Disparities of Adolescent and Young Adult Patients in the Treatment of Malignant Hematologic Diseases

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The Adolescent and Young Adult (AYA) Progress Review Group (PRG) defines the AYA cancer population as patients ranging from 15 to 39 years of age. An estimated 69,000 AYA individuals are diagnosed with cancer each year — six times more than children younger than 14 years.1 The AYA age demarcation was established as a high-risk population after data from the Surveillance, Epidemiology, and End Results (SEER) study showed a lack in improvement in survival for patients with many forms of cancer.2,5 The most common malignancies are leukemia, lymphoma, germ cell tumors, and central nervous system tumors among 15 to 24 year olds, with the incidence of breast cancer, colorectal cancer, and melanoma increasing among older AYA patients1 (Figure).

In 2007, the AYA PRG released a comprehensive guide explaining the disparities experienced by AYA cancer patients that have led to their poor outcomes and lack of progress throughout the years.2,3 These disparities include lack of health insurance, differences in disease biology, delay of diagnosis and treatment, increased toxicities, lower socioeconomic status,4 and overall lack of awareness in the medical field as to the special needs of this population (Table 1). The goal of the AYA PRG was not only to introduce and educate the medical field about this high-risk population, but also to start a systematic mitigation of the disparities. Since the release of the PRG guide, progress has been made, including an increase in AYA-specific scientific peer review publications, formation of AYA oncology programs, development of AYA-specific national workshops and committees, development of clinical trials targeting AYAs, and expansion of inclusion criteria to include AYAs.5,6 Additionally, the European Cancer Registry (EUROCARE) and NCI SEER data have reported improvement in survival rates for the AYA population.7,8 Despite some improvement in survival, AYAs still have lower five-year relative survival rates for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), rhabdomyosarcoma, Ewing sarcoma, and breast cancer compared with children and older adults.9 Notably, the incidence of all invasive cancers continues to increase in AYAs compared with any other age group.10 Although many common malignancies overlap in younger and older patients, research advances in ALL, breast cancer, colorectal cancer, sarcoma, and melanoma have identified age-dependent priorities for the Society.

**Table 1:** List of the Disparities Experienced by AYA Hematology-oncology Patients

<table>
<thead>
<tr>
<th>Access to health care</th>
<th>Psychosocial stressors</th>
<th>Delay in diagnosis</th>
<th>Delay in treatment</th>
<th>Treatment site</th>
<th>Reduced rates of clinical trial enrollment and treatment standardization</th>
<th>Increased toxicity</th>
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<td></td>
<td>reduced rates of clinical trial enrollment and treatment standardization</td>
<td>increased toxicity</td>
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![Common Types of Cancer Affecting AYAs](image)

**More Than an Aspirin a Day to Keep Recurrent Venous Thromboembolism Away**


Whether to extend anticoagulant therapy for a deep vein thrombosis or pulmonary embolism beyond the acute treatment period can be a problematic decision. Anticoagulant therapy reduces the risk of recurrent venous thromboembolic events (VTE), but at the cost of an increased risk of bleeding. Reducing the intensity of anticoagulant therapy1 or switching to aspirin2 have both been proposed as options in patients who wish to continue protection, but the efficacy and safety of these strategies is still uncertain.

Dr. Jeffrey J. Weitz and colleagues reported the results of a double-blind, randomized controlled trial, ‘EINSTEIN CHOICE’ which compared rivaroxaban 10 mg daily (low intensity) with rivaroxaban 20 mg daily (standard intensity) and aspirin 100 mg daily for prevention of recurrent VTE. All 3,365 randomly assigned patients received six to 12 months of anticoagulant therapy prior to enrollment. Patients with provoked or unprovoked VTE were eligible as long as their clinician believed there was uncertainty about the value of long-term treatment. Study duration was up to 12 months. The primary efficacy outcome measure was symptomatic fatal or nonfatal recurrent VTE, and the primary safety outcome was major bleeding.

The results showed that the rivaroxaban 20-mg and 10-mg doses were both superior to aspirin for the prevention of recurrent VTE (rivaroxaban 20 mg, 1.5%; rivaroxaban 10 mg, 1.2%; aspirin, 4.4%; HR [rivaroxaban 20 mg vs. aspirin], 0.34; 95% CI, 0.20-0.59; P<0.001; HR [rivaroxaban 10 mg vs. aspirin], 0.26; 95% CI, 0.14-0.47; P<0.001). Between the two doses of rivaroxaban, there was no difference in the risk of recurrence (HR, 1.34; 95% CI, 0.65-2.75; P=0.42) or the risk of major bleeding (0.5% and 0.4%, respectively). Furthermore, the risk of major bleeding in rivaroxaban arms was similar to aspirin (0.3%). The risk of clinically relevant nonmajor bleeding was not significantly different across the three groups (rivaroxaban 10 mg, 2.0%; rivaroxaban 20 mg, 2.7%; aspirin, 1.8%).

There are important limitations to this study that should be considered. First, the total number of events (80) was small. This is likely due to the substantial proportion of patients with provoked VTE enrolled in the study (60%). This group is known to have a low risk of recurrence without anticoagulant therapy; therefore their inclusion in the study is controversial.1 Additionally, the duration of treatment was limited to one year. Patients facing this choice are deciding if they should continue anticoagulation indefinitely, which can mean decades of treatment. Lastly, the study was not powered to determine if 10 mg of rivaroxaban is noninferior to 20 mg with respect to efficacy.

Overall, the results of the EINSTEIN CHOICE study show that even low-dose anticoagulation is superior to aspirin, and without a higher price to pay with respect to bleeding. Consequently, the key message of this trial is that patients who wish to continue protection from recurrent VTE have little to gain by switching to aspirin. However, what this study does not confirm is that rivaroxaban 10 mg once daily is sufficient for patients with a high risk of recurrence.

AYA Treatment Disparities

(Cont. from page 1)

differences in disease biology within the same malignancy.13 ALL is the most common malignancy in AYAs with a continued increase in incidence in the past 10 years, and still remains the leading cause of AYA cancer deaths.1-3 The overall survival (OS) for AYAs with ALL is 52 percent, compared with 90 percent in children.6 Age-related genetic and biological variation in ALL are well established and likely contribute to the continued poor OS. AYA patients diagnosed with ALL have a higher frequency of genetic alterations that are associated with poor prognosis, such as Ph+ ALL, Ph-like ALL, hypodiploidy, and iAMP21 (Table 2).7-9,11,12 Recent epidemiological data have indicated that AML patients between the ages of 15 and 19 years had a much lower five-year OS compared with younger patients (50% and 66%, respectively), and age is an established poor prognostic factor in adults with AML.13,14 The presence of specific genetic abnormalities also seems to differ between pediatric and AYA AML, but data are limited due to the low number of AYAs treated on AML clinical trials.15 Compared to children younger than 16 years, AYAs aged 16 to 21 years were more likely to have normal cytogenetics, favorable prognostic markers such as NPM1 and CEBPA, and a higher incidence of acute promyelocytic leukemia, but they were also more likely to carry unfavorable markers such as FLT3/ITD (Table 2).15

In addition to biological differences in disease, socioeconomic factors such as lack of health insurance are associated with advanced stage at presentation, delay in diagnosis and definitive treatment, and increased mortality.16,17 Persons between the ages of 18 and 34 years are more likely to be uninsured compared to other age groups.16 In AYA patients with Hodgkin lymphoma, having public health insurance was associated with an increased risk of advanced disease at time of diagnosis.18 Having no insurance or public health insurance, as well as low socioeconomic status, act as barriers to treatment at National Cancer Institute (NCI) Southwest Oncology Group [SWOG]). Such programs further highlight the commitment at ASH to serve both clinicians and scientists around the world and to remain the premier hematology society striving to further the understanding, diagnosis, treatment, and prevention of blood diseases worldwide.

Table 2: Differences in Disease Biology of Hematologic Neoplasms in AYAs

<table>
<thead>
<tr>
<th>Positive prognostic factors</th>
<th>Negative prognostic factors</th>
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<tr>
<td><strong>B-ALL</strong></td>
<td><strong>Ph-like ALL</strong></td>
</tr>
<tr>
<td>ETV6-RUNX1</td>
<td>• Age 1-9 years: 10%</td>
</tr>
<tr>
<td>• Higher incidence in younger patients</td>
<td>• Age 16-20 years: 21%</td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>• Age 21-39 years: 27%</td>
</tr>
<tr>
<td>• Higher incidence in younger patients</td>
<td>AML1 rearrangements</td>
</tr>
<tr>
<td>KMT2A rearrangements</td>
<td>RAS mutations</td>
</tr>
<tr>
<td>NASP</td>
<td>AMP21</td>
</tr>
<tr>
<td>HOX1</td>
<td>SATB2</td>
</tr>
<tr>
<td><strong>Early T-Cell Precursor ALL</strong></td>
<td>• Germline variants are associated with predispition to AYA ALL</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>FLT3/ITD</td>
</tr>
<tr>
<td>Normal cytogenetics, NPM1 and CEBPA</td>
<td>• Incidence increases with age</td>
</tr>
<tr>
<td>• Higher incidence in AYAs</td>
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Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult.
The ASH Global Research Award: Q&A With the Program Chairs

Taking a cue from more than 30 years of success with the ASH Scholar Award program, the new ASH Global Research Award aims to support hematologists during the critical period between completion of training and the establishment of their independent careers. However, this program was created specifically for trainees and early investigators practicing outside the United States and Canada. To better understand its purpose and goals for its first year, The Hematologist discussed the award program with committee Co-Chairs Drs. Ruben A. Mesa and Andrew Roberts.

