ASH WEIGHS IN ON REVIEW OF MEDICARE COVERAGE POLICY FOR ERYTHROPOIETIN-STIMULATING AGENTS

In March, the Centers for Medicare and Medicaid Services (CMS) announced plans to review the Medicare coverage policy for darbepoetin alfa and epoetin alfa after recent studies linked the treatments with increased risk for serious side effects. CMS will review coverage of the medications for uses other than dialysis, as well as a “monitoring policy” that requires a reduction in Medicare reimbursements for the treatments when the red blood cell counts of beneficiaries exceed a certain level. The review follows a March 9 announcement by the Food and Drug Administration (FDA) that manufacturers of the medications must include black box warnings on the labels to physicians and patients about the increased risk for serious side effects linked with the treatments. In addition, the FDA advised physicians that they should use only the lowest dose of the medications necessary to avoid the need for blood transfusions caused by anemia.

Based on the FDA safety alert, CMS issued instructions to local Medicare carriers to prohibit Medicare coverage of erythropoietin stimulating agents (ESAs) — Aranesp, EpoGen, Procrit — when used for the treatment of the anemia of cancer. ESAs used for treatment of anemia due to chemotherapy would not be affected by this change in policy. Some Medicare Part B carriers immediately began to announce new local carrier decisions that require that ESAs should be used only in accordance with its approved product labeling.

(Cont. on Page 2)

**“Silent” Polymorphisms: How Silent Are They?**


When deciphering the human genome uncovered only ~30,000 sequences for human genes, it was difficult to reconcile this finding with the far greater number of proteins and even greater number of phenotypic variations of proteins. The discovery of mechanisms that modulate the quality and quantity of genes by alternative splicing, epigenetic regulation, and microRNA provides growing evidence that diverse phenotypes can be produced by means other than gross gene rearrangements and missense nucleotide mutations.

In this paper, Kimchi-Sarfaty and colleagues provide another mechanism contributing to phenotypic diversity. Single nucleotide substitutions that do not change the amino acid sequence are known as synonymous or “silent” polymorphisms, because it is assumed that they do not change the function of the protein. However, these “silent” polymorphisms may utilize different transfer RNAs (tRNAs) that may differ in translational efficacy. Kimchi-Sarfaty et al. show that a silent single-nucleotide polymorphism (SNP) in the Multidrug Resistance 1 (MDR1) gene alters the function of the gene product. The MDR1 gene encodes an efflux pump, P-glycoprotein (P-gp), which actively transports certain drugs out of cells and plays a major role in the multidrug resistance of cancer cells. The authors show that the presence of a synonymous SNP (C3435T) in MDR1 gene in association with another synonymous SNP (C1236T) or a non-synonymous SNP (G2677T) resulted in a reduction of inhibition of P-gp by cyclosporin A and verapamil. The non-synonymous SNP (G2677T) was excluded as the factor explaining the phenotype; rather the synonymous C3435T was responsible for different P-gp mediated efflux of paclitaxel or other drugs. The inhibition of P-gp function was more pronounced as the concentration of paclitaxel DNA encoding P-gp increased, suggesting that the difference between the wild-type and the polymorphic MDR1, but, surprisingly, the silent polymorphism altered the conformation of the P-gp peptide. This altered conformation appears to result from the “silent” polymorphism codon’s effect on the translation rate, which in turn affects protein folding. The authors theorize that as more P-gp is produced, the role of codon usage is more critical as certain tRNA species become depleted.

Kimchi-Sarfaty et al. present a novel mechanism of altered protein function by “silent” mutations that do not affect the amino acid sequence yet alter the protein folding and function by changing the timing of cotranslational folding. This provides impetus to re-examine the effects of other silent SNPs in other genes and their possible relationship to phenotype and disease states. It remains to be seen if we will soon hear voices from the multitude of other so-called “silent” polymorphisms.

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**XYLINA GREGG, MD, AND JOSEF PRCHAL, MD**

Drs. Gregg and Prchal indicated no relevant conflicts of interest.
THE PRACTICING HEMATOLOGIST

ASH LOOKS TO THE PAST AND PLANS FOR THE FUTURE OF PAY-FOR-PERFORMANCE

LAWRENCE A. SOLBERG, JR., MD, PhD

Dr. Solberg is Professor of Medicine at the Mayo Clinic College of Medicine, Jacksonville, FL. He is also Vice-Chair of the ASH Practice Committee.

The financial incentive for the 2007 PQRI will be a lump-sum bonus payment in mid 2008 of 1.5 percent of allowed charges for covered professional services from July 1 to December 31, 2007, reported to the CMS National Claims History file by February 29, 2008. It is important to note that the 1.5 percent bonus will apply to allowed charges for all covered professional services and not just those charges associated with the specific measures reported on by clinicians.

Total charges, including the beneficiary deductible and co-payment, will be allowed — not just the 80 percent paid by Medicare or the portion covered by Medicare when Medicare is the secondary payer. PQRI-covered services are those paid under the Physician Fee Schedule only. A payment cap that will reduce the bonus below 1.5 percent of allowed charges may apply when an eligible clinician reports relatively few instances of quality measure data or under other circumstances. Eligible professionals in hematology practices will include physicians, nurse practitioners, physician assistants, and clinical nurse specialists. To be eligible, providers must use a National Provider Identification (NPI) on all claims reported to the CMS National Claims History file by February 29, 2008. It is important to note that the 1.5 percent bonus will apply to allowed charges for all covered professional services and not just those charges associated with the specific measures reported on by clinicians.

