NIH LOOKS FOR BEST PRACTICES IN PROMOTING SUSTAINED CAREER SUCCESS FOR WOMEN IN BIOMEDICAL RESEARCH

BARBARA M. ALVING, MD

Dr. Alving is Director of the National Center for Research Resources at NIH.

A SH members are at the forefront of addressing the challenge to ensure opportunities for sustained career success for women entering biomedical research fields. At a recent NIH conference titled “Women in Biomedical Careers: Best Practices for Sustaining Career Success,” Nancy Andrews, MD, PhD, the Dean at Duke University School of Medicine, not only described the reasons why women are leaving academic medicine after beginning promising careers as assistant professors, but also stressed the urgency of ensuring that an extremely valuable and robust talent pool is maintained and cultivated.

In addition, Timothy Ley, MD, Professor of Medicine at the Washington University School of Medicine, provided data to show that women are as successful as men in obtaining research grants, but are less likely to continue to seek renewed funding. He described the current academic culture as “paternalist, developed by men for men.”

Charles S. Abrams, MD

Dr. Abrams indicated no relevant conflicts of interest.

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Nancy Andrews, MD, PhD, the Dean at Duke University School of Medicine, provided the keynote address, “Progress and Promise: Women in Academic Medicine.” Photo: Michael Spencer, NIH Photographer.

Dr. Nancy Andrews, ASH member and Dean of Duke University School of Medicine, provided the keynote address, “Progress and Promise: Women in Academic Medicine.” Photo: Michael Spencer, NIH Photographer.

Computed Tomographic Pulmonary Angiography – Too Good to Be True?


This study by Anderson and colleagues convincingly demonstrates that CTPA is at least as effective as V/Q scans at diagnosing pulmonary embolisms. In fact, the incidence of detected pulmonary embolisms was 30 percent higher in the group randomized to be analyzed by CTPA – a statistically significant difference. Some patients who had negative V/Q scans were subsequently diagnosed as having a pulmonary embolism once they had a CTPA; this suggests that CTPA might be an even more sensitive diagnostic test than V/Q scans.

These findings raise the interesting question about whether our technology is getting too good. Is CTPA capable of diagnosing emboli that are too small to be clinically significant? In the Anderson study, approximately 7 percent of patients diagnosed as having a thromboembolism by CTPA had emboli only in small subsegmental pulmonary vessels. Do we really know that these small clots require therapy? It should be noted that eight patients in the Anderson trial who had no obvious pulmonary embolism diagnosed by either CTPA or V/Q scans ultimately developed a pulmonary embolism (including one patient who died of a clot). This implies that these eight symptomatic patients probably had very small pulmonary emboli that were missed by their initial imaging study. We need to keep in mind that the true value of treating a pulmonary embolism with anticoagulation is to prevent the next one, rather than the thromboembolism that has already occurred. Using this rationale and the currently available data, we should be treating all pulmonary emboli regardless of their size, and perhaps even seeking out technologies that diagnose smaller and smaller clots.

For several decades, ventilation-perfusion (V/Q) scans have been used to detect pulmonary embolisms in patients. It is clear that a normal V/Q scan excludes the diagnosis of a pulmonary embolism, and a high probability V/Q scan essentially confirms the diagnosis. The challenge is what to do with patients who have a non-diagnostic (i.e., low to intermediate probability) V/Q scan.

Computed tomographic pulmonary angiography (CTPA) is an alternative test used to detect pulmonary embolisms that has several advantages over the V/Q scan. It provides a clear (yes or no) result, and it is also capable of detecting non-thrombotic causes for a patient’s symptoms. The downsides of CTPA are that this technique exposes the patient to more radiation than V/Q scans and that it may cause dye-induced nephrotoxicity. In spite of these tradeoffs, CTPA has largely replaced V/Q testing for pulmonary embolic disease. Although CTPA has become widely accepted as a standard test for this disease, there is controversy over whether small-vessel disease can be imaged as well by CTPA as by V/Q scans.

In this single-blinded, noninferiority, multicenter clinical trial, 701 patients were randomized to undergo CTPA and 716 were randomized to V/Q scanning. The results showed that 19.2 percent of the CTPA group and 14.2 percent of the V/Q group were diagnosed with a pulmonary embolism and treated with anticoagulation. Of the patients who were not initially diagnosed with a pulmonary embolism, 0.4 percent of the patients in the CTPA group and 1.0 percent of the patients in the V/Q scan were subsequently diagnosed to have thromboembolic disease.

Charles S. Abrams, MD

Dr. Abrams indicated no relevant conflicts of interest.

The Hematologist
The Hematologist

PROMOTING SUSTAINED CAREER SUCCESS FOR WOMEN IN BIOMEDICAL RESEARCH

(Cont. from Page 1)

Speakers from other organizations, such as Ernst & Young and Deloitte & Touche, discussed their successful programs for ensuring continued advancement of talented women in the workplace. Both described aggressive efforts to recruit and retain women, such as training them for executive positions and providing flexible career paths and opportunities for telecommuting. Both organizations stated that they have been actively addressing the need to retain women in the workforce and enhance diversity for the past 15 years. As a result, in 2007, 33 percent of new partner/principal promotions at Ernst & Young were women.

Representatives from the academic health centers, one of whom was Andrew Schafer, MD, Chair of the Department of Medicine at Weill Cornell, current president of the Association of Professors of Medicine, and immediate past president of ASH, discussed how they were promoting sustained career success through providing or advocating for flexibility in the time for tenure to be achieved and promoting executive leadership programs and initiatives to enhance work/life balance.

The NIH, through its Working Group on Women in Biomedical Careers, co-chaired by Drs. Elias Zerhouni and Vivian Pinn, is developing policies that are in concert with those in universities.

What should professional societies do? Societies and organizations need to include diversity at all levels. The NIH will work with professional organizations and universities to track the career development of women in biomedical research/academic medicine and develop policies that provide family balance, extension of time in tenure track positions, and opportunities for executive training. The loss of talent from the biomedical research workforce is a national issue of the highest priority and must be addressed by the leaders at academic health centers, professional organizations, and the federal government working together. To review the agenda from the meeting and the speaker presentations, please see www.womensscience.nih.gov/bestpractices.

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ASH Recognized on Senate Floor for 50 Years of Hematologic Research and Advancement

On February 14, 2008, Senator Arlen Specter (R-PA) congratulated ASH on its 50th anniversary during a speech on the floor of the U.S. Senate. Below is the text of his speech as published in the Congressional Record.

Mr. President, I congratulate the American Society of Hematology — ASH — on its 50th anniversary and to pay tribute to the contributions they have made in preventing and eliminating blood-related diseases.

The Society has grown substantially from its 200 members at its inception in 1958, to over 15,000 members presently, and is recognized as the world’s premier organization in research promotion, clinical care, education, training, and advocacy in the field of hematology.

Society members consist of practitioners and researchers who have been able to translate federal research dollars into effective treatments for millions of people afflicted with diseases that were at one time untreatable and fatal. The blood and blood-related diseases studied and treated by hematologists include disorders such as leukemia and lymphoma, thrombosis, anemia and bleeding, and congenital disorders such as sickle cell anemia, hemophilia, and thalassemia. The advancements in remedies of these disorders are a direct result of the continuing efforts made by the ASH.

I sustained an episode with Hodgkin lymphoma cancer two years ago. That trauma, that illness, I think, could have been prevented had that war on cancer declared by President Nixon in 1970 been prosecuted with sufficient intensity. All of us know people who have been stricken by fatal diseases and many other maladies. It is my hope that other organizations will use the success of the ASH as an example in contributing to this nation’s desire for finding cures for the most fatal diseases.

As chairman, and now ranking member of the appropriations Subcommittee on Labor, Health and Human Services, I have been an ardent supporter of securing federal funds for the National Institutes of Health, the crown jewel of the federal government, maybe the only jewel of the federal government. Health is the country’s No. 1 capital asset, and the American Society of Hematology has contributed to its success.

Hematologists have been instrumental in pioneering the use of hydroxyurea in the treatment of sickle cell disease and have developed the first successful cure of childhood leukemia. Moreover, hematologists were responsible for the research that led to Gleevec, the first anticancer drug developed to target a molecular problem that causes chronic myelogenous leukemia.

The American Society of Hematology has played an important role in the unprecedented growth and advancement of hematology research. With so many great successes over the past 50 years, I am confident the next 50 years will bring ASH and its over 15,000 members even more accomplishments in treating and eliminating blood diseases.

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LETTERS TO THE EDITOR — SOLICITATION

The Hematologist welcomes letters of up to 200 words. These letters may be in response to editorials or on any subject of interest to our readers. Please include a postal address, e-mail address, and phone number. Publication will be based on editorial decisions regarding interest to readers and space availability. We may edit letters for reasons of space or clarity. The Hematologist reserves the right to publish your letter; unless it is labeled "not for publication."

Letters should be sent to:
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RE: “THE WASTELAND OF RELAPSED ADULT ALL”

To the Editor:

I have a few reservations with regard to Dr. Jerald Radich’s article “The Wasteland of Relapsed Adult ALL” (March/April 2006 issue).

