this study suggesting that more comprehensive sequencing approaches may be needed in the future to precisely identify all Ph-like patients. Given the prevalence, prognostic significance, and potential treatment implications, future efforts are needed to ensure that testing is broadly available.


#### REFERENCES


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#### ERRATA

**ELIZABETH RAETZ, MD**

Dr. Raetz indicated no relevant conflicts of interest.

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**JONATHAN HOGGATT, PHD**

Dr. Hoggatt indicated no relevant conflicts of interest.
Abandoning Induction Chemotherapy

Historically, complaining about induction chemotherapy has been a quixotic exercise. Yes, it represents a suboptimal therapy, but it was the best choice of the time. Building on the choices of the past, we have brought about a deeper and more sophisticated approach, and in so doing have benefited our patients. For both vadastuximab talirine and venetoclax, with modest single-agent activity in the relapsed and refractory setting, the CR rate in the 80 percent range and CR/CRu rates in the 60 percent range,14,15 again compatible with what would be expected for a younger patient population in the setting of induction. Tolerability was better than what would be expected for the same population exposed to intensive induction,13,14 and patients were able to proceed to transplantation when appropriate.

Drug companies and the FDA are tying themselves into a quixotic exercise. Yes, it represents a potentially important step forward in the treatment of acute myeloid leukemia, but it is not as likely to lead to an OS benefit, not to mention the cost savings from an outpatient regimen.13,14

Significant resources, from investigators, granting agencies, and most importantly, study subjects, have been invested in attempting to improve induction chemotherapy. We now need to enter a new era in which this could be eliminated. Perhaps it is the clinicians who need to be weaned from induction; maybe it is the crutch keeping us limping but preventing us from running.

Dr. Pollyea indicated no relevant conflicts of interest.

Restricting the use of vadastuximab talirine and venetoclax with their hypomethylator backbones to older patients, who typically require a more intensive form of reverse age discrimination. The only impediment to a trial that spares induction and offers younger adult (18-50 years old) newly diagnosed AML patients the same treatments that are so successful in elderly unfit patients is consent. In the advanced, and therein lies the paradox: We despise induction chemotherapy — its toxicity, its unpredictability, and its lack of efficacy — yet we show enormous fealty to this conventional approach. Within our community, it is not viewed as contradictory to inveigh against the limitations of induction chemotherapy and simultaneously proclaim it unethical to withhold it.

I believe the way forward is to design a small, pilot, noninferiority study using CR as an endpoint and using a well accepted historical control, in which induction was standard of care. Frequent statistical analyses (such as each time a small cohort of patients completes 1 or 2 cycles) to ensure

Can Apixaban Succeed Where Others Have Failed?

**STUDY TITLE:** A Study of the Safety and Effectiveness of Apixaban in Preventing Blood Clots in Children With Leukemia Who Have a Central Venous Catheter and Are Treated With Pegylated (PEG) L-Asparaginase

**CLINICALTRIALS.GOV IDENTIFIER:** NCT02269653

**SPONSOR:** Bristol-Myers Squibb

**PARTICIPATING CENTERS:** Approximately 58 study sites in North America, Australia, Canada

**STUDY DESIGN:** Randomized, open-label

**ACCRUAL GOAL:** 500

**STUDY SYNOPSIS:** This is a phase III, randomized, open-label study comparing apixaban with no anticoagulants for prevention of a composite of fatal and nonfatal venous thromboembolism (VTE) in children (ages 1-17 years) with a central venous catheter and a new diagnosis of acute lymphoblastic leukemia (ALL), lymphoma or mixed-phenotype acute leukemia. All participants must also receive induction chemotherapy with a corticosteroid, vincristine, and single or multiple doses of pegylated (PEG) L-asparaginase (+/- daunorubicin) and have a platelet count greater than 20×10^9/L. The primary safety outcome is the occurrence of a composite of fatal and nonfatal VTE in children (ages 1-17 years) for prevention of a composite of fatal and nonfatal venous thromboembolism. The primary efficacy outcome is the incidence of VTE in children who are treated with L-asparaginase: results of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) Study. Cancer. 2003;97:508-516.

**RATIONAL:** L-asparaginase reduces plasma concentrations of coagulation factors, particularly antithrombin, which contributes to a high prothrombotic state in patients with acute leukemia. Catheter-associated thrombosis is the most frequent thrombotic complication of this treatment, accounting for 95 percent of the VTE cases in a prospective study of pediatric ALL patients (total incidence of VTE: 22 [36.7%] of 60; 95% CI 12.4-48.8%). Catheter-associated thrombosis is important not only because it leads to limb morbidity, but because it may also compromise administration of chemotherapy due to loss of venous access.