The 74 measures finalized for Medicare are available on the CMS Web site at www.cms.hhs.gov/PQRI. Modifications or refinements will be allowed up to the July 1, 2007, start date, but no new measures for 2007 will be accepted. Of eight measures directed toward hematology and oncology patients, four were developed by ASH. The four developed for solid tumors include one measure applicable to both hematology and oncology patients.

ASH is now working with the CMS Practice Committee’s Hematology Workgroup, led by Steve Allen, MD, as well as through membership in the newly formed Oncology Workgroup.

Looking forward, ASH will be launching an online educational campaign in the spring with information about the 2007 Medicare Physician Quality Reporting Initiative (PQRI) process, hematology measures, and reimbursement. The financial incentive for the 2007 PQRI will be a lump-sum bonus payment in mid 2008 of 1.5 percent of allowed charges for covered professional services from July 1 to December 31, 2007, reported to the CMS National Claims History file by February 29, 2008. It is important to note that the 1.5 percent bonus will apply to allowed charges for all covered professional services and not just those charges associated with the specific measures reported on by clinicians.

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Reporting by hematologists for this initiative will be based on the claims-based quality reporting system used in the 2006 Physician Voluntary Reporting Program, which ended on December 31, 2006. Physicians will report the CPT category II codes on, if these codes are not available, the appropriate G-codes. Successful reporting will depend upon how many quality measures are applicable to the services furnished by the hematologist during the entire reporting period. If no more than three measures are used by the clinician, each measure must be reported in 80 percent of the cases in which the measure was reportable. Clinicians will be able to select the quality measures that will be measured in their practices, but CMS is advising that clinicians report on every quality measure that is applicable to their patient populations to increase the likelihood that they will reach the 80 percent satisfactory reporting requirement and to decrease the likelihood that they will be affected by a cap on their bonus payment.

Stay tuned to the ASH Web site (www.hematology.org) for future updates on the PQRI process. Details related to the cap will be particularly important to understand. Like Janus, we can look back to simpler times, but we must also look forward. For the sake of our patients, their families, and our practices, ASH intends to remain engaged in a sustained effort to positively influence the pay-for-performance domain.
Editor Search Announcement

The American Society of Hematology is in the initial stage of the selection process for the next Editor-in-Chief of The Hematologist (term: 2009-2011).

Candidates with an MD or equivalent medical degree should have a broad and comprehensive knowledge of basic research and clinical investigation in hematology as well as an appreciation of its subspecialty areas, a distinguished research and publications record, high standing among peers, and demonstrated writing, reviewing, and editing skills.

Members of ASH are invited to submit the names of potential candidates, accompanied by a brief, informal endorsement and a brief description of the candidate's editorial experience, to:

The Hematologist: ASH News and Reports
c/o Molly Polen, Managing Editor
1900 M Street, NW, Suite 200
Washington, DC 20036
mpolen@hematology.org

The application deadline is June 8.

2008 ASH™ SCHOLAR AWARDS DEADLINE

The application process for the 2008 Scholar Awards has begun. The letter-of-intent deadline is May 3, and the application deadline is August 30. Applications are only available to those who successfully submit a letter of intent and are confirmed to be eligible. If interested in applying, visit the ASH Web site at www.hematology.org/-education/awards/scholar.cfm for complete details, including eligibility requirements.

ASH™ MENTOR AWARDS DEADLINE IS MAY 4

Mentorship, although known as one of the most important determinants of a successful career, often goes unrecognized. ASH honors this important aspect of career development with the ASH Mentor Awards. These awards are based on the training experiences and successes of the mentees, not the mentor’s personal career achievements. In 2006, the first ASH Mentor Awards were given to Samuel E. Lux IV, MD, for clinical investigation and to Deane F. Mosher, MD, for basic science.

May 4 is the deadline to nominate a mentor for these prestigious awards. For more information about the eligibility criteria and selection process, or to download a nomination form, visit www.hematology.org/education/awards/mentorship.cfm.

LETTER-OF-INTENT DEADLINE APPROACHING FOR EHA-ASH™ INTERNATIONAL FELLOWSHIP AWARD

The American Society of Hematology and European Hematology Association’s EHA-ASH International Fellowship Award will enable hematologists from North America and Europe to conduct research in another country. The intent of the program is to give both clinical and laboratory-based researchers an opportunity to establish new collaborations and experience research in a different environment. This program will benefit not only the individual participants, but also each host institution, with the ultimate goal of building stronger ties between the North American and European scientific communities.

A letter of intent must be submitted in English by September 4, 2007, in order to be eligible to submit a full award application by the October 12 deadline. For complete eligibility requirements and application information, visit www.hematology.org/education/awards/ifa.cfm.

Highlights of ASH™ DVDs

Did you miss the Highlights of ASH meeting in February? If you would like to see the presentations from the meeting and review the workbook, you can now purchase the Highlights of ASH DVD online at www.hematology.org. The DVD includes all nine sessions and four panel discussions, as well as the program and workbook.
ASH President Andrew Schafer, MD, along with members of the ASH Committee on Government Affairs, met with Speaker of the House Nancy Pelosi’s (D-CA) Senior Health Policy Advisor, Wendell Primus, during the Committee’s annual Capitol Hill Day on March 7. Committee members had the opportunity to meet with nearly 40 congressional offices to discuss ASH’s top legislative advocacy issues, including FY 2008 funding for NIH and the importance of the hematology research being conducted through the various Institutes at NIH, ASH support of the Genetic Information Non-Discrimination Act; and ASH support for the Stem Cell Research Enhancement Act. The Stem Cell Research Enhancement Act, which would expand federally funded embryonic stem cell research, passed the House in January and a slightly revised version of the bill passed the Senate on April 11.