1. The article incorrectly quoted the recently published paper by Goldstone, et al. In the original paper, autologous transplant has the least overall survival, not chemotherapy, as per Dr. Radich’s article.

2. One has to be careful interpreting the results of the MRC UKALL XII/ECOG E2993 as the paper did not include a multi-variant analysis for the high-risk group not benefitting from allogeneic bone marrow transplant. The high-risk group included patients who are older than 35 years, have leukocytosis (more than 100 k/L for B lineage and 30 k/L for T lineage), or are Philadelphia-chromosome-positive. The surprisingly high NRM, rather than RRM, hints at older age in the high-risk group rather than leukocytosis or Ph+ as the real reason behind these dismal findings.

Usama Gergis, MD
Assistant Professor of Medicine
Leukemia service
Weill Cornell Medical College

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COVER STORY
FDA ODAC RECOMMENDS APPROVAL OF ROMIPLOSTIM FOR ADULTS WITH ITP

On March 12, 2008, the FDA’s Oncology Drug Advisory Committee (ODAC) unanimously recommended approval of the first of a new class of treatments for ITP – romiplostim – developed by Amgen. These agents stimulate platelet production by mimicking the effect of thrombopoietin. There was no issue about efficacy; platelet counts are increased to safe levels even in patients who are refractory to many previous treatments, including splenectomy. However, there was concern about safety. In studies of ITP, several patients developed an increase of reticulin; this appeared to be reversible with discontinuation of romiplostim. Data were also presented from a preliminary, non-randomized study in patients with myelodysplasia. Several patients developed an increase of myeloblasts that also appeared to be reversible with discontinuation of romiplostim. Therefore, the FDA had recommended that romiplostim be approved with a strict risk-management assessment program that would restrict off-label use. The preliminary outline of the plan includes direct shipment of romiplostim to physicians for each patient, with monitoring of the patient’s course by a case manager. With current concerns that the FDA has not adequately supervised new drugs following approval, this type of restricted access may become more common.

– James George, MD

Dr. George attended this meeting as a consultant for Amgen and has also been an investigator for the clinical trials related to the development of romiplostim.

EHA-ASH INTERNATIONAL FELLOWSHIP AWARD LETTER-OF-INTENT DEADLINE

Don’t miss this exciting research support opportunity! The EHA-ASH award is a partnership between the European Hematology Association (EHA) and the American Society of Hematology (ASH) that gives hematologists in their fellowship or early in their careers the opportunity to establish new collaborations and experience research (both clinical and laboratory-based) in a different environment. The letter-of-intent deadline for the 2008 EHA-ASH International Fellowship Award is September 4. Please note that eligibility is not limited to fellows. To find out more about this program, please visit www.hematology.org/education/awards/ifa.cfm.
INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a consequence of clonal expansion of one or more hematopoietic stem cells with mutant PIGA (located on Xp22.1).1 The protein product of PIGA is a glycosyl transferase that is an obligate constituent of a complex multiprotein pathway required for synthesis of the glycosyl phosphatidylinositol (GPI) moiety that anchors some proteins to the cell surface. As a result of mutant PIGA, progeny of the affected stem cells are deficient in all GPI-anchored proteins (GPI-AP). Although more than 20 functionally diverse GPI-APs are expressed by hematopoietic cells, it is deficiency on RBCs of the two GPI-anchored complement regulatory proteins, CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis), that underlies the hemolytic anemia that is the clinical hallmark of PNH. RBCs lacking CD55 and CD59 undergo spontaneous intravascular hemolysis as a consequence of unregulated activation of the alternative pathway of complement.

THE PERIPHERAL BLOOD OF PATIENTS WITH PNH IS A MOSAIC OF NORMAL AND ABNORMAL CELLS

Although PNH is a clonal disease, it is not a malignant disease, and (for reasons that are unclear) the extent to which the PIGA mutant clone expands varies widely among patients. As an example, in some cases, >90% of nucleated peripheral blood cells may be derived from the mutant clone, while in others, <10% of the circulating cells may be GPI-AP deficient. Another remarkable feature of PNH is phenotypic mosaicism based on PIGA genotype that determines the degree of GPI-AP deficiency.3 PNH III cells are completely deficient in GPI-AP; PNH II cells are partially (~90%) deficient, and PNH I cells express GPI-APs at normal densities (these cells are progeny of residual normal stem cells). Phenotype varies among patients (see Figure 1). Some patients have only type I and type III cells (the most common phenotype), some have only phenotype III cells, whereas other patients have only type II, and type III (the second most common phenotype); and some patients have only type I and type II cells (the least common phenotype). Further, the contribution of each phenotype to the composition of the peripheral blood varies (see F.1). Phenotypic mosaicism is clinically relevant because PNH II cells are relatively resistant to spontaneous hemolysis, and patients with a high percentage of type II cells have a relatively benign clinical course (see F.1).

THE ANEMIA OF PNH IS COMPLEX

The anemia of PNH is complex for three reasons. First, the size of the PNH clone varies widely among patients (see F.1 & F.2). Patients with large PNH clones (see F.2, upper panel) have classic signs and symptoms of PNH (see Table) while patients with small clones (see F.2, lower panel) may have only biochemical evidence of hemolysis with minimal or no clinical manifestations (see Table). Second, PNH phenotype affects the rate of hemolysis, as PNH II cells are significantly more resistant to complement-mediated injury than PNH III RBCs (see F.1). Third, an element of bone marrow failure is present in all patients with PNH, although the degree of marrow dysfunction is variable. In some patients, PNH arises in the setting of aplastic anemia. In this case, marrow failure is the dominant cause of anemia. In other patients, evidence of marrow dysfunction may be subtle (e.g., an inappropriately low reticulocyte count) with the degree of anemia being determined primarily by the rate of hemolysis.

DIAGNOSIS

The primary clinical manifestations of PNH are hemolysis, thrombosis, and bone marrow failure (see Figure 1). Patients with large PNH clones (fatigue, lethargy, malaise, and anemia) dominate the history, but nocturnal hemoglobinuria is a presenting symptom in only about 25% of patients. Directed questioning frequently elicits a history of episodic dysphagia and odynophagia, abdominal pain, and male impotence. PNH should be suspected in patients with non-spherocytic, Coombs’-negative intravascular hemolytic reticulocytosis. Reticulocytosis reflects the response to hemolysis, although the reticuloocyte count may be lower than expected for the degree of anemia because of underlying bone marrow failure. Serum LDH concentration is almost always abnormally high in patients with clinically significant hemolysis and is therefore a valuable surrogate marker for determining and following the rate of intravascular hemolysis. Most patients are iron-deficient because of chronic hemoglobinuria and hemosiderinuria (even in the absence of gross hemoglobinuria). Venous thrombosis, often occurring at unusual sites (Budd-Chiari syndrome; mesenteric, dermal, or cerebral veins), may complicate PNH. Arterial thrombosis is less common. Varying degrees of leukopenia, thrombocytopenia, and relative reticulocytopenia reflect the extent of marrow insufficiency.

Once suspected, diagnosing PNH is straightforward as deficiency of GPI-APs on peripheral blood cells is readily demonstrated by flow cytometry (see F.2). Analysis of both RBCs and PMNs is warranted, as clone size will be underestimated if only RBCs are examined (see F.2). For accurate quantitation of GPI-AP expression on PMNs, samples should be analyzed with in 24 to 48 hours of collection, whereas the window for analysis of RBCs is two weeks if samples are properly stored. Analysis of GPI-AP expression on lymphocytes provides no additional useful clinical information. Using high-resolution techniques available in some laboratories, as few as 0.03% GPI-AP deficient RBCs and PMNs can be detected (see F.2, lower panel). High-resolution flow cytometry is most useful in analyzing samples from patients with aplastic anemia or refractory anemia/MDS who may have very small clones, as some studies suggest that the presence of a small PNH clone predicts both a favorable prognosis and a higher rate of response to immunosuppressive therapy. Bone marrow analysis is warranted to determine cellularity, morphology, and amount of involvement of other hematopoietic cells. Based on the results of laboratory studies, bone marrow analysis, and flow cytometry, patients can be placed into one of three categories based on the recommenda -

Table: Classification of PNH

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate of Intravascular Hemolysis</th>
<th>Bone Marrow Failure Syndrome</th>
<th>Flow Cytometry</th>
<th>Benefit from Eculizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Florid (macroscopic hemoglobinuria is frequent or persistent)</td>
<td>Moderate to severe</td>
<td>Large population (&gt;50%) of GPI-AP deficient PMNs</td>
<td>Yes</td>
</tr>
<tr>
<td>Subclinical</td>
<td>No clinical or biochemical evidence of intravascular hemolysis</td>
<td></td>
<td>Small (&lt;1%) population of GPI-AP deficient PMNs detected by high-resolution flow cytometry</td>
<td>No</td>
</tr>
</tbody>
</table>

**Based on recommendations of the Int’l PNH Interest Group**

Based on macroscopic hemoglobinuria, serum LDH concentration, and reticulocyte count:

- Aplastic anemia (blood smears show less than 1% reticulocytes)
- Karyotypic abnormalities are uncommon.
- Aplastic anemia and refractory anemia/MDS are the most common associated marrow failure syndromes.
- Analysis of PMNs is more informative than analysis of RBCs due to selective destruction GPI-AP deficient RBCs.