**COMMENT:** This trial faces several important hurdles. First, there is the failure of other anticoagulants, such as low-molecular-weight heparin (LMWH) and warfarin, to prevent catheter-associated thrombosis in pediatric patients with cancer. Second, L-asparaginase can cause profound thrombocytopenia and hypofibrinogenemia, which increases the risk of major bleeding, especially within the context of anticoagulant therapy. Lastly, experience with the direct oral anticoagulants is limited, which raises questions about efficacy and safety. Despite these hurdles, there are also important advantages to evaluating apixaban. These include oral administration and reduction/elimination of the need for laboratory coagulation monitoring. Both properties would greatly improve quality-of-life for pediatric patients. Furthermore, apixaban does not depend on the presence of antithrombin to exert its anticoagulant effect, which may improve efficacy in patients receiving L-asparaginase. If successful, this trial will break new ground for cancer patients who require central venous catheters, both pediatric and adult.


Dr. Linkins indicated 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 23, 2017

Dr. Stephen Starko Francis and colleagues report an untargeted virome and bacterial analysis of patients with childhood acute lymphoblastic leukemia (ALL) and reveal a higher prevalence of cytomegalovirus (CMV) infection in ALL patients than in unaffected controls. This increased prevalence was significantly pronounced in Hispanic patients. This suggests that an in utero CMV infection may predispose to the later development of ALL.


Dr. Bob Löwenberg and colleagues report the results of a randomized study of clofarabine added to induction chemotherapy for high-risk myelodysplastic syndromes and acute myeloid leukemia (AML), reporting that the addition of clofarabine improves survival in a subset of intermediate-risk AML.

MARCH 9, 2017

In this week’s plenary paper, Dr. Antonio Cannavò and colleagues examine the significance of nonneutralizing antibodies (NNAs) in predicting factor VIII inhibitor development. They demonstrate that the presence of NNAs before factor VIII exposure moderately increases the rate of subsequent inhibitor formation.

MARCH 16, 2017

Dr. Sophie Chauvet and colleagues report the largest study to date on the treatment outcome of patients with monoclonal gammopathy-associated C3 glomerulopathy and demonstrate that renal outcomes are dependent on hematological therapeutic response.


Dr. Santhosh Dhanraj and colleagues identify biallelic mutations in DNAJC21 in patients with phenotypic Shwachman-Diamond syndrome (SDS), thus adding an important gene mutation to the list that can cause SDS.


In a large data set, Dr. Eliane Gluckman and colleagues demonstrate the role of HLA-identical sibling marrow transplantation in sickle cell disease with a five-year overall survival of 95 percent when performed at an early age (<16 years).

MARCH 30, 2017

This article reports a role for lymphangiogenesis in graft-versus-host disease (GVHD) and postulates inhibition of angiogenesis by targeting VEGFR3 as a potential new therapy for GVHD.


Under the auspices of the European LeukemiaNet, the authors offer a consensus guide regarding the use of allogeneic hematopoietic cell transplantation in adults with myelodysplastic syndromes and chronic myelomonocytic leukemia.

The Committee on Promoting Diversity advises ASH in its efforts to improve minority recruitment into hematology research and practice in the United States and Canada, attract minority hematologists as members of the Society, and develop minority hematologists as leaders. The committee arose from ASH leadership’s recognition in 2003 that very few minority trainees pursue hematology careers, despite the diverse patient population hematologists serve. The committee oversees the Minority Medical Student Award Program (MMSAP) for early-stage medical students, the ASH Harold Amos Medical Faculty Development Program (ASH-AMFDP) for junior faculty with academic appointments, and the Minority Graduate Student Abstract Achievement Award (MGSSAA) for PhD trainees doing hematology-related research. It also sponsors the MMSAP Luncheon and Promoting Minorities in Hematology Reception at the ASH annual meeting. Additionally, the Committee strives to ensure minority representation across the Society through the nomination of minority ASH members for Honorific Awards and committee appointments, and as potential speakers and abstract reviewers for the ASH annual meeting.

In 2016, the Committee launched several exciting new initiatives. The Minority Resident Hematology Award Program (MRHAP), an entirely new program for residents, as well as a more flexible option for medical students at all levels (MMSAP-flex) to complete a research project in 12 months instead of the eight- to 12-week summer period of the traditional MMSAP, were rolled out. These new programs fill existing gaps at critical intervening stages of training in the longitudinal pathway from medical student to hematologist by providing minority trainees with additional opportunities for doing hematology research and interacting one-on-one with both a research and career development mentor. Recipients of these and now all ASH minority awards are eligible to re-apply for subsequent experiences. The final details of a new, full-time 12-month research program for minority medical students are being hammered out, and ASH Executive Committee approval will be sought for a new program to support minority fellows in hematology research.