The Committee also had the opportunity to visit with Representative Michael Castle (R-DE), the chief House supporter of the Hematologist, during the Committee’s annual Capitol Hill Day on March 7. Committee members had the opportunity to meet with nearly 40 congressional offices to discuss ASH’s top legislative advocacy issues, including FY 2008 funding for NIH and the importance of the hematology research being conducted through the various Institutes at NIH, ASH support of the Genetic Information Non-Discrimination Act; and ASH support for the Stem Cell Research Enhancement Act. The Stem Cell Research Enhancement Act, which would expand federally funded embryonic stem cell research, passed the House in January and a slightly revised version of the bill passed the Senate on April 11.

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ASH Advocates for NIH Funding Increase in FY 2008

ASH and other organizations within the biomedical research community have joined forces to advocate an increase of 6.7 percent for the National Institutes of Health (NIH) in FY 2008. This requested funding level represents the expected 3.7 percent rate of biomedical inflation for 2008 plus a 3 percent “catch-up” for lost purchasing power as a result of NIH budgets not keeping pace with biomedical inflation since the completion of the doubling of the NIH budget in 2003.

ASH will continue its NIH advocacy efforts on Capitol Hill in the FY 2008 budget debate. With a very tight year expected for the entire federal budget, significant grassroots support for NIH funding is critical to gain any traction in the budget process. Please see the “Take Action” box on this page, and, for more the most up-to-date information about NIH funding and ASH’s advocacy, please visit the ASH Web site at www.hematology.org.

Medicare Announces Performance Measures for New Physician Quality Reporting Program; ASH to Provide Information for Physicians Through Web Site

Medicare has announced preliminary information and the performance measures for the 2007 Physician Quality Reporting Initiative (PQRI). The pay-for-reporting program, which was authorized by the Tax Relief and Health Care Act of 2006, pays a bonus to Medicare providers who report on quality measures through administrative claims data. The program will begin July 1, 2007. Four hematology measures created by ASH have been approved and included in the program. For more information about PQRI, see the article on page 2. ASH will be providing the latest information for hematologists about the PQRI bonus program through its Web site, www.hematology.org.

ASH Outlines Physician Payment Reform Proposal

ASH, along with 76 specialty societies, sent a sustainable growth rate (SGR) letter to the leadership of the House and Senate health committees and subcommittees outlining a proposal for modifying Medicare’s physician payment formula and replacing the SGR formula. Based on the SGR formula, Medicare is scheduled to cut physician reimbursement by 10 percent in 2008. Congressional lawmakers have indicated that they will likely provide another “short-term fix” so that physicians do not incur a cut next year, but they are searching for proposals to correct the physician reimbursement formula over the long term so that it is linked to quality improvement. For more details on the proposal, visit the ASH Web site at www.hematology.org.

FDA Unveils Its Pandemic Influenza Preparedness Strategic Plan

U.S. Food & Drug Administration (FDA) Commissioner Andrew C. von Eschenbach, MD, has released a comprehensive strategic plan outlining steps taken and additional actions the agency is taking to protect the health of the public should an influenza pandemic occur. For more information on pandemic flu and a copy of the plan, visit www.fda.gov/oc/op/pandemic.
Allogeneic Hematopoietic Cell Transplantation for Patients with Follicular Non-Hodgkin Lymphoma

GINNA G. LAPORT, MD

Follicular non-Hodgkin lymphoma (FL) is the second most frequent subtype of NHL with approximately 15,000 cases per year diagnosed in the United States. Median survival has historically ranged from seven to 10 years, but newer agents such as monoclonal antibodies and radioimmunoconjugates have improved response rates, and early results show that overall survival (OS) may actually be affected. The definitive management of patients with advanced follicular NHL remains under considerable debate due to the numerous treatment options available. Hematopoietic cell transplantation (HCT) has been offered to FL patients as an alternative approach, especially to younger patients, but typically was offered late in their course because of the long natural history inherent to this disease and the treatment-related mortality (TRM) associated with HCT. Refinements in HCT and improved supportive care have lowered TRM and thus may alter this paradigm.

This mini-review will focus on the role of allogeneic HCT. Regarding autologous HCT (AHCT), several previous trials have unequivocally reported improved disease-free survival (DFS), with one randomized trial showing an OS benefit in patients with relapsed FL with chemosensitive disease. But AHCT as consolidation in first remission (CR) has not shown a long-term survival benefit compared to AHCT. Single-arm trials on three large randomized European trials, and thus cannot be recommended as part of front-line therapy.

It is worth noting that most published transplant trials were initiated in the pre-rituximab era, which limits our current knowledge regarding the influence of rituximab on the outcomes of patients undergoing HCT.