**§** Analysis of GPI-AP expression on bone marrow cells can be diagnostic of PNH. The presence of GPI-AP deficient PMNs may suggest a diagnosis of PNH.

**Based on the results of laboratory studies, bone marrow analysis, and flow cytometry, patients can be placed into one of three categories based on the recommenda -

MANAGEMENT

**Hemolysis.** The approval of eculizumab by the FDA has had a great impact on the management of PNH. Eculizumab is a humanized monoclonal antibody that blocks formation of the membrane attack complex (the cytolytic component of the complement system) by binding to complement C5.8 The drug is given as an intravenous infusion (on an every-other-week schedule after an initial five-week loading period), and it is a highly efficacious inhibitor of complement-mediated intravascular hemolysis. Treatment with eculizumab reduces transfusion requirements, improves quality of life, and stabilizes hemoglobin levels. However, the drug is very expensive, and treatment is often limited to patients with advanced disease. Eculizumab does not block the formation of the alternative pathway C3 convertase. By protecting RBCs against complement-mediated lysis, the percentage of PNH cells in the peripheral blood increases in patients receiving eculizumab, and this can be monitored using flow cytometry. Treatment with eculizumab reduces transfusion requirements, improves quality of life, and stabilizes hemoglobin levels. However, the drug is very expensive, and treatment is often limited to patients with advanced disease. Eculizumab does not block the formation of the alternative pathway C3 convertase. By protecting RBCs against complement-mediated lysis, the percentage of PNH cells in the peripheral blood increases in patients receiving eculizumab, and this can be monitored using flow cytometry. Treatment with eculizumab reduces transfusion requirements, improves quality of life, and stabilizes hemoglobin levels. However, the drug is very expensive, and treatment is often limited to patients with advanced disease. Eculizumab does not block the formation of the alternative pathway C3 convertase. By protecting RBCs against complement-mediated lysis, the percentage of PNH cells in the peripheral blood increases in patients receiving eculizumab, and this can be monitored using flow cytometry. Treatment with eculizumab reduces transfusion requirements, improves quality of life, and stabilizes hemoglobin levels.
appropriate candidates for treatment with eculizumab. Prior to recommending eculizumab therapy, PNH clone size (based on flow cytometric analysis of GPI-A expression on PMNs), rate of hemolysis (based on serum LDH concentration), and degree of bone marrow failure (based on blood counts, reticulocytosis, and bone marrow cellularity and morphology) should be determined. Patients who are likely to benefit most from treatment are those with large clones whose clinical manifestations are primarily a consequence of intravascular hemolysis (Classic PNH, see Table). Patients with relatively small clones whose primary clinical manifestations are a consequence of bone marrow failure (PNH in the setting of bone marrow failure from eculizumab). For those patients, treatment should focus on the process that underlies the bone marrow failure. Eculizumab has no role in the management of Subclinical PNH, and, in those cases, treatment should be aimed at the marrow failure process.

The use of steroids (glucocorticoids and androgens) in the management of PNH is controversial. Corticosteroids can be used to mitigate a hemolytic paroxysm, but long-term use is not recommended because of unacceptable toxicity. In my experience, hemolysis is ameliorated in about one-third of patients with Classic PNH treated with danazol, a generally well-tolerated synthetic androgen that does not cause an increase in production of GPI-AP deficient RBCs. Patients should be iron replete before initiating therapy with danazol, and liver function should be monitored regularly. General supportive measures include repletion of iron stores and folate supplementation. Red cell transfusion is safe and may be necessary for treatment of inadequately compensated anemia.

Thrombosis. The mechanism that accounts for the thrombotic risk in PNH is unknown, but thrombembolic complications (often involving unusual sites) are the leading cause of morbidity and mortality in PNH. The mechanism underlying bone marrow failure is the major risk factor for thrombosis in PNH. Whether treatment with eculizumab may obviate the need for prophylactic anticoagulation in the setting of bone marrow failure from eculizumab, the drug should be discontinued and prophylactic anticoagulation with a low-molecular-weight heparin initiated. Treatment with eculizumab may reduce the risk of thrombosis, and patients treated with eculizumab may not require warfarin prophylaxis. However, data are insufficient to support discontinuation of anticoagulation therapy in a patient who experiences a thrombembolic complication prior to initiating therapy with eculizumab. Thrombolytic therapy should be considered in a patient who develops Budd-Chiari syndrome acutely.

Bone marrow failure. Treatment of anemia that is primarily due to bone marrow failure should be aimed at the underlying disease (e.g., aplastic anemia, refractory anemia/MDS). If absolute or relative erythropoietin deficiency is felt to contribute to the anemia, replacement with the recombinant protein is warranted, but patients should be closely monitored as erythropoietin supplementation may exacerbate hemolysis by increasing production of GPI-AP deficient RBCs.

Bone marrow transplantation. Prior to the availability of eculizumab, the primary indications for transplant were recurrent, life-threatening thrombosis and uncontrollable hemolysis. The latter process can be eliminated by treatment with eculizumab, and the former process may also respond to inhibition of intravascular hemolysis. Nonetheless, transplant is the only curative therapy for PNH, and the availability of matched unrelated donors, less toxic conditioning regimens, reduction in transplant-related morbidity and mortality, and improvements in post-transplant supportive care make this option increasingly attractive. The decision to proceed with a transplant is complex, however, and requires input from the patient, an experienced hematologist, and a transplant specialist.

Pregnancy. There are both maternal and fetal risks when PNH occurs during pregnancy with the risk primarily related to thrombembolic complications. Untoward events can be prevented by high-risk obstetric care. Counseling female patients with PNH about pregnancy should take into account age, overall health, PNH clone size and phenotype, extent of hemolysis, degree of bone marrow failure (especially thrombocytopenia), previous thrombosis, and comorbid conditions. Despite the many concerns, successful outcomes appear to be the rule rather than the exception. But management is complicated and should involve the combined efforts of an experienced hematologist and an obstetrician specializing in high-risk pregnancy. Unless there is an absolute contraindication, anticoagulation should be initiated immediately prior to delivery. Heparin should be reinitiated post-delivery as soon as treatment is safe, and prophylaxis with warfarin is recommended for three months after parturition.

Eculizumab is not approved for use in patients who are pregnant. If a patient becomes pregnant while being treated with eculizumab, the drug should be discontinued and prophylactic anticoagulation with heparin should be initiated. Treatment with eculizumab can be restarted in the immediate postpartum period. Whether treatment with eculizumab obviates the need for prophylactic anticoagulation in the postpartum period if the patient has an antecedent history of thromboembolic complications is unknown. Lacking data to the contrary, prophylactic anticoagulation during the postpartum period is recommended for these patients.

SUMMARY

Eculizumab has changed the natural history and management of PNH. But PNH is not a binary disease, and not every patient who has a PNH clone is an appropriate candidate for treatment. In particular, patients with small PNH clones who have primary clinical manifestations of bone marrow failure are unlikely to benefit. Appropriate disease classification (see Table) based on clone size, underlying bone marrow pathology, and rate of hemolysis, along with an understanding of the pathophysiology of the anemia and the heterogeneous nature of the disease, are needed in order to make a rational decision about management.

REFERENCES

ASH GOVERNMENT AFFAIRS COMMITTEE HOSTS ANNUAL CAPITOL HILL DAY
MEMBERS ADVOCATE FOR NIH FUNDING
ROY SILVERSTEIN, MD
Dr. Silverstein is Chair of ASH’s Government Affairs Committee.

The Society’s Government Affairs Committee recently completed another successful Capitol Hill Day where members brought issues important to hematologists to the attention of more than 30 Representatives and Senators and their staff. Committee members came to Washington from around the nation to focus congressional attention on increasing funding for the National Institutes of Health (NIH) and halting the scheduled 2008 cut in Medicare reimbursement rates to physicians.

This year’s Capitol Hill Day coincided with one of the busiest times of the year for Congress — consideration of the annual budget resolution that establishes the annual spending blueprint for every federal department, agency, and program, including NIH. Given the tight budget situation and the President’s drastic proposal to provide no funding increase to the NIH, Committee members met with Representatives and Senators who serve on the Appropriations Committees and advocated for increased funding for biomedical research. Committee members also shared ASH recommendations for language that accompanies the funding bill to include support for hematology research at the NHLBI, the NCI, the NIDDK, the NIA, and the CDC.

Committee members described advances made possible through federally funded hematology research and shared concerns that another year of flat funding for the NIH will have a serious negative impact on research and training in hematology. Through the course of several years’ worth of Capitol Hill Days, many Committee members have established relationships with their Senators and Representatives, and their staffs. Many congressional offices look forward to these meetings each year and recognize ASH and its members as an authoritative voice on the need for increased support for biomedical research.