This award supports hematologists transitioning to careers as independent investigators. Why is this stage so crucial? How is the program different from other ASH career and training award programs?

Ruben Mesa, MD: The transition from one’s training program to becoming an independent investigator is truly one of the most challenging for individuals. The Global Research Award program’s goal is to expand the reach of academic hematology and make specific contributions to the development of meaningful scientific research. This award is distinct from other ASH programs in its breadth and scope, offering at a global level some of the opportunities previously only available in the United States and Canada.

Andrew Roberts, MD: ASH recognizes that careers in academic and research-focused hematology vary widely around the world, and that the type and scope of investigator-led research that makes a difference also differs between regions and countries. This means that programs appropriately designed for emerging investigators in North America may not be fit-for-purpose in Africa, Asia, Latin America, or Europe. The ASH Global Research Award has been designed with this heterogeneity in mind. It aims to identify outstanding people early in their careers and support them to conduct programs that will advance hematology in their region. It is structured to enable as far a competition as possible between applicants from different regions by recognizing inherent differences in opportunity, infrastructure, and regional need.

Why is global collaboration so important to hematology, and how does this program support that?

RM: Global collaboration is integral in hematology. For example, decreasing morbidity and mortality rates of acute promyelocytic leukemia in Latin America was a collaborative effort made with the assistance of ASH. This award will further aid global collaboration by supporting promising investigators from a range of countries, including those with less-developed research infrastructures. Additionally, since these awards connect individuals with leaders in their areas of research, this will enhance collaboration.

AR: Global collaboration is integral to many areas of hematology research (e.g., the genomics of acute myeloid leukemia, childhood bone marrow failure syndromes) and essential when it comes to addressing the needs of patients in areas of the world where resource limitations preclude use of therapies routinely available in North America. ASH is hopeful that the ASH Global Research Award will not just advance the development of future leaders, but also create networks that enable major blood disorders to be tackled in a global fashion.

What are some of the goals for the program in its first year? Do you expect to face any challenges? If so, how will they be overcome?

RM: The goals of the award in its first year are to build awareness of the program and to have a broad range of applicants representing many different countries, particularly from the developing world. As with any new award, it will take time to get the word out and refine the functionality of the program. The steering committee has deliberated extensively on the parameters of the program in terms of eligibility and flexibility in using the award. We will refine these parameters further and learn how best to communicate the spectrum of opportunities available to investigators who participate.

AR: The fact that we will receive a diverse array of proposals from applicants who come from a variety of training systems, cultural backgrounds, and economic environments means that assessing the applications against each other will not be straightforward. We have established a review system that should be able to deal with this heterogeneity fairly, but this will be tested carefully as we go forward. I expect that we will need to adjust the system as we learn more about what this award can achieve in different parts of the world.

What is the long-term vision for the award program, and how do you hope to see it evolve?

RM: The long-term vision of the award is to increase tools to foster a global hematology community. This will include educational efforts like the Clinical Research Training Institute in Latin America, and Asia and Highlights of ASH in various regions. We hope to see this program grow through engagement with other national societies and organizations.

AR: Wouldn’t it be great if the ASH Global Research Award becomes as empowering and enabling for early-career hematologists in Asia, Africa, Latin America, and Europe as the ASH Scholar Award has been for its peers in North America? That’s part of the long-term vision. Additionally, connecting the best from many parts of the world is a great way to drive collaboration and strengthen the global hematology community.
Ask the Hematologist

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The Question
How do you approach giving bad news to patients and their families?

The Response
Doug had essential thrombocytopenia (ET) that eventually transformed into post-ET myelofibrosis. He required splenectomy 13 years ago. His thrombotic diathesis, refractory to warfarin, was controlled with enoxaparin or fondaparinux for the next decade. With time, he developed increasing circulating blasts, and year after year, we kept expecting transformation to acute leukemia. Now a trail 76-year-old, Doug spoke with me several times about this possibility. He became transfusion-dependent, but throughout the next six months, he continued to enjoy work in his yard.

When he bled spontaneously into his arm, fondaparinux was reduced. A week later, he bled into the retroperitoneum. With the patient hospitalized and hypotensive, we transfused while exploring angiography. He looked like hell. And I was late for heme-onc clinic. Years ago, I would have encouraged him to “hang in there,” reassuring him that he was under excellent hospitalist care, and pleading to return that evening. I now recognize, however, that this was inadequate. For this probable impending disaster, I had to “break the bad news” openly and prepare him and his wife.

As hematologists-oncologists we break bad news frequently — diagnosis, recurrence, progression, incurability, prognosis, impending death — but most of us have had little formal training in this area. Dr. Walter F. Baile and colleagues taught a wonderfully useful approach called “SPIKES,” which I have outlined and modified in this article.

Setting
If at all possible, never give bad news by phone or in the hallway. Sit, with TV and cell phones off. It may require having other family members present, as well as extra chairs. Pull your chair close to the patient’s bed or chair, nonverbally signaling your connection and your therapeutic alliance, perhaps holding a hand or touching an arm, making sure you face both patient and family, and using eye contact as you speak. At this point, we are setting the stage.

Perception
Ask the patient and family what they think is going on. This simple act engages them (a critical element in good communication) and sends the message that what they think matters, such that we start with their perception of the situation. Furthermore, in this way we’re more likely to reframe or educate successfully, especially if any misunderstandings are openly expressed first.

Invitation
This simple step, however phrased (e.g., “Shall I share the results of the scan with you now?” or “Is this a good time to tell you what I believe is happening?”), shows respect, focuses attention, and essentially asks for permission. We are about to announce something unpleasant. We may disappoint and occasionally devastate the recipients of the news we are about to deliver. Do it gently and with humility. Many patients and families feel violated when we tell them terrible things, so obtaining permission first signifies they’ve agreed to hear it and are ready to allow us into their world.

Knowledge
When it is time to break the news, patients and families benefit from a brief summary of what we knew (or thought we knew), what we hoped for, and finally, what we have now learned. Speak slowly, make eye contact, use simple terms, and if you must use medical jargon, translate as you go. Beware of providing too many details, and gently but resolutely cut to the chase. Most patients, especially during emotionally charged times, are best served with clear, nonmedical language. Then explain what the bad news means. If you pause after relating what the findings are, the patient and family may ask what the findings mean. In this way you have allowed them to once again invite you to tell more.

Empathic Response/Emphatic Silence
This is new territory for many of us. After hearing bad news, patients and families often feel traumatized and overcome with emotion. Rather than speaking up, changing the subject, or moving to therapeutic options, a little silence is often best. Silence is powerful and valuable. When you do speak, an “empathic response” is your best move: Speak words that acknowledge that your patient is feeling something. The response may be a statement or question; go with what feels right at the time. For example:

“Must this be very bad news for you to hear.”
“I imagine this is very disappointing.”
“Is this a big surprise, or did you kind of expect this?”

And our own feelings count as well:

“I’m so sorry, and I am really disappointed, too.”
“I was also hoping we’d have more time.”

Try not to immediately shift away from the uncomfortable silence, the sadness, or the tears. This is how we process tragedy.

Summary/Strategy
Summarize, and decide where to go next. It may be treatment options, agreeing to meet next week, directly addressing prognosis, and/or discussing hospice care.

For Doug, the nature of our talk was my acknowledging and preparing for the very real possibility that, despite our best efforts, this could rapidly lead to demise and death, even today. We would do our best, but it looked bad. He and his wife understood, and months earlier we all agreed that heroic care was not appropriate. In fact, he never got to angiography; that afternoon he passed away, before I finished clinic and with family at his side.

Dr. Baile and colleagues have written extensively on this important communication skill. “SPIKES” was published as a six-step protocol with attention to the oncology community in 2000.

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There are obstacles, of course, to implementing the “SPIKES” protocol. Hematologists often are in a rush, whether in clinic or on rounds in the hospital. Portals that allow patients direct access to their results online seem to enhance patient autonomy, but at the price of meaningful interpretation and context, and this can seriously undermine the doctor-patient relationship. The same is true of the electronic medical record if we’re trying to listen to and talk with patients. The most important elements, however, are our own levels of comfort with handling the intense feelings of the sick and vulnerable, and the extent to which we truly believe that the nuanced, challenging, and exceptionally important task of breaking bad news skillfully and sensitively is our responsibility.

As hematologists, we need to enhance our own palliative care skill sets, since most of the work falls on our shoulders. We should also be aware of an ever-increasing workforce of highly trained palliative care professionals who can assist us when the going gets rough, and when hematologic care becomes something much bigger — care of the critically ill human being, of the aggrieved family, and of the dying.