ALLOGENEIC MYELOABLATIVE HCT

Allogeneic HCT (alloHCT) represents the only treatment modality with curative potential for patients with advanced FL. In contrast to AHCT, alloHCT utilizes the graft-vs.-lymphoma effect mediated by donor T cells to eradicate minimal residual disease and ameliorates potential tumor cell contamination in the graft. Although no randomized trials have been performed, several studies have consistently reported a lower rate of relapse compared to AHCT. The TRM associated with myeloablative alloHCT has invariably offset the benefit conferred by lower relapse rates. An International Bone Marrow Transplant Registry (IBMTR) report compared the outcomes of 904 patients with FL who underwent either matched-related alloHCT (n=176), purged AHCT (n=131), or unpurged AHCT (n=597). The risk for relapse was 54 percent lower in the allogeneic group (p<.001) and 26 percent lower in recipients of purged autografts (p=.04) than in recipients of unpurged autografts.

Few relapses occurred in the allogeneic group after one year, as opposed to a continuous relapse pattern in the autologous patients. However, the risk of TRM was 4.4 times higher after alloHCT than after AHCT (p<.001), resulting in comparable five-year probabilities of OS (52 percent after allogeneic, 62 percent after purged autologous, and 55 percent after unpurged autologous). In another large registry series from Europe, the outcomes of 1,185 patients with NHL who underwent myeloablative alloHCT (including 231 patients with indolent NHL) were compared to the results of 14,687 AHCT recipients. In the IBMTR study, the relapse risk was significantly lower among the allogeneic recipients, but OS was compromised due to the prohibitive TRM of 38 percent at four years.

ALLOGENEIC REDUCED-INTENSITY HCT

Reduced-intensity conditioning (RIC) incorporates a less intensive preparative regimen and relies more on the immunotherapeutic effects of the allograft to confer anti-tumor activity rather than the cytoreduction of high-dose chemotherapy. The goal of RIC is to induce adequate immune suppression of the recipient to allow engraftment, but the level of cytoreduction varies among the numerous RIC regimens. Some regimens rely more on the immunotherapeutic effects of the allograft to confer anti-tumor activity rather than the cytoreduction of high-dose chemotherapy. The goal of RIC is to induce adequate immune suppression of the recipient to allow engraftment, but the level of cytoreduction varies among the numerous RIC regimens. The incidence of grade II-IV acute GVHD and chronic GVHD were 20 percent and 64 percent, respectively.

Only one patient died from a treatment-related complication. These results were recently updated with a total accrual of 47 patients. With a median followup of 34 months, the three-year DFS, OS, and risk of progression were 88 percent, 85 percent, and 3 percent, respectively. These encouraging data support the existence of a graft-vs.-lymphoma effect, although longer followup is necessary to confirm a true plateau in survival.

A recent analysis from the IBMTR confirmed the benefit of non-myeloablative transplantation. In 1997, less than 10 percent of matched sibling allograft transplants reported to the registry employed RIC regimens with this percentage, increasing to 80 percent by 2002. In this report, the outcomes of 120 myeloablative recipients were compared to 85 RIC recipients. Even after adjusting for OS, and TRM did not differ between the two groups. The three-year DFS and OS were 65 percent and 55 percent, and 70 percent and 64 percent, respectively. However, relapse/progression was higher in the RIC group, 21 percent vs. 9 percent (p<.05). It should be noted that nearly one-third of patients had chemotherapy-resistant disease and that the RIC recipients had an older median age (50 years vs. 45 years) and a longer time from diagnosis to transplantation (34 vs. 24 months). Chemosensitivity and recipient performance status were better predictors of outcome than conditioning regimen utilized.

SUMMARY

Although relapse/progression occurs significantly less often after myeloablative alloHCT compared to AHCT, this modality cannot be routinely recommended due to prohibitive TRM. However, younger patients beyond first remission or who have exhausted all other options may better tolerate and benefit from such a regimen. RIC regimens have shown promising results and have broadened eligibility of alloHCT to older patients and patients who have failed prior AHCT.

The advent of prognostic indices such as the Follicular Lymphoma International Prognostic Index (FLIPI) and gene-expression profiling may allow earlier identification of patients who could benefit from alloHCT sooner rather than later.

REFERENCES


Dr. Laport indicated no relevant conflicts of interest.
Pinpointing the Endothelial Cell Precursors

Endothelial progenitor cells (EPCs) are the focus of intense investigation because of a need to define the cells for their use as potential therapeutic tools in conditions such as cardiovascular damage and to understand their relationship to hematopoietic precursors. Although animal models indicate that new vessel formation following injection of endothelial progenitor cells is a promising therapeutic intervention, the findings are not recapitulated in humans, and the true endothelial potential of EPCs is under question. This paper re-addresses the isolation and definition of the population of cells that form endothelial cells (EPCs; endothelial colony-forming cells) and compares them to CFU-EC (endothelial colony-forming units) that are defined by commercially available assays. Comparing two distinct cell culture strategies, the investigators established that ECFCs originate from adherent cells whereas CFU-ECs arise from a non-adherent population. Yoder et al. note that CFU-ECs express hematopoietic markers and, more specifically, have myeloid regenerating capacity but no ability to form blood vessels. CFU-ECs differentiate into phagocytic macrophages, whereas the EPCs proliferate and form vessels, but do not form hematopoietic cells. Finally, taking advantage of the newly described JAK-2 mutation, the investigators put forth an argument that because all CFU-ECs but only a small fraction of ECFCs contain the mutation, the former are derived from a hematopoietic precursor and the two populations are not clonally related.