The highlight of this year’s Capitol Hill Day was meeting with Representatives Edward Markey (D-MA) and Jesse Jackson, Jr. (D-IL), to present them with the 2007 ASH Award for Public Service. Representatives Markey and Jackson were the only two members of the House to vote against legislation to reauthorize and restructure the NIH when the bill was overwhelmingly approved in September 2006 by a vote of 414 to 2. This legislation as originally drafted contained a number of flaws that could have been detrimental to future research at the NIH, most notably a proposed 5 percent ceiling in future annual increases for the NIH. Like Representatives Markey and Jackson, ASH was one of only a small number of research organizations that opposed this legislation. Ultimately, as a result of ASH’s significant advocacy efforts and the leadership of Representatives Markey and Jackson, the final legislation that was signed into law contained significant improvements to the original version.

Representatives Markey and Jackson met with the entire Government Affairs Committee. They voiced their strong support for the Society’s advocacy efforts and their sincere appreciation for being selected as the 2007 award co-recipients, and they vowed to continue their efforts in support of the NIH. Representative Markey, in particular, thanked the Committee for their efforts during Capitol Hill Day to gain congressional support for the effort he was leading in the House to increase fiscal year 2009 funding for the NIH.

Every ASH member can play an important role in the Society’s advocacy efforts. By participating in the ASH Grassroots Network and visiting the ASH Advocacy Center, you can also have your voice heard in the halls of Congress. For more information about ASH advocacy efforts and the ASH Grassroots Network, visit www.hematology.org/takeaction, or contact the ASH Policy & Practice Department at 202-776-0544.

ASH GOVERNMENT AFFAIRS COMMITTEE HOSTS ANNUAL CAPITOL HILL DAY
MEMBERS ADVOCATE FOR NIH FUNDING

HEADLINES FROM WASHINGTON

Legislation Introduced to Prevent Medicare Physician Payment Cuts

Sen. Debbie Stabenow (D-MI) introduced S.2785, the Save Medicare Access Act of 2008. The bill would avert the 10.6 percent cut scheduled to take effect July 1 and the additional cut of 5 percent or more scheduled in January. Payments would continue at their current rate through the remainder of 2008 and then would rise by 1.8 percent in 2009. ASH has endorsed the legislation and is working to have the legislation passed before July 1.

NHLBI Announces Realignment of Sickle Cell Disease Research Program

The National Heart, Lung, and Blood Institute (NHLBI) announced a comprehensive and innovative restructuring of its research program in sickle cell disease (SCD). NHLBI is working on expanding funding and reconfiguring current programs for basic and translational research, increasing opportunities for drug development via the NCI’s Rapid Access to Interventional Development (RAID), and developing evidence-based guidelines for all SCD patients. NHLBI is also developing a new Clinical Trials Research Network (CTRN), similar to NCI’s Children’s Oncology Group (COG), designed to open clinical trials to more patients and expand support of genomic research in SCD.

ASH submitted recommendations in response to NHLBI’s request for public information regarding the top scientific and clinical priorities in SCD. The Society is pleased to see many of its recommendations incorporated into the realignment, including recommendations to develop improved and new treatments, expand funding for all types of research, and create a new model for clinical trials. To view ASH’s recommendations, go to www.hematology.org/policy/statements/01092008.cfm, and to view NHLBI’s new plan, visit www.nihbli.nih.gov/meetings/workshops/Sickle-Cell-Announcement.htm.

New Medicare Demonstration Program Aims to Show Advantages of Electronic Health

Medicare is looking for 12 communities across the country that can bring together a broad cross-section of community leadership, leverage resources, and recruit small and medium-sized primary care physicians to design and implement a plan to demonstrate the advantages that electronic health records (EHR) can improve the quality of patient care.

As many as 1,200 physician practices nationwide could be eligible for incentive payments of up to $58,000 per physician — up to $290,000 per practice — over the five-year life of the demonstration. E-mail EHR_Demo_communityselctions@cms.hhs.gov for more information.

ASH Advocates for NIH Funding Increase in FY 2009

ASH and other organizations within the biomedical research community have joined forces to advocate for an increase of 6.6 percent for NIH in FY 2009.

In March, the House and Senate passed differing versions of the FY 2009 Budget Resolution, which sets forth a budget blueprint that each Appropriations subcommittee will use as a guideline in drafting their respective funding bills this year. The Senate-passed Budget Resolution includes funding to provide for a potential total increase for NIH of $3 billion (or approximately 10.3 percent) over President Bush’s proposed funding level.

As this issue of The Hematologist went to press, the outlook for the entire appropriations process remained unclear. The President has said that he will veto any appropriations bill that exceeds his request for discretionary spending. Meanwhile, House Appropriations Committee Chairman David Obey (D-WI) has publicly stated that unless the President is willing to negotiate on funding levels for programs such as NIH, Congress will simply wait to enact a final FY 2009 budget after a new president takes office in January 2009, more than a quarter of the way through the fiscal year.
CONGRESS SEeks ASH EXPERTISE FOR HEARINGS ON PERFORMANCE-ENHANCING DRUGS

Performance-enhancing drugs have been a central issue on Capitol Hill in recent months, with scandals in professional baseball leading to congressional investigations into the illegal use of both anabolic steroids and, more recently, human growth hormone (HGH). In the midst of all the controversy, another substance with supposed performance-enhancing properties began to interest Congress: vitamin B12. Most notably, pitcher Roger Clemens claimed that his trainer Brian McNamee injected him with B12, rather than with the more dangerous (and illegal) HGH.

For insight into the effects of medically inappropriate use of B12 and other therapeutic agents, the House Committee on Oversight and Government Reform contacted ASH. Several ASH members provided background on the issue for congressional staff, including the economic and medical impact of its inappropriate over-use nationwide, both among athletes and non-athletes. Dr. Ralph Carmel, a hematologist at New York Methodist Hospital, provided specific information on the taking of B12 by injection (as Mr. Clemens claims he did), including the specific method of delivery and potential side effects.

The Committee also invited Dr. Susan Shurin, noted hematologist and Deputy Director of the National Heart, Lung, and Blood Institute (NHLBI), to testify at a hearing on February 12. Dr. Shurin emphasized that giving B12 to healthy athletes is not medically sound, noting that, while the vitamin is indeed useful in treating B12 deficiencies that can lead to “pernicious anemia… [difficulty] with position sense, nerve damage, depression, memory loss, and dementia,” there is no evidence linking B12 to improved athletic performance in an otherwise healthy person. “Claims are made that vitamin B12 administration will improve energy levels, memory, concentration, and mood. All of these are true when persons deficient in vitamin B12 are treated; however, there is no evidence at all of those clinical benefits when the vitamin is given to persons who are not deficient,” Shurin said. She also told the Committee that, except in the case of specific medical conditions such as inflammatory bowel disease that would prevent gastrointestinal absorption of B12, there would be no reason to inject the vitamin rather than take it orally.

The congressional hearing concerning the use of B12 was part of a series of nationally televised hearings related to the use of performance-enhancing drugs by major league baseball players. As a result of these hearings, former NY Yankee Roger Clemens is under investigation for perjury and Members of Congress have concluded that there is a need for greater oversight of the way such agents reach the public.

FDA ADVISORY COMMITTEE RECOMMENDS CHANGES TO ESAs

Editor’s Note: Dr. Silver presented testimony to the FDA on behalf of ASH.

On March 13, the U.S. Food & Drug Administration’s (FDA) Oncologic Drugs Advisory Committee (ODAC) met to review the cumulative data on the risks of erythropoiesis-stimulating agents (ESAs) when administered to patients with cancer. The advisory committee recommended to continue the ESA indication for treatment of chemotherapy-induced anemia; however, the panel also recommended several changes to the safety labels on the drugs Aranesp, Epogen, Procrit, and Mircera. These changes will place significant restrictions on their use for patients with cancer.

By a vote of 13 to 1, ODAC recommended that ESAs continue to be marketed for use for treatment of chemotherapy-induced anemia in patients with cancer. While the panel rejected a proposal to modify the current indication to restrict use only to patients with small-cell lung cancer, it supported recommendations to amend the label and include statements that ESA usage is not indicated for patients receiving “potentially curative treatments,” patients with head and neck cancer, or patients with metastatic disease of the breast. The panel did not reach consensus on when to initiate ESA therapy. The panel also supported requiring implementation of an informed consent/patient agreement for the treatment of anemia in these patients, but the panel rejected a recommendation calling for the FDA to mandate a restricted distribution system for oncology patients receiving ESAs.

As this issue of The Hematologist was going to press, it was unclear what the impact of the ODAC meeting will be. ODAC’s recommendations are non-binding. The FDA will review the recommendations and make its own decision on how to revise the drug labeling. Specifically, it is not clear what ODAC’s recommendations would mean for treating patients with hematologic malignancies. For example, if adopted, does ODAC’s recommendation to exclude potentially curative treatments mean that ESAs could only be used for palliative care? Would limited-stage, low-grade lymphoma be considered potentially curable? Most significantly, perhaps, at this time it is unclear how the Centers for Medicare & Medicaid Services may interpret this and whether Medicare’s current coverage policy may be altered as a result. In addition, ASH will continue to work with local Medicare carriers to ensure their policies regarding coverage for patients with MDS are not adversely affected by ODAC’s recommendations.