Dr. Hausdorff indicated no relevant conflicts of interest.
Histiocytoses: Clonal Disorders of Hematopoiesis Driven by MAP Kinase Signaling

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Histiocytoses (or histiocytoses) describe a group of diseases believed to be derived from dendritic cells, monocytes, and/or macrophage lineages, which result in an accumulation of lesional cells and ensuing damage in a variety of tissues throughout the body. The protein clinical manifestations of histiocytoses, which affect children as well as adults, combined with their diverse histologic presentation and rarity, has made these diseases among the most challenging hematologic disorders to diagnose and categorize. In histiocytoses such as Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), and juvenile xanthogranuloma (JXG) were considered to be inflammatory, non-neoplastic conditions, with potentially similar origins to hemophagocytic lymphohistiocytosis (HLH). However, a series of discoveries regarding the molecular genetic causes of histiocytoses over the last several decades has马拉松ed our understanding of nearly all subtypes and has led to potent targeted treatments for patients affected by these conditions. We now understand that LCH, ECD, and JXG are clonal disorders with a high frequency of somatic mutations resulting in activation of the MAP kinase signaling pathway. These advances have been described in a number of excellent recent reviews.1,2 In this article, we summarize some of the most important findings regarding histiocytoses.

Classification of Histiocytoses

In the World Health Organization (WHO) classification of hematopoietic malignancies, histiocytic neoplasms are included under the rubric of “mature lymphohistiocytic, and dendritic neoplasms.”3 There are currently nine WHO-recognized entities including histiocytic sarcoma, LCH, Langerhans cell sarcoma, indeterminate dendritic cell tumor, interdigitating dendritic cell sarcoma, follicular dendritic cell sarcoma, fibroblastic reticular cell tumor, disseminated JXG, and ECD. These entities are differentiated from one another based on histologic and/or immunophenotypic characteristics with distinct genetic alterations only defined for a few. Additionally, it is also important to be aware of an alternate classification system for histiocytic and dendritic cell neoplasms recently proposed by the Histiocyte Society.4 The different eponyms that have been used for systemically histiocytoses are shown in Figure 1A.

Somatic Mutations Drive Histiocytoses

Despite categorization of histiocytoses by lymphoid neoplasms in the WHO classification, it is important to note that 1) gene expression analyses of LCH and ECD indicate that these disorders bear greater resemblance to myeloid lineages than dendritic cells,5-7 2) genetic analyses have identified that mutations in histiocytoses lesions can be found in CD34+ and circulating myeloid cells in patients;8,9 and 3) functional analyses suggest that at least some histiocytoses are derived from hematopoietic precursors.10 These observations suggest that LCH, ECD, and JXG may actually be appropriately considered clonal disorders of the myeloid lineage.

Interestingly, a series of studies performing mutational analysis of histiocytic lymphoid biopsies has identified that both LCH and ECD are characterized by approximately 50 percent of patients having a BRAF V600E mutation (Figure 1B). The BRAF V600E mutation is common to a variety of epithelial cancers, strongly resembles to myeloid lineage cells than dendritic cells, and is common to a variety of epithelial cancers, strongly resembles to myeloid lineage cells than dendritic cells. Additionally, the majority of recurrent mutations that have been identified are mutually exclusive activating mutations affecting MAP kinase signaling, with the most common being the BRAF V600E mutation. Reproduced by permission from the American Association for Cancer Research.

Examples of responses of BRAF V600E and MAP2K1 mutant adults with Erdheim-Chester disease (ECD) to molecularly targeted therapies. (A) Positron emission tomography (PET) scan and brain MRI of a BRAF V600E-mutant ECD patient with skeletal and pararenchymal brain lesions pre- and post-treatment with the BRAF inhibitor vemurafenib. (B) PET scan of a MAP2K1 Q56P-mutant ECD patient with disease infiltration in facial sinuses, heart, and kidneys pre- and post-treatment with the MEK1/2 inhibitor cobimetinib.

Therapeutic Targeting of BRAF and MEK in Histiocytosis

Based on the success of targeting BRAF V600E mutant melanoma with RAK and MEK inhibitors, the discovery of BRAF V600E-mutant LCH and ECD led to efforts to determine the efficacy of these agents for adults with histiocytosis. A number of clinical studies have now demonstrated the efficacy of vemurafenib, and/or macrolide lineages, and in the one clinical trial that has been published, a cohort of 22 ECD and four LCH patients experienced a response rate of 64 percent to vemurafenib (Figure 2A).11 Extended follow-up of this study has identified that these responses are durable, with a median treatment duration now of 14.9 months (range, 2.43 months).12

Given that the use of vemurafenib requires documentation of histiocytoses such as Langerhans cell histiocytosis and Erdheim-Chester disease and any potential benefit in these disorders, one clinical trial that has been published, a cohort of 22 ECD and four LCH patients experienced a response rate of 64 percent to vemurafenib (Figure 2A).11 Extended follow-up of this study has identified that these responses are durable, with a median treatment duration now of 14.9 months (range, 2.43 months).12

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Conclusions and Unanswered Questions

The discovery of recurrent clonal mutations activating the MAP kinase pathway in histiocytosis as well as the response of these patients to small molecules inhibiting this pathway has been remarkable. Despite these successes, there is a need to continue genetic analysis of the variety of histiocytoses that are derived from lymphoid progenitors. Given that the use of vemurafenib requires documentation of histiocytoses such as Langerhans cell histiocytosis and Erdheim-Chester disease and any potential benefit in these disorders, one clinical trial that has been published, a cohort of 22 ECD and four LCH patients experienced a response rate of 64 percent to vemurafenib (Figure 2A).11 Extended follow-up of this study has identified that these responses are durable, with a median treatment duration now of 14.9 months (range, 2.43 months).12


Dr. Abdel-Wahab indicated no relevant conflicts of interest.
Shifting the Focus of Medical Research From the Bench to the Bedside

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Unlike other commentators who have been featured in these columns, I had no role models to guide me in my career path because clinical research, as we know it today, was not being performed in the mid-1960s. Instead, clinician researchers focused their efforts on understanding the pathophysiology of disease and not on solving the problems that they encountered in clinical practice; their research in the laboratory was disassociated from their activities in the clinic.

After I graduated from medical school at Melbourne University in Australia, in 1959, I completed four years of residency training in internal medicine and an additional year in laboratory hematology. It was then that I developed an interest in research, but I had no idea how to go about obtaining the necessary training. I sought advice from Professor Carl de Gruchy, a prominent Australian hematologist, who suggested that I specialize in thrombosis. He said that thrombosis bridged hematology and cardiology and would become an important field in medicine. He encouraged me to locate suitable training positions, so I applied for, and obtained, research fellowships at Washington University in St. Louis, Missouri, where I worked with Drs. Sol Sherry and Tony Fletcher; the London Post Graduate School in London, U.K., where I was fortunate to be Professor John Dacie’s sole trainee; and in Toronto, Canada, where I worked for Dr. Fraser Mustard. These researchers were giants in their fields, and of the many lessons that I learned, two stand out and continue to serve me well: First, to succeed in research, a person requires passion, “stick-with-it-ness,” and stamina. Second, don’t give up on a problem because you lack the expertise to solve it.

In 1968, I returned to a faculty appointment at Melbourne University in the Department of Medicine headed by Professor de Gruchy. I chose venous thromboembolism (VTE) as my clinical field and used the training received overseas to set up a platelet/coagulation/thrombosis laboratory. My laboratory research was opportunistic and mainly phenomenological, though I did use the laboratory to support clinical studies with anticoagulants and with streptokinase. I was shocked to realize that almost all patient management decisions lacked a firm scientific basis. Even more shocking to me was that physicians caring for patients were unaware of the flimsy evidence on which they made many of their clinical decisions. Venous thrombosis and pulmonary embolism (PE) were diagnosed on clinical grounds, and anticoagulant management was haphazard and not standardized. It was then that I decided that I would focus my research on problems that I encountered in my clinical practice and that I would use my laboratory to complement patient management. This shift in research philosophy, in which the research question is driven by patient-important problems and in which the laboratory is used to help explain unexpected findings in clinical trials was novel at the time and provided the basis for evidence-based medicine.

I performed clinical studies which convinced physicians that they should use heparin (with aprotinin) to limit bleeding in both mothers and their fetuses. (with prosthetic heart valves) to limit bleeding in patients with acute coronary syndromes, I was surprised that thromboplastin time and thrombin time were uncorrelated with the clinical benefit. I was also surprised that thromboplastin time was more rapid in patients with stroke compared to those with other CV events. I also obtained local funding for a nonrandomized trial that showed that streptokinase was much more effective than heparin in lysing PEs. I also performed an experimental study in pregnant rabbits to determine the optimal time to switch from warfarin to heparin in pregnant mothers (with prosthetic heart valves) to limit bleeding in both mothers and their fetuses.