The connection between early hematopoietic precursors and the ability to form blood vessels or support blood cell development continues to be defined, and this paper moves us one step closer to understanding the divide between these processes. The investigators do a careful job of delineating differences between the two populations of cells and note that previous identification of the precursor cells was defined by cell surface markers that may have selected for a population of cells with hematopoietic potential. Their assay relies on growth and colony formation in cell culture on defined surfaces and demonstrates that, from a pooled population of mononuclear blood cells, there were cells capable of both replicating and forming blood vessels that did not have hematopoietic markers. In contrast, the CFU-ECs did not replicate and were not capable of forming blood vessels. In part, the identification of unique populations may be obscured by the selection markers used, and, as the authors point out, the vascular formation potential of the cells was not reviewed — this may be a necessary component of analysis. With clearer insight into the cells of interest, it may be time to revisit cell-based therapy and characterize the molecular connection between these two populations of cells.

LILLI PETRUZZELLI, MD, PhD
Dr. Petruzzelli indicated no relevant conflicts of interest.

Flossing May Prevent Plaque (of a Different Sort!)

A n aggressive treatment of periodontal disease decreases chronic systemic inflammation and thereby improve vascular function and slow progression of atherosclerosis? To address this intriguing question, investigators from Connecticut and London performed a randomized, blinded clinical study of a group of otherwise healthy subjects with objective signs of moderate periodontitis. One group was treated once with a standard oral hygiene regimen, while the others received an aggressive protocol that included extensive plaque scaling, dental extractions, and topical antibiotics. Subjects were then monitored for six months with serial assessments of endothelial function, oral health, and plasma markers of inflammation, including interleukin 6, CRP, and IL-6, with a more modest increase in markers of coagulation and endothelial activation (vWF, PAI-1, and soluble E-selectin). These data are consistent with the systemic entry of periodontal pathogens that is known to occur after therapy of this type. Within a week, levels of the markers began to drop, and by six months they were back to or below baseline. Of greater interest, beginning at about one month, the intensively treated group showed improvement in endothelial function, assessed by ultrasound measurement of flow-mediated dilation (FMD) of the brachial artery. At the end of the study, these subjects had further improvement in FMD with lower neutrophil counts and soluble E-selectin levels than the controls.

An association between chronic inflammation and atherothrombotic disorders is supported by abundant epidemiologic and laboratory evidence. A pathological hallmark of early atherosclerosis is accumulation of inflammatory leukocytes in the vessel wall, and among the best predictors of atherothrombotic risk are circulating levels of “markers” of chronic inflammation (e.g., leukocyte count, CRP, factor VIII, fibrinogen, and myeloperoxidase). Patients with chronic inflammatory diseases such as lupus and rheumatoid arthritis are known to be at increased risk for coronary disease and stroke. Recently, chronic periodontal infection has been hypothesized to represent a potentially reversible source of chronic systemic inflammation, and periodontal pathogen have been associated with activation of inflammatory cells in the atheromatous vessel wall. The potential importance of this hypothesis is supported by the population incidence of severe periodontitis, which is as high as 3 percent in some estimates. Using a simple, non-invasive assessment of endothelial function that tests the integrity of endothelial-dependent vasodilating pathways (mostly nitric oxide), these authors demonstrated that a single intensive treatment of severe periodontal disease was associated with a sustained improvement in dental health, endothelial function, and markers of chronic inflammation. It is important to note that the endpoints of this study were surrogate markers for inflammation and vascular health, and that subjects were monitored for only six months, but nevertheless the data are consistent with known pathophysiological data and support the need for a larger study examining the effects of intensive treatment of periodontal disease on atherosclerosis progression and coronary events.

ROD SILVERSTEIN, MD
Dr. Silverstein indicated no relevant conflicts of interest.
Novel Mouse Models of Human Myeloma

The majority of studies to date of human multiple myeloma (MM) cells in vivo have utilized xenograft models. Specifically, human MM cells have been injected subcutaneously into SCID mice in order to evaluate the ability of agents to inhibit tumor cell growth and associated angiogenesis, as well as prolong host survival. A model in which fluorochrome-labeled human MM cells are injected via the tail vein into SCID mice and then migrate and grow primarily in bone has allowed for gene microarray and proteomic studies in MM cells vs. BM as MM cells bind in the BM milieu, both before and after novel drug treatments. Direct injection of MM cells into fetal bone chips implanted subcutaneously into SCID mice (SCID hu model) allows for the study of human MM cells in the context of human extracellular matrix proteins and accessory cells in vivo. This model has been refined by injecting fluorochrome-labeled cytokine-dependent MM cells directly into human bone grafts within SCID mice, which allows for evaluation of cellular and gene changes triggered in tumor vs. BM by MM cell binding, both before and after treatment with novel agents.

These models have therefore delineated the genetic changes and sequelae induced when MM cells bind to the BM, and conversely validated the ability of novel agents to abrogate these genetic changes and induce tumor cell cytotoxicity even in the BM milieu.

XBP-1 is a transcription factor required for plasma cell differentiation, which is also highly expressed at a gene and protein level in MM cells vs. normal plasma cells. Interleukin-6 (IL-6) upregulates both transcript and protein levels of XBP-1 in MM cells; conversely, knockdown of XBP-1 decreases viability and sensitizes MM cells to dexamethasone. The novel agent, 2-methoxyestradiol, downregulates XBP-1 transcripts and protein in MM cells, whereas the proteasome inhibitor Bortezomib works, at least in part, by targeting XBP-1 and the unfolded protein response.