I testified before the advocacy panel on behalf of ASH and the American Society of Clinical Oncology (ASCO) regarding the safety and appropriate use of ESAs. The testimony emphasized that pending the publication of more definitive and peer-reviewed data on safety signals in the target population of the ASH-ASCO guideline, our organizations do not see sufficient evidence of harm to support recommending complete cessation of the use of ESAs across all patients with malignancies. Further, I reminded the advisory committee that there is compelling evidence to support safe use of ESAs in anemic patients with low-risk myelodysplasia. The testimony also addressed the need to better inform patients about the risks and benefits of ESA therapy and that additional studies are necessary to address lingering safety questions.

ASH will continue to meet with the FDA and Congress about its concerns regarding the impact these potential restrictions could have on patients with hematologic diseases and will keep the membership apprised of all developments.

Dr. Silver consults for Gerson Lehrman Group, Lehman Brothers, and BlueCross BlueShield of MI.
id Mark McGwire use it or not? We all have our opinions, but we do know that his wife used it. The drug is human growth hormone. Human growth hormone (HGH) is known to improve muscle strength and has been claimed as an anti-aging agent, because it can increase lean body mass and bone mineral density, although there are limited data to support this claim. However, growth hormone is important in thymopoiesis. Administration of HGH or its proximal mediator, insulin-like growth factor-1 (IGF-1), can reverse thymic involution in aging mice and accelerate immune recovery in immune-compromised animals, including hematopoietic cell transplants (HCTs). HGH is produced by thymocytes, thymic epithelial cells, and mature lymphocytes. Under steady state, HGH and IGF-1 do little, but under periods of stress, they do have a beneficial effect.

There are accumulating data suggesting that following ablative HCT, especially in adults in the setting of T-cell depletion or cord blood transplantation, lack of adequate immune reconstitution is an important source of morbidity and mortality. We know that the thymus is the major site for the generation of new T cells and that functional recovery of the thymus is likely the single most important factor in allowing a patient to recover his or her adaptive immunity. Therefore, methods to improve and accelerate thymic function are an area of great interest and clinical need.

In this article, investigators performed a prospective, randomized study in 22 HIV-1–infected adult patients who were on highly active antiretroviral therapy (HAART). They received either daily subcutaneous injections of HGH for 12 months or were observed and then were crossed over to the other arm. This study confirmed the group’s previous observation that there was an increase in thymic mass and moderate increased numbers of naïve CD4+ T cells. HGH use increased de novo T-cell production as measured by the T-cell receptor excision circles (TRECs) and also increased peripheral T-cell expansion. An increase in thymic mass was also documented by CT scans. It is not clear how long this increase was sustained after the completion of the study.

Can we apply this study to patients receiving an HCT? In many ways, patients receiving an HCT can also have a significant impairment in T-cell numbers and function. CD4+ T cells may take several years to normalize, and peripheral homeostatic proliferation of a limited T-cell repertoire may result in significant skewing of these T cells as demonstrated by TCR spectratyping results. The overall result may be a limited ability of T cells to respond to new challenges. This restricted response can also be seen in aging individuals’ response to viruses, where fewer naïve T cells result in a lower frequency of responder cells.

Performance-Enhancing Drugs


Would HGH or IGF-1 work in HCT? Based on the results reported above, the expectation is that this approach could have a beneficial effect on immune recovery with certain caveats. For example, the effects of prior radiation to the chest or total body irradiation will destroy thymic epithelial cells. Graft-versus-host disease (GVHD) is another complication that has a direct effect on the thymus. In these two circumstances, there may not be sufficient residual thymic tissue for HGH to have an impact in thymopoiesis, although it could still expand the peripheral T cells. There is also the concern for increasing the risk of GVHD and other known side effects of this agent. Understanding how T cells are increased could identify specific patients that could benefit from HGH. Ultimately, we need a clinical trial with HGH transplantation to enhance the immune system’s performance.
C

honic lymphocytic leukemia (CLL) is associated with profound suppression of the humoral, innate, and cellular components of the immune system. CLL cells are transformed B lymphocytes but lack classic co-stimulatory molecules typically present on normal B cells. The lack of co-stimulatory molecules on CLL cells, along with the production of soluble cytokines that dampen T-cell function, at least in part explain why autologous or even allogeneic T cells do not promote cytolysis toward these “stealth-like” tumor cells. To address this issue, Kipps and colleagues developed a strategy in which an adenovirus encoding the co-stimulatory molecule CD154 is used to infect CLL cells in vivo. The enhanced CD154 expression on CLL cells produces an activated B-cell phenotype that promotes T-cell activation. 1 This results in T-cell recognition and cytolysis of CLL tumor cells in vivo, even those that did not encounter the virus. After extensive preclinical work and regulatory hurdles due to the increased concern over gene therapy trials, this group initiated a phase I study employing this approach that showed promising early and delayed anti-tumor responses. 2 Additionally, broad evidence of immunologic activation of T cells was noted, together with enhanced sensitivity of CLL cells to activation-induced cell death mediated by p73. 3,4

As a follow-up to this study, Dr. Kipps’ laboratory has now identified that a subset of CLL patients treated with this therapy developed “self” monoclonal antibodies directed at the tumor antigen ROR1A. Following identification of ROR1A as an autologous self antigen, the authors went on to demonstrate that this antigen is not expressed on normal B cells or other tissues in patients with CLL. Additionally, ROR1A appears to signal through WNT5a and NF-κB. Here the story becomes more complex, as CLL cells do not express WNT5a. However, WNT5a is expressed by accessory dendritic cells, which potentially provide stromal support to CLL tumor cells. Evidence for a stromal interaction of ROR1A and WNT5a is provided by demonstration that co-culture of CLL cells with a WNT5a-expressing cell line enhances survival, whereas addition of a ROR1A blocking antibody antagonizes survival. The relevant in vivo accessory cell remains to be identified, but this finding emphasizes the importance of the microenvironment in providing survival signals to leukemia cells. These results also provide a potential mechanism for the death of transformed B cells long after therapy and possibly explains the prolonged disease stabilization experienced by many patients following treatment with CD154 gene therapy. 5 Furthermore, this work constitutes one of the first demonstrations in CLL of a safe therapy to break immunologic tolerance against a “self tumor antigen.” 6 Without persistent bedside-to-laboratory translational research, this observation would have been lost.

Clinical investigation in the area of gene therapy is quite difficult, and before undertaking such an approach for phase II-III studies, it is clearly important to have a strong indication that this strategy could truly benefit patients long-term. The identification of induction of ROR1A antibodies in CLL patients receiving CD154 gene therapy as described in this paper provides such encouragement and shows that this line of clinical investigation warrants further pursuit. 7 A clinical trial using the human CD154 gene via a similar adenovirus vector has completed phase I investigation 8 and will move forward to phase II testing soon. The strategy of enhancing CD154 expression in CLL cells using gene therapy or another method has exciting potential for the treatment of CLL. Furthermore, the use of ROR1A-directed therapeutic antibodies against CLL cells represents an option that should be actively pursued based upon the data presented in this paper and others. 9 Most importantly, the paper by Kipps and colleagues highlights the great value of rigorous bedside-to-laboratory translational investigations of novel therapies. Such detailed correlative work that allows understanding of the mechanism of action of a new therapeutic agent should be included in virtually all clinical trials of targeted agents, so that expected (and more importantly, unexpected) findings, such as the induction of ROR1A antibodies noted in this report, can be discovered.

GVHD Has Proteomics Come of Age?


Although graft-versus-host disease (GVHD) is a life-threatening complication of hematopoietic stem cell transplantation (HSCT), its current diagnosis mainly depends on clinical manifestations and invasive biopsies. Early diagnosis of GVHD, preferably based on unbiased laboratory screening tools, may increase the safety of allogeneic HSCT and thus further broaden its applicability to even larger patient populations. In the past, many efforts were made to use single-protein biomarkers, which were specific for infection or inflammation after allogeneic HSCT but not specific for acute GVHD. Although some of these reports seem to hold promise, in many cases there was a high probability that a single marker was not specific, thus making the potential diagnosis of similar diseases difficult. It is reasonable to believe that the simultaneous monitoring of more than one protein or peptide within a sample holds greater promise for the differential diagnosis of diseases, including GVHD. Recently, the application of proteomic tools allowing screening for differentially expressed or excreted proteins in body fluids is becoming more important.

Using proteomics, a Japanese group from Sapporo screened for plasma proteins specific for GVHD in the mouse model. One peak retained a discriminatory value in two diagnostic groups (GVHD and normal controls) with increased expression in the disease, decreased expression during cyclosporine treatment, and was barely detectable in syngeneic transplantation. Purification and mass analysis identified this molecule as CCL8, a member of a large chemokine family. In human samples, the serum concentration of CCL8 correlated closely with GVHD severity. All non-GVHD samples contained less than 48 pg of CCL8 per mL. In sharp contrast, CCL8 was highly up-regulated in GVHD sera. Strikingly, two patients with severe fatal GVHD had extremely high levels of CCL8. Thus, CCL8 seems to be a promising specific serum marker for the early and accurate diagnosis of GVHD.

This study is of major importance for several reasons:

- It confirms preliminary results reported by Weissinger and co-workers1 published in Blood in which authors describe the application of capillary electrophoresis coupled online with mass spectrometry to 13 samples from 10 patients with acute GVHD of grade I and more and 50 control samples in a training set. The subsequent blinded evaluation of 599 samples enabled diagnosis of acute GVHD greater than grade II, even prior to clinical diagnosis, with a sensitivity of 83 percent and a specificity of 76 percent.