My clinical colleagues were very cooperative, supportive, and collegial. I was hailed as a success in Melbourne, but I sensed that my clinical research lacked rigor. Then, in 1969, my life changed! I was invited to pay a visit to the newly formed Faculty of Health Sciences at McMaster University in Hamilton, Ontario. When I visited, I was impressed with the energy, enthusiasm, creativity, and other outstanding qualities of the founding members. I was offered an appointment but was torn by obligations to my family and colleagues in Melbourne. Two factors swayed me. My wife told me that we should “go for it.” Additionally, I had several long discussions with Dr. David Sackett when I visited McMaster. David, who at my age (mid-30s) was founding Chairman of the Department of Clinical Epidemiology and Biostatistics, was the missing link that I was seeking in order to perform worthwhile clinical research. He taught me how to focus my research on patient-important questions and outcomes and to design rigorous clinical studies required to change clinical practice. Soon after I moved to McMaster (in December 1969), I met Dr. Michael Gent, a mathematician who morphed into an outstanding biostatistician. The three of us became firm friends and colleagues, each with our own groups of investigators, some of whom stayed and joined the McMaster faculty and others who moved to Faculties in Canada, Australia, Europe, Asia, and the United States. Some of my earlier fellows and recruits such as Drs. John Kelton, Jeffrey Weitz, and Mark Levine branched out into their own fields and became international leaders in their respective areas. Others such as Drs. Russell Hull, Graham Turpie, Jeffrey Ginsberg, Harry Buller, Giancarlo Agnelli, Philip Wells, Gary Raskob, Agnes Lee, Mark Crowther, David Anderson, Clive Kearon, and John Eikelboom remained in clinical research and became international leaders in their respective fields. But I most remember my contributions to the international normalized ratio in North America. We demonstrated the benefit of aspirin in stroke prevention, established standards for the short- and long-term treatment of VTE, the diagnosis of venous thrombosis and PE, and the out-of-hospital treatment of venous thrombosis. We performed pivotal studies on the prevention of venous thrombosis with anticoagulants and mechanical devices, and my group was one of three that demonstrated the clinical advantages of low-molecular-weight heparin. More recently, we were involved in several of the pivotal studies that have helped direct antiplatelet anti-coagulants in the prevention of stroke in atrial fibrillation, and in the prevention and treatment of VTE.

I remain involved in clinical practice and retain my passion for discovery and for teaching new fellows. My students have become my teachers. Drs. Sackett and Gent (who were never my students) taught me methodology and the rudiments of biostatistics. Dr. Weitz taught me biochemistry, and Dr. 

This shift in research philosophy, in which the research question is driven by patient-important problems and in which the laboratory is used to help explain unexpected findings in clinical trials was novel at the time and provided the basis for evidence-based medicine.
When I first met Jack, I had a foundation in basic science, but I had not acquired the ability to align bench research with patient care. In the area of translational research, Jack Hirsh was a master without peer. He did not invent the concept of evidence-based medicine, but he was certainly one of the first clinician-scientists to harness its remarkable power to answer important clinical questions. Each week, the clinical and research directors would sponsor our meetings. The educational experience was remarkable. Jack taught that if you had an idea and you couldn’t explain it as informally as a successful one. Above all, he showed us the power of unabridged optimism in a field where most experiments fail and some patients are beyond our help. We made our pilgrimages to Jack’s office where he would assume his characteristic posture: leaning forward, listening intently, one hand under each thigh, legs swinging below the chair. Like blooded fighters, the research fellows would explain our (often) failed experiments, while Jack asked questions. Throughout this process, our initial sense of defeat (a sense of pending doom) turned into faint hope, and then miraculously into outright optimism. We came to believe that we were on the threshold of success, and only a few more experiments in a slightly different direction could lead to victory. A key principle of research that Jack taught me is, “What is the question?” Those four plain words represent not just the question of that particular experiment, but the value of the research itself. Our ability to ask and answer Jack’s trademark question is what separates workmanlike experimentation from truly important research.

I have learned through a nearly four-decade-long career in medicine that the search is not a solo sport. Everything depends on the people around you. They set the circumstances, the example, and occasionally the limits that define our professional progress. At McMaster, Jack was building a team. He was the force that built a team of achievers, consecutive clusters of McMaster health scientists who went into the worlds of academia and medicine and became leaders. He made research a team sport by the sheer force of his example and leadership. I can count at least fifty scientists, half a dozen departmental chairs, and at least three medical school deans scattered across Canada and the United States who owe big parts of their careers to Jack. I am one of them.

Jack’s intensity in research also extended to sports. With each passing decade, Jack picked up and invariably conquered a new sport, taking them on with a ferocity that exhausted everyone, except of course himself. I watched him cycle through one sport per decade, including tennis, squash, and jogging. All the same. All predictable. Seldom did Jack’s energy wane. Instead, it would take about a decade for accumulated injuries to impose a switch. Jack’s current sport is golf. I recall playing golf with Jack in the first few years he took up the sport. He was estailing (with some authority) the value of a natural swing. To the casual observer, the swing could only be called natural if shoulder entrapment prohibits raising the club face higher than waist-level. That day, I defeated Jack, who vowed never to play him again since I knew I could never replicate the outcome. His swing has improved, his game has improved (he often scores his age), and his former students receive the frequent news of the hole-in-one. He’s up to four from the white tees.
Bone Marrow Fecundity: Turning Over New Stem Cells in Aplastic Anemia


A n insurmountable limitation in treating bone marrow failure has always been the number of residual stem cells. That is, until now. Dr. Danièle M. Townesley and colleagues from the National Institutes of Health have demonstrated in a nonrandomized historically controlled trial that the addition of eltrombopag, an oral thrombopoietin receptor agonist, to standard therapy, improves rates of hematologic response in patients with severe aplastic anemia.

The empty bone marrow seen on trephine core biopsy in aplastic anemia is a stark and accurate indication of depleted hematopoietic precursors; the cells are simply not there. Sensitive flow cytometry designed to enumerate the immature precursor cells corroborates this morphologic impression. Multiple lines of evidence have established immune-mediated destruction of stem cells as the cause of bone marrow failure. Cytotoxic lymphocytes, cytokines, and a relative paucity of Tregulatory cells lead to loss of stem-cell progenitors. The exact cause of immune dysregulation is unknown, but it may be associated with acquired mutations in cytokotol T cells, leading to constitutive activation, in combination with the loss of the immune modulating effect of Tregulatory cells. As such, immunosuppression, in the form of horse antithymocyte globulin and ciclosporin, have been the cornerstone of therapy. The historical overall response rate to standard immunosuppressive therapy in aplastic anemia is 66 percent. With the addition of eltrombopag to standard immunosuppressive therapy, Dr. Townesley and colleagues have improved the overall response rate to 94 percent at six months.

The researchers divided patients two years and older with previously untreated severe aplastic anemia into three cohorts. All cohorts were treated with a standard immunosuppressive regimen of ATGAM (Pfizer Inc.) and ciclosporin. Eltrombopag was added to the standard regimen in three dosing schedules varying in the timing and duration of eltrombopag therapy. The primary endpoint was complete hematologic response at six months, defined as an absolute neutrophil count of at least 1,000/mm³, a hemoglobin level of at least 10 g/dL, and a platelet count of at least 100,000/mm³. The primary safety endpoint included overall safety profiles in the six months of therapy. Secondary endpoints included survival and clonal evolution, defined as a new clonal cytogenetic abnormality or characteristic changes in the bone marrow consistent with the myelodysplastic syndrome or acute myeloid leukemia.

The overall complete response rate in all three cohorts was 98 percent—a significant improvement over the historical control cohort (p=0.0001). The cohort with the longest duration of eltrombopag therapy had the highest complete response rate (p=0.0001). Significant adverse events attributed to the drug included grade 2 cutaneous eruptions in two patients. The overall survival rate at two years was 97 percent. Results of bone marrow cellularity and CD34⁺ cell counts are shown in the Figure (available in the online version of this article at www.hematology.org/thehematologist).

A significant secondary endpoint in this study was clonal cytogenetic evolution. The potential for clonal cytogenetic evolution was of particular interest because of the well-known predisposition of patients with aplastic anemia to experience clonal hematopoiesis. In the milieu of bone marrow failure, the small number of residual stem cells attempt to maintain peripheral counts, which leads to telomere attrition resulting in chromosome instability and increasing the odds of harmful mutations. The eventuality was of particular concern in a trial in which both diminished immunosurveillance and growth promotion were stimulated in tandem. Clonal cytogenetic evolution occurred in seven patients at two years. It is important to note that the rates of clonal evolution in all three cohorts were within the range of what would be anticipated with immunosuppression alone.

The mechanism by which eltrombopag improves recovery of peripheral counts in aplastic anemia is unknown. The results are particularly surprising because endogenous levels of erythropoietin and other hematopoietic growth factors are markedly elevated in patients with aplastic anemia but are clearly unable to promote effective hematopoiesis. Furthermore, therapy with granulocyte colony-stimulating factor in aplastic anemia is usually ineffective. Dr. Townesley and colleagues speculate that improved bioavailability of the synthetic agonist may play a role in its efficacy.

In summary, the potential additional of growth agonist into the immunosuppressive amantamanum is a promising and exciting development. A large randomized placebo-controlled trial of eltrombopag (RACE. ClinicalTrials.gov number: NCT002099974) is underway and will hopefully replicate the results of Dr. Townesley and colleagues and shed more light on potential risks of relapse and clonal evolution.