In this paper, Carrasco and colleagues describe a genetically based model of MM, generated by overexpression of XBP-1 spliced isoform (XBP-1s) in the lymphoid system, which faithfully reflects human MM. Specifically, mice transgenic for Eu-directed XBP-1s develop pathognomonic features of monoclonal gammopathy of unclear significance (MGUS) which progress to MM with time, including serum monoclonal protein, bone marrow plasmacytosis, renal disease, and lytic bone disease. In this model, genomic analysis of premalignant B cells and MM cells showed dysregulation of genes with known relevance to human MM, including cyclin D1, MAF, MAFB, and uncovered pathogenetic insights into MCL-1 and FES/JUN. This model therefore offers a unique opportunity to identify genetic changes mediating the development of MM, as well as the progression to MM. Overal of additional genetic abnormalities (p16, p53) offers the opportunity to shorten the prolonged latency time of this model and define their role in MM pathogenesis.

Finally, this model provides a unique system both for identifying novel targets and validating novel targeted therapies.

Predicting Outcomes in CLL

CLL is a highly heterogeneous disorder with markedly disparate clinical course and variable therapeutic response among patients. A number of phenotypic and molecular markers have been shown in retrospective studies to correlate with the pace of disease progression, time to first treatment, and treatment response. In this paper, Grevor and colleagues prospectively analyzed CLL cells from patients in the US Intergroup phase III trial (E2997) for markers of fludarabine (F) single agent vs. fludarabine plus cyclophosphamide (FC) as initial therapy for symptomatic patients who require treatment. Pre-treatment samples were analyzed for Ig VH (immunoglobulin heavy chain variable gene) and p53 mutation status, expression of ZAP-70, CD38 and other phenotypic markers, and cytogenetics by FISH (fluorescent in situ hybridization). The study demonstrated significantly improved complete and overall response rates in patients receiving FC, as detailed in an accompanying report. Two hundred and thirty-five of the 278 study patients had the correlation marker analyses performed. None of the markers correlated with response to either treatment arm. However, patients with the del(17p13.1) or del(11q22.3) had a significantly shorter progression-free survival (PFS) with either F or FC therapy. Interestingly, mutations in the p53 gene located at the chromosome 17p locus did not correlate with outcome, suggesting another relevant gene or genes in the deleted segment.

The clinical and biologic heterogeneity of CLL, reflected in definable subsets of disease using molecular and phenotypic markers, has led to the hypothesis that a risk-adapted therapeutic approach may be feasible. This study by Grevor et al. is among the first to prospectively apply these markers in a randomized multicenter trial. The results confirm a significantly shorter PFS for patients with del(17p) or del(11q) despite similar responses to induction therapy. Such high-risk patients would be logical candidates for alternative initial treatment or consolidation approaches. It will be important to validate these findings in ongoing and future CLL clinical trials, and to standardize methodologies and endpoints for positive vs. negative marker expression. The predictive value for any marker may well differ depending upon the therapeutic regimen applied, as shown by a recent study wherein CLL patients with the del(11q) responded as well to the PCR regimen (pentostatin, cyclophosphamide, rituximab) as the FL regimen (fludarabine plus cyclophosphamide) with either F or FC therapy. The use of prognostic markers thus will be a moving target, but nonetheless one that helps us know where to aim.


KENNETH ANDERSON, MD
Dr. Anderson indicated no relevant conflicts of interest.
**Rituximab in ITP – When and Why Does It Work?**


Despite the increasing use of rituximab in the treatment of idiopathic thrombocytopenic purpura (ITP), there is a remarkably small amount of literature describing its efficacy and toxicity. The authors of this study reviewed all of the articles on this topic published between 1997 and 2004 and found only 19 reports that described five or more patients (313 total patients). Of these 19 reports, nine were published only in abstract form. The median duration of followup was only 9.5 months (range: 2 to 25 months). All of the publications were case reports, case series, or single-arm cohorts, and there were no randomized trials. The reported response rates were higher in studies that contained small numbers of patients, making definitive conclusions about the response rate difficult.

Pre-treatment platelet counts varied between 1,000 – 89,000/µl. Almost all of the patients had been previously treated with corticosteroids, and approximately half of the patients had failed a splenectomy. Patients were treated with four weekly doses of 375mg/m2 in 16 of the 19 studies, while the remainder did not state the dose, or varied either the dose or the duration of therapy. The overall response rate (platelet count >50,000) was 63 percent, and the complete response rate (platelet count >150,000) was 48 percent. The median duration of a response was 10.5 months (range: three to 20 months). Although the median time to a response was 5.5 weeks, it was curiously as short as two weeks in some series (more on this topic later). The majority of the treatment-induced toxicity was infusion-related serum sickness, or other allergic responses. Nine deaths were reported, and most of these events were hemorrhagic or due to an underlying comorbidity. Several patients died of infections, but not clearly related to treatment.

Splenectomy has long been considered the gold standard of therapy for patients who require treatment for chronic ITP. It produces long-term response rates of 85-70 percent, and many of the remaining patients derive some benefit from the procedure. Although splenectomy has an impressive response rate, it is associated with approximately 1 percent operative mortality, as well as a lifelong increased risk of opportunistic infections. The alternative standard therapy is chronic immunosuppressive drug therapy.

The monoclonal antibody against CD20-positive B cells, rituximab, has received recent enthusiasm as an immunosuppressive agent for a wide variety of autoimmune diseases. It is clear that rituximab can induce remissions in ITP. Although, it has been difficult to estimate its true efficacy since the literature is biased by small case series touting high response rates. By restricting analysis to publications that report response rates based on more than five patients, Arnold and colleagues identified only 10 papers and nine abstracts that focused on rituximab efficacy in ITP. Their results place the response rate of rituximab in the same category, but probably not better than most other immunosuppressive agents. However, rituximab still does have the advantage of a relatively good safety profile.