The study by Horí and colleagues took advantage of a murine model (in which many parameters could be controlled for) to set up the search for specific markers that allows the characterization of proteins following a huge amount of work that would not have been easily feasible from human samples analyzed by Weissinger and colleagues.1

CCL8 discovery makes the bridge even stronger between chemokines and acute GVHD pathobiology. Indeed, the migration of cells from vascular to extra-vascular compartments implies a sequential cascade of events, involving interplay between adhesion molecules and chemokines. Acute GVHD requires that effector cells reach their target tissues. Lymphocytes do not enter specific tissues because they “recognize” a given antigen; they enter because they possess the requisite combination of homing receptors and chemokine receptors to engage the endothelium at the target tissue(s). Because GVHD is relatively organ-specific — principally affecting the skin, gut, and liver — our increasing knowledge of the pertinent adhesion molecules directing effector-cell trafficking to these sites offers novel therapeutic approaches for prevention or treatment of GVHD.

Finally, the use of proteomics opens the door to exciting developments in the understanding of GVHD, the main one (at least in my opinion) being to use this tool to, finally, try to understand why and how some patients may develop a self-limited disease with an accompanying graft-versus-leukemia effect while others will develop a fatal steroid-resistant disease.


Role of miR223 in Myelopoiesis


New avenues of discovery have opened over the last decade with the discovery of microRNAs (miRNAs). MiRNAs are small RNAs of approximately 22 nucleotide length, which are transcribed from genomic DNA like messenger RNAs (mRNAs) but do not encode proteins. Their main function is that of gene regulation by targeting specific sequences in the 3′-untranslated region of mRNAs. It is estimated that the human genome encodes 300 to 500 miRNAs, and that ~30 percent of all genes are regulated by miRNAs. Differential expression of different miRNAs during hematopoiesis was first reported in 2003, and the specific regulatory functions of several miRNAs have since been elucidated.

The expression and processing of miRNAs has been reviewed in detail elsewhere. In this paper, Johnnidis, et al. focus on miR223, which is expressed at low levels in hematopoietic stem and progenitor cells, and at higher levels in common myeloid progenitors with steadily rising expression with further granulocytic differentiation. In order to investigate the function of miR223, the investigators created mice that lacked expression of miR223 (miR223 knockout [KO] mice). These mice showed a surprising finding within the hematopoietic system. Since miR223 expression is upregulated with granulocytic differentiation, it was predicted to promote granulocytopenia and hence the mice were expected to lack granulocytes. Instead, these mice actually had higher numbers of granulocytes, which were hyper-responsive causing a hyperinflammatory state in the mice. The neutrophil count was twice that of wildtype (WT) mice, and this increase was found to be due to an increase in the number of granulocyte progenitors and enhanced neutrophil differentiation.

Using bio-informatics, the investigators found more than 100 potential target genes for miR223 but focused on mef2c, a transcription factor known to play a role in myelopoiesis, as it was the only gene with two conserved miR223 complimentary “seed” sites in its 3′UTR (untranslated region). Indeed, when the investigators created mice that lacked both miR223 and mef2c, they found that the mice had normal granulocyte numbers. However, the hyperinflammatory state persisted. Thus, while the increased neutrophil count of the miR223−/− mice is caused at least in part through loss of downregulation of mef2c by miR223, a distinct mechanism is likely responsible for the hyperinflammatory state.

The investigators have identified a role for miR223 in regulating granulocytopenia and granulocyte activation. MiR223 inhibits translation of Mef2c, a transcription factor that promotes myeloid progenitor proliferation and likely other factors, thereby keeping granulopoiesis in check. It is intriguing that the increasing expression of miR223 with granulocytic differentiation appears to function as a built-in repressor or brake in the system, ultimately to prevent hyperinflammatory states, supporting the importance of the regulatory functions of miRNAs in hematopoiesis.

Clinical Penetrance of HFE Hereditary Hemochromatosis, Serum Ferritin Levels, and Screening Implications: Can We Iron This Out?


Since the discovery of the homozygous C282Y mutation of the HFE gene as the major cause of hereditary iron overload in Caucasians of Northern European descent, numerous studies have attempted to define the risk of iron-overload-related disease and a practical rationale for screening. The interpretation of cross-sectional population and family-based studies has been controversial, related to controls, ascertainment bias, observer bias, insufficient control groups, and variable definitions of disease penetrance. Longitudinal cohort studies have involved relatively few HFE homozygotes and mostly women, thus raising issues about gender bias and other confounding variables. The report by Allen, et al. supports prior observations that iron-overload-related symptoms (n=11) serum ferritin >1,000 µg/L (most likely middle-aged males) and phlebotomy reverses this process. Thus, using a ferritin of >1,000 µg/L for screening, rather than the conventional thresholds of >200 µg/L for premenopausal women and >300 µg/L for other adults, may fail to identify some high-risk homozygotes before irreversible liver injury develops. Despite new understanding, a risk-adapted screening and management approach to HFE hemochromatosis still awaits answers to the following questions:

• How do genetic, lifestyle, and other co-factors affect progression or “non-expression” of iron overload and liver disease?

• Are other tissues [joint, endocrine, cardiac] at risk? If so, by what mechanisms?

• What clinical and/or biochemical parameters [e.g., ferritin level] should be used to initiate therapeutic phlebotomy?


Combination Proteasome Inhibitor Therapy


The proteasome inhibitor bortezomib, which primarily targets the chymotryptic-like (CT-L) proteolytic activity of the proteasome, is an effective therapy for patients with relapsed refractory multiple myeloma [MM] and is superior to high-dose dexamethasone therapy for relapsed MM. Excitingly, when combined with dexamethasone it has increased frequency and extent of response both before and after high-dose melphalan and autologous stem cell transplantation. In older non-transplant patients, initial therapy with bortezomib combined with melphalan and prednisone achieved significant increases in overall and extent of response, associated with prolonged progression-free and overall survival. More recently, several next-generation proteasome inhibitors have shown promise at overcoming bortezomib resistance in preclinical models and are under clinical evaluation. Carfilzomib more potently inhibits the CT-L proteolytic activity and is under evaluation in two phase II clinical trials in MM, having shown early signs of responses in phase I studies. NPI-0052, a second-generation proteasome inhibitor targeting CT-L, trypsin-like (T-L), and caspase-like (C-L) proteolytic activities, is also in phase I clinical trial in MM. Finally, CEP-18770, which is also entering clinical trials, is an oral inhibitor of CT-L proteolytic activity. At present, the qualitative or quantitative extent of proteasome inhibition associated with clinical efficacy in MM remains to be defined.

Conventional therapies for cancer have been combined to both increase tumor-cell cytotoxicity and decrease attendant toxicity, frequently allowing for use of lower doses of therapy. Chauhan and colleagues provide preclinical evidence suggesting that similar principles may also apply with novel targeted therapies. In particular, it was observed combining bortezomib with NPI-0052 induced synergistic activity against MM cell lines in the bone marrow milieu in vitro, as well as in vivo in a human plasmacytoma xenograft model. The bio-logic sequelae triggered by the combination included activation of caspase-8, 9, 3, and PARP; induction of endoplasmic reticulum stress and JNK; suppression of CT-L, C-L, and T-L proteolytic activities; and blockade of NF-κB signaling.

Immunostaining showed growth inhibition, apoptosis, and decrease of human MM cells, as well as decreased associated angiogenesis, in treated mice. Most importantly, these effects were observed when combining these inhibitors, which are inactive when they are observed alone, at low doses. With these low doses, combination therapy was very well tolerated. These studies suggest, as with conventional combination chemotherapy, that combining proteasome inhibitors may enhance efficacy, delay or overcome drug resistance, lessen attendant side-effect profile, and ultimately improve patient outcome in MM.


Michael Linenger, MD
Dr. Linenger indicated no relevant conflicts of interest.

Kenneth Anderson, MD
Dr. Anderson indicated no relevant conflicts of interest.
The NIH peer-review system is not exactly a sinking ship, but the boat is taking on water at an alarming rate and has reached a “tipping point” with respect to efficiency and efficacy. The problem stems from a large increase in grant applications submitted to NIH (now an astounding 80,000/year), an NIH budget that is not keeping up with inflation, and an overburdened research community that is not as willing to serve on study sections. In response to these stresses on peer review, NIH Director Elias Zerhouni assembled a working group to study the problem and make recommendations for change. They solicited input from all stakeholders, including professional societies, such as ASH, and received nearly 3,000 specific comments on their Web site — a strong indication of the importance of the issue and anxieties evoked by any discussion of peer review at times of funding uncertainty. The detailed draft report can be viewed at [enhancing-peer-review.nih.gov](http://enhancing-peer-review.nih.gov).