Expanding Host Tumor Immunity, One Neoantigen at a Time


D r. Michael Khodadoust and colleagues use liquid chromatography and tandem mass spectrometry to perform direct proteomic analysis of 17 primary mantle cell lymphoma (MCL) samples and two MCL cell lines to identify major histocompatibility complex (MHC)-associated tumor neoantigens (Figure). Through immunoprecipitation, they isolated 24,000 unique MHC-I-associated peptides and 12,600 unique MHC-II-associated peptides. Combining this with whole-exome sequencing and direct sequencing of immunoglobulin (Ig) heavy- and light-chain–variable regions, the researchers found that of the approximately 13 to 175 nonsynonymous somatic mutations per patient, only mutated peptides derived from Ig genes were presented by MHC. For all others, only unmutated parts of the protein were presented. Interestingly, MHC presentation was polarized such that nearly all Ig-variable neoantigens were presented by MHC-II, whereas the majority of Ig-constant neoantigens were presented by MHC-I. Of the Ig-variable neoantigens, just about half of them were the result of somatic hypermutation or V-D-J recombination.

Using synthetic neoantigen peptide tetramers with affinity for HLA-DP*0401, they screened the blood of three patients with an HLA-DP*0401 allele for neoantigen-specific CD4⁺ T cells and found them in one of the three patients. These CD4⁺ T cells appeared to be memory T cells and lacked PD-1 expression, and were skewed towards a Th1/Th17 phenotype. T-cell receptor (TCR) sequencing identified two dominant T-cell clones, both of which were induced upon neoantigen peptide autologous vaccination. Ex vivo expanded neoantigen specific CD4⁺ T cells stimulated by autologous neoepitopes resulted in the production of IL-4 and granocyte and could mediate the killing of autologous lymphoma cells in an antigen-specific manner.

Non-Hodgkin lymphomas (NHLs) are susceptible to immune attack, as evidenced by the efficacy of allogeneic stem cell transplantation, but can evade host-immune recognition. Attempts to harness the host’s own immune system against the lymphoma with immune checkpoint blockade have been less successful than in Hodgkin lymphoma or certain solid tumors. Dr. Khodadoust and colleagues examined a panel of primary MCL samples and cell lines by direct proteomic antigen profiling to identify tumor neoantigens and their potential to elicit an antitumor immune attack. They demonstrate the feasibility of such an approach and identify genes in the Ig-variable region to be the major source of MHC-presented lymphoma neoantigens. Strikingly, these neoantigens are presented almost exclusively in the context of MHC class II, and the cognate neoantigen-specific CD4⁺ T cells are skewed to a Th2 phenotype. Why or how is unclear at this point, but it may lead to tumor immune evasion, or even tumor cell progression via support and activation by cognate helper T cells. To note this, these CD4⁺ T cells are able to mediate tumor cell killing in an antigen specific manner and autologous tumor vaccination results in induction of anti-tumor CD4⁺ T cell clones. This has therapeutic potential, especially in a group of diseases with relatively low mutation burden, which may be predicted to be less responsive to immune checkpoint blockade. Identification and ex vivo expansion of autologous neoantigen specific CD4⁺ T cells has the potential to be a new form of cell therapy for these patients.
HERDOO2 Score: How Long to Treat With Anticoagulation?


Patients with unprovoked venous thromboembolism (VTE) – deep vein thrombosis (DVT) and/or pulmonary embolism (PE) – have a 30 percent risk of recurrent VTE over five years if anticoagulation is stopped after the initial three to 12 months of acute VTE treatment. While men have a higher risk of recurrence than women (over 5 years, 36% vs. 24%, respectively), the risk in both is considered to be high enough that evidence-based guidelines recommend long-term anticoagulation for patients with unprovoked VTE, independent of sex, if they tolerate anticoagulation well and are not at high risk for bleeding.²³

In 2008, Dr. Marc A. Rodger and colleagues published the “HERDOO2 rule,” created from the results of a prospective multicenter cohort study of 646 participants with a first, unprovoked VTE treated with short-term anticoagulation.³ No predictors for a low-risk of recurrence were found in men, but in women, a low-risk group was identified (Table). They concluded that women with unprovoked VTE with a HERDOO2 score of 0 to 1 could discontinue anticoagulation, while women with a score of at least 2, and all men, should continue.

The work of Dr. Rodger and colleagues is a validation study of this HERDOO2 rule.²⁷ 2,785 subjects (44.3% female) with first unprovoked VTE (proximal DVT or PE) who had completed five to 12 months of anticoagulation were enrolled at 44 medical centers in seven countries. Index VTE events associated with minor or weak risk factors, such as travel, exogenous estrogens, minor immobilization or minor surgery were considered unprovoked and eligible for enrollment; patients with strong thrombophilies were excluded. Women with a HERDOO2 score of at least two and all men were advised to continue long-term anticoagulation; women with a score of zero were advised to discontinue anticoagulants. Patients were followed for one year and assessed for the primary outcome, recurrent major VTE (proximal DVT and segmental or greater PE). Not all patients followed the recommendation to discontinue or continue anticoagulation based on the decision rule’s risk assessment, allowing a risk of recurrence assessment in the various groups listed below.

In low-risk women who discontinued anticoagulation (n = 591), VTE recurrence per patient-year was 3.0 percent (95% CI, 1.8-4.8%). In high-risk women and men who discontinued anticoagulation (n = 323), it was 8.1 percent (95% CI, 5.2-11.9%). In high-risk women and men who continued anticoagulation (n = 1,802), it was 1.6 percent (95% CI, 1.1-2.3%), and in high-risk women who discontinued anticoagulation (n = 101), VTE recurrence per patient-year was 7.4 percent (95% CI, 3.0-15.2%).

This study validated the original HERDOO2 rule: Women with a first unprovoked VTE event and a HERDOO2 score of 0 to 1 have a low risk of recurrent VTE and can safely discontinue anticoagulants, whereas women with a score of at least 2, and all men, have a high risk of recurrence and should continue long-term anticoagulation. Noteworthy is that 51.3 percent of women with unprovoked VTE were classified as low risk, appropriate for discontinuation of anticoagulation. Thus, long-term anticoagulation, as recommended by existing guidelines, could be avoided in a substantial number of women if following HERDOO2.

We do not routinely use the HERDOO2 score for decision-making on length of anticoagulation in women with a history of unprovoked VTE, for five reasons. 1) There is equivocal evidence in the literature that the predictors identified in the HERDOO2 cohort are universal predictors in women with unprovoked VTE with a HERDOO2 score of 0 to 1 could discontinue anticoagulation, while women with a score of at least 2, and all men, should continue.


Redefining Induction Failure

Traditionally, remission status has been determined by bone marrow morphology at the end of the induction phase of treatment in acute lymphoblastic leukemia (ALL). Minimal residual disease (MRD) assessment has been routinely performed in conjunction with morphologic evaluation to determine the depth of remission, and MRD response is the most powerful prognostic determinant. Although the vast majority of children achieve a remission (<5% blasts by morphology) with frontline induction therapy, not all patients experience a complete response. Notably, patients with discordantly low MRD (<0.1%) and high morphologic blasts (≥5%) showed improved outcome compared with those patients who had concordant MRD levels, which was confirmed in a meta-analysis. Thus the new definition doubles the number of induction failure patients, who are therefore candidates for alternative therapies.

The authors analyzed the relationship between morphologic response and molecular MRD at the EOI. While there was concordance between MRD and morphologic responses in the vast majority of cases, 61 patients with discordantly high MRD levels of at least 5% had a five-year EFS of 47% that was comparable to morphologic induction failure (5-year EFS, 50.7%). Discordantly high MRD in patients with morphologic remission was more common in children with T-cell ALL (8%) than B-lineage ALL (1.5%), p<0.001. Conversely, another very small group of six discordantly low MRD patients was identified with morphologic induction failure (M2) with MRD less than 0.01% and this group had a five-year EFS of 100%.

Approximately one third of the induction failure patients defined by both morphology and MRD levels of 5% or greater fell into the “B-other” cytogenetic group, with expanded testing for genetic fusions was performed. Notably, EB1F1-PDGFRB fusions, which have been successfully identified in approximately 10% of patients with induction failure, were detected in 10% of patients with discordantly high MRD levels. The authors concluded that incorporating MRD assessment into routine clinical practice will be important for helping to frame the discussion with patients and their families, especially given the evolving maturity of the data. Importantly, in the deferred arm, 21% of patients were not able to receive a salvage transplant due to relapse, and there were also an increased number of myeloma-related deaths.

The DETERMINATION trial (NCT01208662) is an on-going investigation in the United States that parallels the IFM study with the same trial design. The DETERMINATION trial is actively accruing patients, and the findings from this study will be an important complement to the IFM study. The main difference in the U.S. arm of the trial is the duration of maintenance lenalidomide. In the U.S. arm, patients were started on maintenance lenalidomide until relapse, whereas in the IFM study, maintenance was for one year only. Maintenance lenalidomide is increasingly being adopted as standard practice in the United States based on trials showing improvement in PFS, and in a meta-analysis, improvement in OS.

Results from DETERMINATION will provide greater clarity on how long to use maintenance lenalidomide and whether longer maintenance will narrow the gap in PFS between upfront and deferred transplant approaches. Additionally, the larger number of patients, when combined with the IFM study, may help identify subgroups who benefit more from upfront transplant. In the IFM study, there was no statistically significant improvement in PFS for patients with high-risk disease, but based on the International Myeloma Working Group (IMWG) response criteria, achieving MRD negative status resulted in improved disease control irrespective of treatment arm. This may help clarify if patients with aggressive disease may consider a deferred transplant approach. Overall, the results from the U.S. arm, combined with the IFM 2009 results, will provide valuable guidance on the place of autologous stem cell transplantation and help individualize treatment for newly diagnosed patients.