Does this mean that rituximab is a reasonable alternative treatment for ITP patients who require chronic therapy? Although it is being used with increasing frequency as hematologists become more familiar with the drug, we really cannot state definitive efficacy rates or long-term toxicity data to our patients as we can for splenectomy treatment. It is also unclear how anti-B-cell therapy for ITP can sometimes produce a response within a few days. Circulating IgG has a half-life of approximately three weeks, so if rituximab’s effect is to stop all additional immunoglobulin production, its response should not be apparent for several weeks to months. One possible explanation for the rapid effect is that rituximab-coated B cells may compete with immunoglobulin-coated platelets by the reticuloendothelial system. However, it is surprising that enough antibody-coated B cells are generated after rituximab therapy to mimic a “WinRho-like” effect. If this model for the rapid rituximab effect is correct, then one would predict that it would not be seen in post-splenectomy patients. Thus far, this does not appear to be the case.

Although rituximab is clearly a useful agent in the treatment of ITP, the published data is currently a little thin. It would therefore be worthwhile and beneficial for both patients and physicians to study rituximab in a larger cohort. Only then will we be able to definitively understand the efficacy and toxicity of this therapy for ITP.

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**Expansion Hopes Within Reach?**


The bone marrow is a remarkable organ. Every time your heart beats, millions of cells are created. The turnover of these cells requires a tightly regulated balance between the formation of all these blood cells and their senescence and death. Our bodies are able to choreograph this birth and death routine in part due to stem cells, which differentiate and self-renew with each division. The characterization of hematopoietic stem cells has been a remarkably fruitful area of research. Our bone marrow contains at least two types of stem cells, the hematopoietic stem cell (HSC) and a stromal stem cell that is able to give rise to cartilage, adipose tissue, muscle, and bone. One area of exciting research has been the identification of multipotent adult progenitor cells (MAPCs) which could be coaxed from the bone marrow and which are thought to be the precursors for the non-hematopoietic cells. In this paper, Catherine Verfaillie’s laboratory describes convincing data demonstrating that these MAPCs can be expanded in vitro for more than 40-BO population doublings without senescence and that these cells are capable of multilineage engraftment in immunodeficient mice, although approximately 1000-fold more MAPCs were required compared to purified HSC. The HSC derived from these MAPCs are able to serially transplant into secondary and tertiary recipients and the lymphocytes derived from these MAPCs were fully functional. Moreover, using green fluorescent protein transgenic mice and congenic mice, the data suggests that fusion did not occur.

One of the many holy grails in hematology is the ability to expand hematopoietic stem cells. This goal has been elusive in that when bone marrow is placed in culture, there can be a dramatic increase in committed precursors, but there seems to be a limit in the number of true HSCs that expand. Consequently, when these expanded cells are returned to the recipient, there is little beneficial clinical effect that can be observed. These MAPCs, in contrast, seem to be able to expand for prolonged periods ex vivo without evidence of senescence. The promise of these MAPCs is that they can contribute robustly to hematopoesis, generating myeloid and lymphoid cells that can be serially transplanted. Moreover, no tumor formation was observed, which will be important in therapeutic applications. The immediate applications include expansion of HSCs for bone marrow reconstitution or the use of these cells to induce transplantation tolerance. It is not clear yet how these adult MAPCs will function compared to embryonic stem cells or whether these cells will be able to be more broadly used for regenerative medicine outside of hematopoiesis. However, if these results hold true there is the possibility of a readily expandable population of cells that can make blood is truly exciting.

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**CHARLES ABRAMS, MD**
Dr. Abrams indicated no relevant conflicts of interest.
**Enhancing Hematopoietic Function with Parathyroid Hormone**


This study investigates the potential clinical utility of expanding the hematopoietic stem cell (HSC) niche in the bone marrow (BM) with parathyroid hormone (PTH). Although still controversial, several lines of evidence suggest that osteoblasts support HSC expansion and/or survival in the BM, and therefore comprise at least part of the HSC niche. HSCs are found in close association with osteoblasts, osteoblasts support progenitor cells in *in vitro* BM cultures, selective depletion of osteoblasts from adult mice causes a decrease in HSC in the BM, and interventions that increase bone trabecular surface area in mouse BM increase HSC numbers. The laboratory of Dr. David Scadden published previously that *in vivo* administration of PTH leads to increased osteoblast numbers, increased bone trabeculae, and an increase in the number of HSC. Furthermore, PTH administration enhanced survival in a mouse BMT model in which suboptimal numbers of HSC were transplanted. These exciting findings suggest that PTH could provide therapeutic benefit to patients undergoing BMT.

The discovery that PTH stimulates bone formation is not new, but this anabolic function is a bit counterintuitive. The role of PTH *in vivo* is to increase plasma calcium levels by promoting calcium release from the bone, increasing renal tubular calcium resorption. Consistent with its effect to induce release of calcium from bone, continuous administration of full-length (84 amino acid) PTH leads to bone loss and can cause osteoporosis. In contrast, intermittent PTH administration leads to bone formation. Furthermore, the 34 aa amino terminus of PTH maintains the anabolic activity of full-length PTH without causing bone loss. The PTH amino-terminal fragment, known as teniparatide, has been used in promising clinical trials for treating osteoporosis, and was used in this study.