The report identified key principles and significant challenges and outlined a series of potential “actions.” Among the more interesting and controversial recommendations were to shorten the length of the application and the reviewers’ summary, eliminate “unscored” (triage) for the lower tier of applications, add a “not recommended for resubmission” rating, eliminate amended applications so all would be considered de novo, and focus review on scientific merit and impact, rather than on specific weaknesses of approach. Noting that the current NIH scoring system is out of step with principles of modern psychometric science, the group recommended aligning applications and reviews with explicit criteria (e.g., impact, investigator, innovation/originality, plan, and environment [including institutional support]). The panel also suggested several strategies to address problems related to poor competitiveness of first-time grant applicants and clinical research projects and with review of “transformative” and multidisciplinary research. To reduce stress on science support systems, the panel made several recommendations that are sure to raise some hackles, including establishment of a minimum-percent effort (e.g., 20 percent) for investigators on research grants and re-examination of incentives in the current NIH system that drive expansion of the research enterprise. The implication is that NIH should pay less and universities/medical centers should pay more.

The report also noted less controversial recommendations. These included enhancing and standardizing training of reviewers and study section chairs, developing incentives for successful scientists to serve on study sections, continuing to pilot use of electronic review tools, introducing more flexibility into the system for reviewers, developing two-way communication between reviewers and applicants, and mandating periodic data-driven assessment of the entire peer-review process.

An implementation plan will soon be developed by NIH, but whatever form the final renovations take, it is highly likely that the relationships between the extramural research committee and the NIH are going to change dramatically.

**ASH Comments on Final Draft of the NIH 2007-2008 Peer Review Self-Study**

ASH submitted remarks to NIH in response to the Final Draft of the NIH 2007-2008 Peer Review Self-Study that was submitted to NIH Director Elias Zerhouni at the end of February. The Final Draft marked “the end of the diagnostic phase of the peer-review enhancement effort” and provided the research community with only a brief time period to respond and submit comments.

The notes submitted by ASH on March 17 reflected the Society’s concerns with the brief amount of time set aside for comments and a number of the proposals put forth in the Final Draft and encouraged “the NIH director to solicit broad input from the multiple NIH stakeholders in developing the second phase (implementation) of the plan.”

These comments followed comments submitted last year by the Society in response to a request for information seeking “comments regarding NIH’s support of the biomedical and behavioral research, including peer review.” The remarks offered the Society’s support of maintaining the peer-review process, encouraging senior investigators to serve on study sections, and finding ways to make the entire process less burdensome. Read ASH’s remarks at [www.hematology.org/policy/testimony/ASHPeerReviewMarch2008.pdf](http://www.hematology.org/policy/testimony/ASHPeerReviewMarch2008.pdf).

**CLINICAL ALERT UPDATE ON HEPARIN RECALL**

On February 11, 2008, the U.S. Food and Drug Administration (FDA) advised health-care practitioners to limit use of Baxter’s injectable blood-thinning drug heparin due to serious allergic reactions and hypotension in patients who receive high “bolus” doses of the drug. Since then, Baxter Healthcare Corporation has temporarily stopped manufacturing multiple-dose vials of the injectable heparin. They have also recalled all of their multi-dose and single-use vials of heparin. And, as a precautionary measure, they have recalled heparin lock flush solutions.

Then on March 21, a second supplier, B. Braun Medical Inc., began recalling lots of heparin as a precautionary measure. To date, the company has not received any adverse event reports related to this issue.

Supplies of heparin have been recalled in France, Italy, and Canada, and they are contaminated or are suspected of being contaminated. Batches of the drug have recently been recalled in Germany and Japan, as well.

After launching an investigation in both the United States and abroad, the FDA found a heparin-like compound present in some of the active pharmaceutical ingredients produced by Scientific Protein Laboratories (Baxter and Braun’s supplier). The contaminant has been indentified as a modified form of a cheap and widely used dietary supplement sold to relieve joint pain. FDA officials are currently investigating whether the compound, chemically modified chondroitin sulfate, was intentionally added or was added by accident. In either case, it is not part of the prescribed manufacturing process. Heparin is made from the intestines of pigs, and chondroitin sulfate can be produced from pig cartilage.

For more information, including questions and answers on heparin sodium injection, go to [www.fda.gov/oc/qanda/heparin.html](http://www.fda.gov/oc/qanda/heparin.html).
Ernst R. Jaffé, MD (1925-2008)

With the death of Dr. Ernst Jaffé on February 16, 2008, the American Society of Hematology (ASH) lost a visionary founder and a gifted leader of hematology. Present at their creation, he provided wise and devoted leadership to the Albert Einstein College of Medicine, ASH, and Blood.

In 1974, Dr. Jaffé succeeded Dr. William Dameshek as Editor-in-Chief of Blood. Two years later, this premier hematology publication became the official journal of ASH. Concluding his service as editor in 1978, Dr. Jaffé became a leader of the ASH educational program for many years, and in 1983 was elected president of ASH. Subsequently, he developed support for post-doctoral research training and research grants from the Henry and Lillian Stratton Foundation. In 2003, ASH called on Dr. Jaffé to serve as the first Chair of Development Task Force, where he worked to secure funding for the Clinical Research Training Institute.

Dr. Jaffé was born and grew up in Chicago. He was the son of two physicians; both immigrated from Vienna. His father, Richard Jaffé, was already a famous pathologist who became the head of pathology at Cook County Hospital. Dr. Jaffé went to college and medical school at the University of Chicago. He completed his internship and residency in medicine at the Columbia-Presbyterian Medical Center in New York City. In 1954, he began his fellowship in hematology at Columbia with Irving London.

A year later, Dr. Jaffé went to the Albert Einstein College of Medicine from Columbia as a post-doctoral fellow with Dr. London, who was the founding Chair of Medicine at this newly established medical school. He was Head of the Division of Hematology, Department of Medicine, from 1970 until 1982 when he became Acting Dean. Dr. Jaffé remained on the faculty at Einstein in a series of academic advancements until his retirement as Senior Associate Dean and Distinguished University Professor of Medicine in 1991.

Dr. Jaffé’s research focused on red cell enzymes. In a series of landmark studies of methemoglobinemia, congenital and acquired (toxic), he defined the clinical manifestations and management of this disorder. He collaborated in studies of the first family to be described with phosphoglyceratekinase-associated hemolysis. Other studies focused on G-6-PD deficiency and cryptogenic hemolysis associated with abnormal membrane lipids. Having served several years as co-editor of Seminars in Hematology, Dr. Jaffé had broad interests in all aspects of blood and its disorders.

Dr. Jaffé also served on many committees of the National Institutes of Health (NIH) and on the Blood Services Committee of the American Red Cross. He was chairman of the Association of American Medical Colleges (1989-90) and president of the Society for Experimental Biology and Medicine (1993-95). Dr. Jaffé was a member of the International Society of Hematology, the American Federation for Medical Research (then the American Federation for Clinical Research), the American Physiological Society, the American Society for Clinical Investigation, and the Association of American Physicians.

Dr. Jaffé is survived by his wife of 57 years, Jane Sylvestre, two children, Dr. Stephanie Jaffé Green and Richard Jaffé, and four grandchildren. For those who wish to donate, a scholarship fund has been established at Albert Einstein. Donations may be made to:

The Ernst R. Jaffé Scholarship Fund
Office of Institutional Advancement
Albert Einstein College of Medicine
1300 Morris Park Ave.
Bronx, NY 10461

In addition, members have expressed an interest in making a gift to ASH in Dr. Jaffé’s memory. Donations can be made to the Stratton-Jaffé Endowment for the support of ASH scholars. To make a gift, please visit www.hematology.org/makeagift.

- Helen Ranney, MD

Peruse Dr. Jaffé’s article “The American Society of Hematology: a success at age 50.” This article was published in the January issue of Blood. Dr. Jaffé co-authored the article with current ASH president Dr. Kenneth A. Kaushansky. It discusses the origins of the Society and the Society’s journal, Blood. Go to http://bloodjournal.hematologylibrary.org/cgi/content/full/111/1/11 to read the article.

Highlights of ASH® 2008

At left, photos from Highlights of ASH, held on February 8-9, in Austin, TX.

Drs. Ari Melnick and Jane Winter led a distinguished panel of speakers at Highlights of ASH. The expert panel of speakers included Richard Larson, MD; Amit K. Verma, MD; Selina Luger, MD; Mitchell Weiss, PhD, MD; James George, MD; Robert Orlowski, MD; Neil E. Kay, MD; Barbara Konkle, MD; and Mark Crowther, MD, MSC, FRCP.C.

The stimulating educational sessions covered myelodysplasia, acute leukemia, microRNAs, ITP, TTP, thrombophilia, multiple myeloma, lymphomas, CLL, thrombosis, and the impact of microarray and molecular studies on personalized diagnosis and therapy.

If you missed this informative meeting, you can still experience it for yourself by purchasing the Program Book or a DVD-ROM. The DVD features audio from each of the 11 sessions synced to the speaker’s slides. Purchase your copy of the meeting DVD-ROM and Program Book through the ASH Store at www.hematology.org.
As more biomedical journals around the world institute Web-based electronic submission and publication systems, the dissemination of scientific information worldwide has less respect for national borders. Blood aims to be a venue for the publication of the very best basic and clinical research in hematology from around the world, with no mandate — official or unofficial — to publish more papers emanating from the United States and North America, even though it is owned and published by ASH. We have strong participation from the international community of hematologists as authors and reviewers and are a truly global publication. Still, some confusion seems to remain. It has stimulated this editorial, in hope that Blood’s submission, editorial, and publication processes will become more transparent to our worldwide community of hematologists.