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Dr. Yee and Dr. Raja indicated no relevant conflicts of interest.

Is Uptfront Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma the Standard?

High-dose melphalan with autologous stem cell transplantation is an important consolidation strategy for treating multiple myeloma and is considered standard treatment in combination regimens such as lenalidomide, bortezomib, and dexamethasone (RVD) can achieve deep responses with minimal toxicity. Recently, the Intergroup Francophone du Myelome (IFM) reported the results of a large phase III trial, IFM 2009, that was designed to answer the question of when to undergo autologous stem cell transplantation: upfront as part of the initial treatment, versus at time of relapse.

In this trial, all patients (N=700) received standard induction with RVD for three cycles followed by stem cell collection. The patients were then randomized to upfront transplant with high-dose melphalan and autologous stem cell transplantation, followed by consolidation with two additional cycles of RVD. The other half went on to five additional cycles of RVD for a total of eight cycles. Following completion of initial treatment, both groups received maintenance lenalidomide for one year. The median progression free survival (PFS) was significantly longer in the upfront arm than in the deferred arm, 50 versus 33 months (p<0.001). Depth of response was also higher in patients who received intensive therapy initially, based on achieving complete response (58% vs. 48%), or having absence of minimal residual disease (92% vs. 85%; p<0.001). (Of note, MRD was measured by a flow cytometry assay with a sensitivity of 1 x 10^-5, which is less sensitive than current assays such as next-generation sequencing). Overall, patients who were MRD-negative had improved PFS and overall survival (OS) compared with MRD-positive patients (HR, 0.3 and 0.34, respectively). However, at four years, OS was similar, at 81 percent versus 82 percent between the MRD-negative and MRD-positive arms, respectively. As expected, there were more adverse events related to induction and gastrointestinal adverse effects in the upfront transplant arm. Also of interest were four cases of acute myelogenous leukemia in the upfront arm versus one case in the deferred arm.

The results from this study are key for helping to frame the discussion with patients and their families, especially given the evolving maturity of the data. Importantly, in the deferred arm, 21% of patients were not able to receive a salvage transplant due to relapse, and there were also an increased number of myeloma-related deaths.

The DETERMINATION trial (NCT01208662) is an ongoing investigation in the United States that parallels the IFM study with the same trial design. The DETERMINATION trial is actively accruing patients, and the findings from this study will be an important complement to the IFM study. The main difference in the U.S. arm of the trial is the duration of maintenance lenalidomide. In the U.S. arm, patients were started on maintenance lenalidomide until relapse, whereas in the IFM study, maintenance was for one year only. Maintenance lenalidomide is increasingly being adopted as standard practice in the United States based on trials showing improvement in PFS, and in a meta-analysis, improvement in OS.

Results from DETERMINATION will provide greater clarity on how long to use maintenance lenalidomide and whether longer maintenance will narrow the gap in PFS between upfront and deferred transplant approaches. Additionally, the larger number of patients, when combined with the IFM study, may help identify subgroups who benefit more from upfront transplant. In the IFM study, there was no statistically significant improvement in PFS for patients with high-risk disease, but based on the International Myeloma Working Group (IMWG) response criteria, achieving MRD negative status resulted in improved disease control irrespective of treatment arm. This may help clarify if patients with aggressive disease may consider a deferred transplant approach. Overall, the results from the U.S. arm, combined with the IFM 2009 results, will provide valuable guidance on the place of autologous stem cell transplantation and help individualize treatment for newly diagnosed patients.


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The Hematologist: ASH NEWS AND REPORTS
Cellular Heterogeneity Based on Microniches


Recent work from Dr. Alon Oyler-Yaniv and colleagues outlines research strategies for the future, and may help to explain some of this heterogeneity. The premise of their work is that cell-to-cell communication via cytokines in tissues is dependent on the ability of that cytokine to diffuse from the source, and on the number of cells consuming the cytokine. Therefore, in a tissue with a high number of cells that have a receptor for the cytokine (consumers), the relative distribution of a cytokine produced by a cell will be low, creating a small “cytokine niche” (Figure). In contrast, a tissue with a low number of consumers will have more distribution, creating a larger niche.

To test the effect of diffusion-consumption on cytokine responses, the authors chose to use a model of regulatory T cells (Treg) as the consumers, as they have high levels of the high-affinity IL-2 receptor a chain (IL-2Rα) bonded to the IL-2 receptor. Because normal tissue culture plates have cells at too low a density to be representative of solid tissue density and to allow the medium to uniformly mix, the authors fabricated their own 96-well plate that they named “the clusterwell plate.” This allowed cell suspensions to be loaded into the plate and then centrifuged to create densely packed cell cultures. Using this clusterwell plate, the authors created cell suspensions with various ratios of Tregs and of CD4 depleted splenocytes, which do not respond to IL-2 and are thus “ inert cells” in their model system. This created scenarios where the total number of cells was the same, but the number of consumers was altered. To measure the effects of diffusion-consumption, the authors intracellularly stained for pSTAT5, which is immediately downstream of the IL-2 receptor. The authors demonstrate that as the density of consumers decreased, a larger fraction of the CD4+ IL-2Rα cells were exposed to IL-2 and were positively stained for pSTAT5. In contrast, as the consumer density increased, pSTAT5 staining decreased. In fact, labeled cells at the bottom of the well were unable to respond to IL-2 when consumer density was higher, demonstrating a restricted cytokine distribution in these cultures.

To visualize these microniches created by diffusion-consumption of IL-2, the authors developed an imaging assay they called PlaneView imaging. The authors mixed either to create an imaging assay they called PlaneView imaging. The authors mixed either

Typical process of gene therapy for hematopoietic disorders. Hematopoietic stem and progenitor cells (HSPCs) can be modified directly, as is the case for currently used therapies. The genetically modified HSPCs are then transplanted back into the patient. When HSPCs are modified directly, modification may not occur in every cell. Goodman MA et al, Ther Adv Hematol. 2015;6:302-315; copyright © 2016 by SAGE Publications. Reprinted by Permission of SAGE Publications, Ltd.

Cautiously Optimistic About Gene Therapy in Sickle Cell Disease: A New Arrow in the Quiver for Cure


Although recently, two major barriers limited cure for individuals with sickle cell disease in the United States: 1) the availability of related donors for bone marrow transplantation in sickle cell anemia; and 2) second, myeloablative conditioning regimens had typically been too toxic for adults. Over the past 10 years, however, breakthroughs have been made in addressing these intrinsic challenges, making cure a realistic outcome in an increasing number of children and adults with SCD. The first strategy is nonmyeloablative HSCT; it has recently been successfully applied in adults with SCD, with HLA-mismatched siblings. To increase the pool of donors, the most promising experimental strategy is the use of hematopoietic transplantation with posttransplant cyclophosphamide—a nonmyeloablative strategy—with greater than 90 percent donor availability. Gene therapy is now a second strategy to increase the donor pool, at least in children with SCD.

Dr. Jean-Antoine Ribeil and colleagues should be congratulated on performing the first ever successful gene therapy trial in SCD. The technical, scientific, and research governance barriers were significant, and the authors clearly addressed each one successfully. Equally laudable is the bravery of the patient and the participant’s family. The family’s altruism and trust in both their clinical and research teams should not be taken lightly. The gene therapy was designed using the LentilGlobin BB305 (Bluebird Bio) vector, which encodes for the human hemoglobin B genetic variant. Briefly, bone marrow harvest was obtained twice, and CD34+ (stem) cells were transduced with the LentilGlobin BB305 vector. Next, a myeloablative dose of busulfan with area under the curve 13.36 μmol/l was administered, and after a two-day washout period, the transduced CD34+ (5.6 x 10^6 CD34+ cells/kg) were infused. Following completion of the procedure, the participant did not report any vaso-occlusive pain episodes, and the level of donor globin production was approximately 50 percent.

Why the optimism? As a proof of principle, gene therapy for SCD is a therapeutic paradigm shift. Theoretically, donor availability is no longer an obstacle for children and adults with SCD. With the rapid pace of transplant biology research, conditioning regimens are expected to evolve from myeloablative to nonmyeloablative approaches. Until such advances, gene therapy will most likely be restricted to children rather than adults with SCD who may not tolerate the current high dose of busulfan.

Why the caution? Children with SCD living in low- and middle-income countries are not likely to have the benefits without the outweigh the unknown late potential adverse effects of busulfan in this population.
“And Then There Were 10”: Dendritic Cells and Monocytes Undergo a Reclassification


Taxonomy is a science that struggles to be fashionable. The great evolutionary biologist Steven Jay Gould commented that “Taxonomy is often regarded as the dullest of subjects, fit only for mindless ordering and sometimes denigrated as mere ‘stamp collecting.’” Yet, medicine needs order, and who could deny that the classic chart of “blood cell differentiation” beloved of scuffed laboratory walls, is imprinted onto the hippocampal map of all hematologists?