2017 has also been a busy year with the launch of the new ASH Institutional Representative (AIR) Program, or “AIR-ASH,” that aims to improve minority medical student and trainee awareness of hematology as a career. It highlights the many research and career development programs ASH offers through creation of a formal volunteer role for faculty to serve as representatives of the Society at their own institutions. AIR faculty will conduct information sessions on a career in hematology and ASH opportunities and interact with relevant minority student/trainee organizations. The new role provides more advanced junior and mid-level faculty who are ASH members with an opportunity to serve the Society and develop relationships with institutional, regional, and national leaders at ASH. A three-year pilot program is planned, with 15 representatives in the first year. The program could have a major Society-wide impact and, if successful as a pilot, could be introduced to additional institutions targeting all medical students, trainees, and faculty with an interest in hematology.

The first ASH Award for Promoting Leadership in Diversity will be presented at the 2017 annual meeting. This is a new Honorific Award created by the committee to honor hematologists who have demonstrated extraordinary commitment to diversity and inclusion in the field of hematology. Society members can stay abreast of these and other new ASH minority recruitment initiatives and the activities of the committee by accessing the Minority Recruitment Initiative webpage at www.hematology.org/Awards/3866.aspx.
A Joe Mikhael Icebreaker Fulfilled

BY JASON GOTLIB, MD, MS
Editor-in-Chief, The Hematologist; Professor of Medicine, Stanford University School of Medicine, Stanford, CA

Dr. Joseph Mikhael is Chairman of the ASH Committee on Communications, and each year, he opens the Communications Committee meeting with an icebreaker question to loosen the mood and to have everyone gain a better appreciation of our nonhematology lives. Joe reminds us hematologists, that like other professionals, it is important to seek outlets outside of work to maintain balanced lives, as has been profiled in the “PASHions” column in ASH Clinical News. At the 2016 Annual Meeting, he asked us what is on our bucket list of activities and places to visit. Committee members had many interesting responses that elicited excitement about shared dreams of distant lands and exotic adventures. When my turn came, I mentioned that I wanted to spend time with sloths. To me, the room grew palpably and uncomfortably silent, and I thought I could read Joe’s thoughts, “What is it with this guy?”

This April, I had a unique opportunity to make good on my awkward icebreaker response. I travelled to the Manuel Antonio region of Costa Rica with my wife Lenn and granddaughter Kenya. We visited Kids Saving the Rainforest (KSTR; www.kidsavingtherainforest.org), a nonprofit center whose mission is to protect the diverse wildlife of Costa Rica’s Pacific Coast by rehabilitating wildlife, conducting original scientific research, training volunteers, and promoting conservation. Unbelievably, KSTR was started in 1999 by two nine-year-old girls (Kenya’s age), Janine Lacare and Aislin Livingston, who were living in Costa Rica at the time and were concerned about the disappearing rainforest and its effects on native wildlife, such as the titi (squirrel) monkeys.

Lenn, Kenya, and I had a wonderful day with the KSTR staff and were educated about the reasons that different animals landed in their arms for rescue, including orphaned babies, injury (e.g., electrocution burns), and an increasing number of households returning illegally obtained wild rainforest “pets” because of their inability to manage their special needs or for fear of stiff fines or prison sentences. While some species undergoing rehabilitation are candidates for release, some will never be able to thrive upon return to the wild and ultimately become more permanent residents of sanctuaries such as KSTR. In addition to planting thousands of rainforest trees, one example of a program to increase numbers of endangered species such as the titi monkey is the “monkey bridge program,” which places rope bridges over the roads of Manuel Antonio to reduce their risk of electrocution by power lines or being hit by cars.

As volunteers, we had an opportunity to prepare meals consisting of fruits and vegetables (and hibiscus flowers for sloths) and spend time feeding the sanctuary’s rainforest residents. While we saw various species including titi monkeys, spider monkeys, capuchin monkeys, marmosets, anteaters, parrots, hawks, and Geoffroy’s tamarins, the highlight residents. While we saw various species including titi monkeys, spider monkeys, capuchin monkeys, marmosets, anteaters, parrots, hawks, and Geoffroy’s tamarins, the highlight of the day was seeing the two-toed sloths being prepared for release.

For more photos of Dr. Mikhael’s time at KSTR, please visit The Hematologist online.