I would like to emphasize that anyone can submit a paper to Blood. There is no requirement that the corresponding author, or any author, be an ASH member, and there is no need for an ASH member to sponsor a submitted paper. Although ASH owns the journal, the editorial process, peer review, and final decisions are completely independent from the Society, as are our editorial policies. The submission fee for an article is the same for ASH members and non-members.

Blood’s burgeoning submission rate, in combination with economic and practical limitations on page numbers, means that over the past five years a lower percentage of submitted articles were published in comparison to previous acceptance rates. As a result, some unhappy authors of rejected papers, in particular international authors, may be questioning whether their papers were given the same consideration as papers submitted from the United States. I would like to assure the readers that Blood’s processes and policies ensure impartiality and fairness.

In 2007, there were 5,236 initial article submissions to Blood (including review articles, perspectives, and letters to the editor), of which 1,544 were accepted for publication, for an overall acceptance rate of 29 percent. The number of submissions has increased every year this decade, more than doubling since 1997. More than half (57 percent) of submitted papers come from outside North America, and 48 percent of published papers are from outside North America.

The acceptance rate for papers submitted from North America is indeed higher (38 percent vs. 23 percent for those from outside North America). The decisions are based primarily on recommendations from reviewers, and our statistics show that 58 percent of reviewers were from outside North America in 2007, roughly the same percentage as the origin of submitted papers during the same time period. Our 100-member editorial board currently has 23 non-North American members. Since the editorial board members are chosen almost entirely based on a record of accepted review requests and on the quality of their reviews, the easiest way to get nominated to this board is to accept review requests and to communicate to the Associate Editor handling your area of expertise your willingness to review papers for Blood.

After 10 years as an Associate Editor and now several months of screening and assigning papers as Editor-in-Chief, I can offer some guidance and suggestions on how international authors can improve their acceptance rate in the future.

• First, a proportionally higher number of papers submitted to Blood from outside the United States and North America are clearly outside the scope of the journal, with almost no relevance to clinical or research hematology. Almost daily, the journal receives papers that focus on atherosclerosis, diabetes, inflammatory bowel disease, lupus or other multi-system autoimmune disorders, cardiac physiology, and a host of other topics. I cannot be sure why these non-hematologic papers more frequently originate from outside North America; perhaps it is because the authors are less familiar with the journal or focus more intensely on the impact factor in choice of submission venue, since Blood has such a high impact factor compared to most other subspecialty bio-

medical journals. I would recommend carefully checking the Author Guide (especially the sections on scope and on article types) before submission.

• Second, we receive many single or small-series case reports from outside North America, in particular from the developing world. Blood cannot accommodate clinical reports that do not offer definitive new insights into disease biology or treatment. It is commendable that authors from institutions with limited resources wish to contribute to the international literature, and in rejecting these types of papers, I make sure to explain Blood’s position and encourage the authors to resubmit to more appropriate venues, often with suggestions for improvement of the paper, to increase their chances for successful publication in a more specialized journal.

• Third, a minority of papers submitted are written in such poor English that they are literally incomprehensible. In the rejection letter we strongly suggest that the authors obtain professional assistance before possible resubmission to Blood or any other English-language journal. In fact, Blood provides links to multiple language services for non-English-speaking authors to make this process easier.

Papers deemed inappropriate based on any of these three factors are immediately rejected by the editors without a full external peer review, saving the authors time and allowing rapid resubmission to a more appropriate journal. Review of statistics over the past two years indicates that the difference in the acceptance rate for North American versus non-North American papers completely disappears if only papers undergoing full peer review are considered.

I hope this message will help prospective authors understand Blood’s objectives and the processes leading to publication in the journal. Hematologists and scientists worldwide are welcome to participate fully in Blood as authors, reviewers, and readers. Only with the help and contributions from the international scientific community can Blood continue its mission to remain a global platform for the exchange of the best scientific research in the field of hematology.

FURTHER ASSISTANCE

Feel free to send a pre-submission inquiry e-mail to bloodeditor@hematology.org. Include the abstract and a brief narrative about the work. Please title your message “Pre-submission query to Editor.” Taking advantage of this pre-submission process could save you time and the effort of submitting the article to Blood only to find that the topic is outside our areas of interest, or clearly not novel or high-priority enough to be considered for publication. Pre-submission communication is also strongly encouraged for review articles, “Perspectives,” and “How I Treat” submissions, since relevance to readership, lack of overlap with invited or already submitted articles, and timing of submission are particularly critical for successful publication in these categories.
Ernest Beutler, Independent Thinker and Astute Observer

Dr. Rosse is Florence McAlister Professor of Medicine Emeritus, Duke University, and past president of ASH.

Ernest Beutler, MD, was born in Berlin, Germany, in 1928. With the advent of Hitler, he and his family moved to the United States in 1935 and settled in Milwaukee, WI. At age 15, he went to college at the University of Chicago. The intellectual character there fitted his keen mind and he remained at the University of Chicago for medical school and house staff training. He was attracted to hematology by the force of personalities of hematologists at Chicago, particularly Leon Jacobson, and, when he was commissioned as a Second Lieutenant in the Army, he was assigned to work with the Malaria Research Project, where he investigated the abnormality of the red cells that resulted in hemolytic anemia when primaquin was ingested. He noted that these cells had more Heinz bodies than normal when treated with certain chemicals, including iodosacetamide. He deduced and then proved that glutathione was more easily oxidized and, from this, that the enzyme glucose-6-phosphate dehydrogenase (G-6-PD) was diminished, opening an entire field of endeavor in hematology and genetics. The defect was shown to be X-linked, and, from the great heterogeneity of expression in obligate heterozygotes, he independently deduced that they must be variable chimeras due to the suppression of one or the other X chromosome in individual cells. This insight led to the demonstration of clonality in some tumors and in paroxysmal nocturnal hemoglobinuria (PNH) before more refined molecular genetic tests were available.

From Chicago, Dr. Beutler moved to the City of Hope in Duarte, CA, for 18 years, and then ultimately to the Scripps Clinic and Research Foundation in La Jolla, where he remains. His research has been far-ranging and yet nearly always related to the red cell. His early interest in iron deficiency later emerged in extensive and influential studies of hemochromatosis. His interest in enzymes led to consideration of other deficiencies besides G-6-PD and into galactosemia and Gaucher disease; he cloned the gene for the latter disease and developed replacement treatment for it. His interest in red-cell preservation stemmed from a clinical need and a curiosity about cell aging. While at City of Hope, he, along with Karl Blume, was one of the pioneers in bone marrow transplantation and showed that it could be used effectively in the first remission of AML. In all, he has authored more than 800 publications, 19 books, and more than 300 book chapters of enormous influence on hematology. It has been correctly stated that he is not constrained by conventional thinking, and he has had the satisfaction of seeing that his approach and his thinking have been confirmed time and time again.

In addition to his leadership in scientific advancement, Dr. Beutler has played a highly significant role in the promotion of the field of hematology. He has trained many students who are universal in his praise. He has occupied many positions of influence, including that of president of the American Society of Hematology, and has received numerous awards and lectureships. None of this seems to have diminished his primary work.

With so many publications, he amassed references that he found difficult to access. To remedy this, he developed a computer program that he called Reference Manager, which eventually became widely used.

Music has always been an important part of his life, and he took violin lessons in Berlin from a famous virtuoso, Szymon Goldberg, a family friend. His wife, Bonnie, whom he married the day before graduating from medical school, is an avid amateur pianist. They have raised four children, three of whom have followed in his medical footsteps and one in his computer footsteps. All have been successful in their endeavors.

The characteristic that has led Dr. Beutler in the paths he has taken may have been nurtured during his college days through a program by Robert Maynard Hutchins, which emphasized independent thought and habits of analyzing things for oneself. Dr. Beutler was and is able to see things that others don’t, just as Newton saw more in an apple dropping than a chance for a snack.
The ASH Web site offers a convenient way for ASH members to find information relating to upcoming Society events and provides easy access to the many valuable products and services offered by ASH.

Participate in ASH’S 50TH ANNIVERSARY and learn more about the rich history of ASH and hematology by visiting www.hematology.org/about/50thanniversary. On this Web page you can meet legends in hematology and read their oral histories, in which they reflect upon their careers. Check out the latest additions — Dr. James L. Tullis, ASH’s first president, and Dr. Ralph O. Wallerstein. Be sure to sign the guestbook for these and other hematology notables in the Legends of Hematology section at www.hematology.org/education/legends.

Read about the latest hematology DRUG APPROVALS from the FDA. On March 20, the FDA Approved Treanda for Patients With CLL. (www.hematology.org/policy/resources/fda/03202008.cfm)

Review the 2007 ASH ANNUAL REPORT. The report highlights the new endeavors that the Society launched in 2007 and also provides updates of important ongoing activities in research, clinical practice, training, and other areas. Check out the report at www.hematology.org/images/pdf/2007_ASH_Annual_Report.pdf.

Read THE HEMATOLOGIST ONLINE (www.hematology/publications/hematologist) and catch up on the latest news in the field of hematology right on your desktop.