Classification systems reflect current technology, and it is no surprise to witness the inexorable dominance of molecular biology. In this remarkable article, Dr. Alexandra-Chloe Villani and colleagues at the Broad Institute deliver a radical revision of the classification of dendritic cells and monocytes.

The breathtaking capabilities of contemporary molecular biology lie at the heart of the analysis. In particular, the work focuses on the use of RNA-Seq, a procedure in which all of the mRNA sequences inside a cell are sequenced such that a complete map of the transcriptional activity can be generated. This technology is the mRNA equivalent of “next generation DNA sequencing” and is rapidly replacing microarray analysis. Perhaps even more remarkable is that this work was done on single cells. This combination of detailed transcriptional assessment and single-cell analysis offers remarkable possibilities for future biological insights. Of the 30,000 genes available within our DNA, around 5,000 are expressed at any time in a single cell, and RNA-Seq normally sequences around 1 million reads such that the technology can discover not only which genes are being expressed but also how many mRNA transcripts are present in the cell.

Dendritic cells (DCs) are relative youngsters within hematopoiesis, characterized by Dr. Ralph Steinman in 1973, and broadly classified into conventional DCs (cDCs), which express CD11c, and CD123+ plasmacytoid DCs (pDCs). In this data-rich but wonderfully accessible article, the authors undertook RNA-Seq on 2,400 single DCs (defined as HLA-DR+ lineages) and monocytes (CD14+ lineages) from a single individual. Sequence data were analyzed through a statistical approach called principal component analysis (PCA), which categorized dendritic cells into six major subgroups, while monocytes fell into four subtypes. Surface markers were then used to confirm that the cells retained the original RNA profile, and show that the pattern was common in 10 different subjects.

Several novel findings emerge from the reclassification of dendritic cells into six subtypes, termed DC1 to DC6. DC11c conventional DCs can be subdivided into those that are CD14+ or CD1C+, or indeed lack both of these molecules. In the new classification, the CD141+ subset becomes DC1 and is renamed CLEC9A+ DC on the basis that CLEC9A is a perfect discriminative marker. The CD1C+ subset is split into two groups, with differential MHC class II or monocyte gene expression (termed DC2 and DC3), while the DC4 group represents the CD1C and CD141 “double negative” group. DC6 is a completely new subset, representing 2 to 3 percent of DCs, and has been termed “ASC DC” on the basis of expression of AXL and SIGLEC genes. Finally, DC6 represents the original DC pDC subset.

Also of note was the finding of a small population of cDC progenitor cells, representing one in 5,000 of the DC population, with a CD100/CD44+ developmental phenotype. Morphology plays a role here and shows these cells to possess a high nuclear-to-cyttoplasmic ratio with circular or indented nuclei.

The team went on to study monocytes, defined as CD14+ lineages, and delineated four subtypes – two major subgroups defined by CD14+ and CD16 expression, and a further two, one with cytotoxic genes and one with an unknown function.

Several practical lessons are readily apparent from this classification. Functionally, the DC1 through DC6 subgroups are capable of staunching strong T cell responses, whereas DC6 operates primarily for interferon production. The functional activity of a progenitor pool will, of course, depend for features such as phenotype and function, and assesses cells in their resting state, with or without considering factors such as inflammation. Nevertheless, this report represents a considerable advance in our understanding of these important innate immune subunits. We can now expect this approach to be used for cell subsets within the hematologic landscape. That hippocampal map of the cell is going to get a lot more complicated.

The AYA population is a unique, high-risk group of patients facing malignant diseases at an age where their vulnerability to independence is. It is a time at which they can emotionally comprehend the burden of their disease, yet may not be as extensively socially, financially, and emotionally supported as their adult counterparts, and may not have the comparable support structure as younger patients. Although we should be proud of the progress that has taken place in the past decades, we cannot lose momentum — we need to build the strong and sustainable foundation for treatment that our AYA patients deserve.

Dr. Isenalumhe indicated no relevant conflicts of interest.

21. Weiss AR, Nichols CR, Freyer DR. Enhancing adolescent and young adult-focused hematology/oncology programs. The AYA committee began this process by comprehending the burden of their disease, yet may no be as extensively socially, financially, and emotionally supported as their adult counterparts, and may not have the comparable support structure as younger patients. Although we should be proud of the progress that has taken place in the past decades, we cannot lose momentum — we need to build the strong and sustainable foundation for treatment that our AYA patients deserve.

The Hematologist: ASH NEWS AND REPORTS
NIDDK Announcement: Resources and Funding Available for Research in Nonmalignant Hematology

TERRY ROGERS BISHOP, PHD, ON BEHALF OF THE NIDDK CCEH CONSORTIUM

Program Director, Division of Kidney, Urologic, and Hematologic Diseases; National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health; Bethesda, MD

The Hematologist: Ash News and Reports

The Division of Kidney, Urologic, and Hematologic Diseases (KUD) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a consortium of Cooperative Centers of Excellence in Hematology (CCEH). Each center is composed of three to four biomedical research core facilities providing state-of-the-art cellular and molecular biology tools or reagents and expertise. They each award pilot and feasibility projects as well as providing structured enrichment programs with visiting scholars and institutional presentations.

The NIDDK-supported consortium seeks to build and provide research infrastructure in the field of nonmalignant hematology. This activity helps to achieve the NIDDK director’s vision of maintaining a vigorous investigator-initiated research portfolio; preserving a stable pool of talented new investigators; fostering exceptional research training and mentoring opportunities; and ensuring knowledge dissemination through outreach and communications. The consortium accomplishes its mission primarily by sharing resources of the CCEH consortium and fertilizing collaborations across disciplines.


This year (fiscal year 2017) the consortium piloted a Partner Pilot and Feasibility (PPF) program to initiate collaborations by funding projects that use cores located at two different centers. In the fall of 2017, the PPF program will begin to accept applications from investigators in U.S.-based institutions to partner with one of the center’s core facilities. These PPF projects need to include plans for collaboration and not simply describe use of the core facilities. Interested applicants are strongly encouraged to contact the core director of the facility prior to submission of the application.

The consortium consists of 17 core facilities that provide:

- CD34 purified primary human hematopoietic stem/progenitor cells, granulocyte colony-stimulating factor mobilized and nonmobilized apheresis collections
- Xenotransplantation studies (including highly engineered humanized mice and large animal models)
- High-resolution microscopy (with cytoskeleton and hematopathology expertise)
- Time-lapse microscopy
- Human induced pluripotent stem cells generation
- Multiple genome editing procedures, predominantly, CRISPR/Cas-9
- Assistance with retroviral/lentiviral design and production
- Assistance with hematopoiesis assays (e.g., murine bone marrow collection, fluorescence-activated cell sorting, colony-forming units)
- CRISPR libraries
- Zebrafish and other model organisms for the study of human hematologic diseases
- Metabolomic profiles on large and small numbers of cells
- Heme and iron quantitative assays
- Angiogenic assays, especially during hematopoietic development in the fetal liver
- Flow cytometry assays.

The table below provides contact information for the currently funded NIDDK CCEHs.

For more information, access each center’s website. The charge for each service is available by contacting the center directly. Additionally, each center is seeking collaborations for new pilot and feasibility projects that will grow into successful NIDDK R01 awards.

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**Reverse Kostmann Disease**

HAX1

**Volume 1, Issue 14**

**Blood Advances**

**13**
Are We Recruiting an Army for Magneto? Optimizing Iron Utilization in Hemodialysis

STUDY TITLE: Proactive IV Iron Therapy for Hemodialysis Patients (PIVOTAL)

CLINICALTRIALS.GOV IDENTIFIER: None (this is a European trial)


SPONSOR: King's College Hospital NHS Foundation Trust

STUDY DESIGN: Multicenter, prospective, open-label, randomized controlled trial

TARGET ENROLLMENT: 2,080

PARTICIPATING CENTERS: 50 clinics in the United Kingdom

ACCRUAL GOAL: 2,080

STUDY DESIGN: PIVOTAL is a multicenter, prospective, open-label, randomized controlled trial investigating the effects of two different doses of intravenous (IV) iron in patients with chronic kidney disease on hemodialysis. The primary study endpoint is to compare the effect of a proactive high-dose IV iron regimen with a reactive low-dose IV iron regimen on all-cause mortality and the incidence of nonfatal cardiovascular events (myocardial infarction, stroke, and hospitalization for heart failure) in patients on hemodialysis. Secondary endpoints include the comparison of the two regimens on erythropoiesis-stimulating agent (ESA) dose requirements, red blood cell transfusion requirements, complications of hemodialysis treatment, and patient quality of life. Safety concerns of IV iron will be analyzed by incidence of vascular access thrombosis, hospitalization, and other adverse events. Researchers will recruit and randomly assign 2,080 hemodialysis patients from 50 clinics to one of two treatment arms. Patients assigned to the proactive arm will receive 400 mg/month IV iron sucrose, unless their ferritin is greater than 700 µg/L and transferrin saturation is greater than 20% (the lower limit of normal is 20%). Ferritin, and transferrin saturation in the era of erythropoiesis-stimulating agent (ESA) dose requirements, red blood cell transfusion requirements, complications of hemodialysis treatment, and patient quality of life. Safety concerns of IV iron will be analyzed by incidence of vascular access thrombosis, hospitalization, and other adverse events. Researchers will recruit and randomly assign 2,080 hemodialysis patients from 50 clinics to one of two treatment arms. Patients assigned to the proactive arm will receive 400 mg/month IV iron sucrose, unless their ferritin is greater than 700 µg/L and transferrin saturation (TSAT) is greater than 40% in patients assigned to the reactive arm will receive 700 µg/L IV iron sucrose, unless their ferritin is less than 200 µg/L and TSAT is less than 20%. Eligible patients are at least 18 years old and newly established (<12 months duration) on hemodialysis for end-stage renal failure receiving an ESA for anemia, and with a ferritin level less than 400 µg/L and TSAT lower than 30%.

Can Chemoinmunotherapy Be Bettered As Front-Line Therapy for CLL in Fit Patients?

STUDY TITLE: A Phase III Multicenter, Randomized, Prospective, Open-Label Trial of Standard Chemoinmunotherapy (FCRBV) Versus Rituximab Plus Venetoclax (RVe) versus Obinutuzumab (GA101) Plus Venetoclax (GVe) versus Obinutuzumab Plus Ibrutinib (RVe) versus Obinutuzumab (GA101) Plus Ibrutinib (GVe)

CLINICALTRIALS.GOV IDENTIFIER: NCT02956051

SPONSOR: German CLL Study Group

COLLABORATING STUDY GROUPS: Nordic CLL Group, HOVON and SAKK

ACCRUAL GOAL: 920 eligible patients

PARTICIPATING CENTERS: 160 centers across Germany, Austria, Switzerland, The Netherlands, Belgium, Denmark, Sweden, Norway, and Finland

STUDY DESIGN: This is a multi-arm phase III, randomized, open-label clinical trial that compares chemoinmunotherapy with three combinations of non-DNA damaging drugs as first-line therapy for fit patients. Standard chemoinmunotherapy is fludarabine, cyclophosphamide, and rituximab (FCR) for patients 65 years or younger, and bendamustine-rituximab (BR) for patients older than 65 years. Two of the experimental arms contain a combination of the BCL2 inhibitor, venetoclax, with an anti-CD20 antibody (either rituximab or obinutuzumab); the third also includes the BTK inhibitor,ibrutinib with obinutuzumab or venetoclax. The co-primary endpoints are peripheral blood (PB) minimal residual disease (MRD) negativity at 15 months and progression-free survival (PFS), each will be tested independently, enabling the stopping of an experimental arm if either endpoint is significantly different in a favorable direction. The primary comparison for MRD negativity is between the chemoinmunotherapy and the obinutuzumab-venetoclax (GVe) arms. The primary comparison for PFS is between the chemoinmunotherapy and obinutuzumab-ibrutinib-venetoclax (GVe) arms. The secondary outcomes are multiple and include complete response rates, duration of response, overall survival, safety, and quality-of-life. Efficacy outcomes may be compared among other arms in a predefined hierarchical sequence.

RATIONALE: The chemoinmunotherapy combination FCR was first reported in 2005 and was confirmed as the gold-standard front-line therapy for fit patients in 2010. The alternative BR regimen is less effective but is better tolerated and is a standard for older fit patients. Both produce significant acute toxicity and carry risks of late complications such as myelodysplastic syndromes or acute myeloid leukemia, and yet, for most patients, the treatment is not curative. Therefore, more effective therapies with less toxicity are needed. New targeted agents avoid some of the toxicities associated with DNA damage, show efficacy as single agents, and preliminary efficacy and tolerability in combination.
The trial’s complex design combines pragmatism with sophistication, reflecting the tension between the large sample sizes needed to compare multiple regimens for multiple endpoints and the imperative to accrue rapidly and deliver answers in the shortest timeframes. It complements the first randomized study of a non-DMN-damaging regimen (ibrutinib-rituximab) versus chemoimmunotherapy (FCR) in fit patients 70 years of age or younger. The National Cancer Institute-sponsored U.S. intergroup study (NCT02048813) led by Dr. Tait Shanafelt and highlighted in the May/June 2015 issue of The Hematologist, completed accrual in June 2016, and the first interim analysis for its primary endpoint of PFS will be next year, two years after the last accrual.

Once we have the results of the primary analyses for both these trials, physicians and patients will know whether chemoimmunotherapy can be bettered as front-line therapy for CLL without TP53 dysfunction in fit patients. Of course, even if the trials are positive, important questions are likely to remain incompletely answered. For example, which non-DMN damaging regimen is best? What are the optimal durations of use for individual targeted therapy elements (time-limited, until MRD negativity is achieved, or indefinite)? Do the trial outcomes equally favor therapy elements (time-limited, until MRD negativity is achieved, or indefinite)?

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Compliance with ibrutinib-rituximab (GMR) during acute lymphoblastic leukemia maintenance therapy is critical for sustained remission. Dr. Wendy Landier and colleagues show that self-reporting markedly overestimates compliance, highlighting the need for better monitoring methods to improve compliance and outcomes.


Compliance with ibrutinib-rituximab (GMR) during acute lymphoblastic leukemia maintenance therapy is critical for sustained remission. Dr. Wendy Landier and colleagues show that self-reporting markedly overestimates compliance, highlighting the need for better monitoring methods to improve compliance and outcomes.


Dr. Katarina Riesner and colleagues investigate the role of angioinvasion in graft-versus-host disease (GvHD) and show that, rather than occurring as a response to infiltrating leukocytes, angioinvasion occurs very early after transplantation and is involved in the initiation of GvHD.


Dr. Prashant Hiwarkar and colleagues present encouraging data suggesting that brincidofovir provides excellent activity and safety in controlling adenoviremia during the early lymphopenic phase after hematopoietic stem cell transplantation.


May 11, 2017


Dr. Kirsten Fischer and colleagues present efficacy and safety data from a preliminary study of first-line venetoclax and obinutuzumab in chronic lymphocytic leukemia patients with comorbidities.

May 18, 2017


Dr. Lenka Hovorkova and colleagues report that discordant results of DNA-based minimal residual disease monitoring of BCR-ABL1 and immunoglobulin/T-cell receptor gene rearrangements suggest an unexpectedly high percentage of childhood acute lymphoblastic leukemias may in fact be chronic myeloid leukemias in lymphoid blast crisis.

Blood Strengthens Its Position As the Top Journal in Hematology

The newly released 2016 Journal Citation Reports (Clarivate Analytics, 2017) contains excellent news for Blood:

• Impact Factor increased from 11.847 to 13.164!
• With 161,962 total citations generated in 2016, Blood is the most-cited journal in hematology, #19 out of the 12,085 journals
• 0.31660ct Index Factors score ranks Blood #1 in Hematology, #23 out of all journals

The newly released publication metrics in terms of impact factor, number of citations, and Eigenfactor mark the significance of the Blood journal for hematology and beyond — Editor-in-Chief Bob Löwenberg, MD, PhD

The major complication of thrombolytic therapy with tissue plasminogen activator (tPA) in the setting of stroke is hemorrhagic conversion. Using a mouse model, Dr. Fabrizio Simão and colleagues demonstrate that hemorrhagic complications are mediated by tPA-induced upregulation of plasma kalikrein, inhibition of which increases the effectiveness of tPA and reduces hemorrhagic complications.

April 27, 2017


In this plenary paper, Dr. Tetsuji Yoshizato and colleagues offer a detailed genomic analysis of a substantial cohort of 797 patients with myelodysplastic syndrome and secondary acute myeloid leukemia who received unrelated stem cell transplants, and identify unique predictors of outcome.


Dr. Timothy M. Cox and colleagues report on a cohort of more than 150 adults with type 1 (non-neuronopathic) Gaucher disease who remained clinically stable after switching from recombinant human glucose-6-phosphatase deficiency replacement therapy to eliglustat tartrate, an oral inhibitor of glucocerebrosidase synthase (a substrate reduction therapy).

May 4, 2017


Dr. Bethany L. Walton and colleagues infused red cells into normal mice to demonstrate that elevated hematocrit is an independent contributor to arterial thrombosis, as it increases the frequency and duration of platelet interactions with the growing thrombus.

May 11, 2017


Dr. Kirsten Fischer and colleagues present efficacy and safety data from a preliminary study of first-line venetoclax and obinutuzumab in chronic lymphocytic leukemia patients with comorbidities.

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Not All Neutrophils Are Created Equal

NABEEL R. YASEEN, MD, PhD
Professor, Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, IL

A peripheral blood smear review was requested on a 58-year-old man with a history of plasma cell myeloma. Representative images from the blood smear are shown below.

Based on the neutrophil morphology, this patient was likely treated with:

A. Bortezomib, lenalidomide, dexamethasone
B. Carfilzomib, lenalidomide, dexamethasone
C. Autologous stem cell transplantation
D. Allogeneic stem cell transplantation

For the solution to the quiz, visit The Hematologist online, www.hematology.org/Thehematologist/Images.

Dr. Yaseen indicated no relevant conflicts of interest.

Put your fellow readers to the test, and send us your Image Challenge submissions! Email case descriptions and image files to the Managing Editor at jllorens@hematology.org.

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