Three clinically relevant scenarios were tested in this manuscript using murine models. First, PTH was administered to test for enhancement of mobilization. Pre-treatment with PTH led to a two-fold increase in the number of HSC in the peripheral blood with no effect on the WBC. These findings suggest that PTH can enhance PBSC mobilization by expanding the BM HSC pool. The investigators next tested whether PTH could prevent the depletion/exhaustion of HSC that can occur with repeated rounds of chemotherapy followed by G-CSF to promote WBC recovery. Mice were exposed to five rounds of cytoxan, each of which was followed by treatment with G-CSF alone or G-CSF plus PTH. After this regimen, PTH led to an increase in the number of HSC in the BM and the number of HSC that could be mobilized into the peripheral blood in response to G-CSF, suggesting that PTH can protect the marrow from the HSC depletion that can occur with repeated rounds of chemotherapy. The third clinical question addressed was really a continuation of this group’s previous studies. The investigators had already shown that PTH administration enhanced survival after lethal radiation and administration of low doses of HSC. Here they proved that this effect of PTH was mediated, at least in part, via its ability to promote (indirectly) HSC self-renewal.

Clinical studies are underway to determine whether PTH can promote engraftment in adult recipients of cord blood transplants. Clinical trials using PTH in the setting of BMT for lymphoma are also being initiated. Perhaps future studies will reveal other therapeutic indications for PTH. There are other features of the HSC niche that could be targeted. For example, the sinusoidal endothelium in the BM also supports HSC survival/proliferation, and enhancement of these cells may also provide important clinical benefits. Pharmacological agents could also be targeted to pathways that regulate HSC interactions with the niche, such as those stimulated by notch, N-cadherin, and/or angiopoietin.

DiVane E Krause, MD, PhD

Dr. Krause indicated no relevant conflicts of interest.
The Voice of the Hematologist: Results of the 2006 ASH™ Annual Meeting Survey

ANDREW SCHAEFER, MD
Dr. Schaefer is the President of ASH.

The extent of the extraordinary range of clinical and research interests encompassed by our Society was brought into clear focus with the results of the 2006 annual meeting survey. These results gave the ASH leadership the opportunity to hear the “voice” of ASH meeting attendees, which is invaluable in charting the future of the Society.

After the 2006 meeting, as in 2002, the Society conducted a survey to better understand who attendees are, their level of satisfaction with the meeting, potential areas of improvement, and the directions attendees would like to see the Society take in future meetings. Their responses offer some insight into the wide-ranging clinical and scientific interests of ASH members and reveal a dynamically shifting portrait of the Society as a whole.

One of the most striking results was the breadth of clinical and research interests expressed by meeting attendees. On the clinical side, leukemia, lymphoma, and myelodysplastic syndromes comprised the top three interests (51, 42, and 37 percent of respondents, respectively). However, no individual category claimed the interest of more than a bare majority of responders, further underscoring the great variety of clinical hematology interests.

The majority of researchers (52 percent) likewise focused on various scientific aspects of hematologic malignancies. Again, however, the data show that no interest carried a clear majority, and hematosis (19 percent), hematopoiesis (18 percent), and transplantation (17 percent) garnered the largest numbers. There is also emerging interest in health services and outcomes research related to hematology.

Meeting attendees hailed from diverse locations. While 61 percent came from the United States, the remaining 39 percent traveled from around the world to attend. Of the latter, the majority were from Europe, but many came from Asia, Canada, and elsewhere. In contrast, visitors from abroad made up only 27 percent of attendees in 2004. The growing number of international attendees reflects the increasing global impact, with over 90 countries worldwide represented by its membership.

In terms of the meeting itself, three out of four attendees had attended at least one meeting prior to 2006. In fact, most are meeting veterans with the average 2006 attendee participating in more than two prior annual meetings. The primary reason that most attended the 2006 meeting was for their own information/education (86 percent), although about two-thirds (65 percent) also cited the sense of community, with opportunities to interact with colleagues and make new contacts.

Interestingly, when asked about the balance between basic science and clinical sessions, over half of the respondents indicated that they were “just right”; 21 percent said they preferred more clinical sessions, and the same number (21 percent) preferred more science. Seventy-eight percent of respondents indicated that they are likely to attend the meeting again in 2007. Although the overall satisfaction of the meeting is high (91 percent), ASH is always striving to improve the meeting and to stay ahead of the latest advances in the science and practice of hematology. This attendee feedback is an essential step towards achieving that goal.

THE PRACTICING HEMATOLOGIST

PROCESS FOR RECERTIFICATION: THE GOOD, THE BAD, AND THE UGLY

JONATHAN S. SERODY, MD

Dr. Serody is Elizabeth Thomas Professor of Medicine, Microbiology, and Immunology for the Program in Stem Cell Transplantation at the University of North Carolina.

Over the past fifteen years there has been an increasing emphasis on the credentialing of physicians from hospitals, insurance companies, and practice plans. As a result, obtaining board certification for a subspecialty discipline has become critical to the success of subspecialty physicians, including hematologists. Starting in the year 1990, maintenance of certification in a subspecialty of internal medicine required completion of a certification program every ten years. This entailed passing modules that assessed medical knowledge or physical diagnosis skills in addition to a secure examination in that discipline.

Beginning in 2004 the ABIM added additional modules that are required for maintaining certification called practice improvement modules (PIMs). PIMs are Web-based self-evaluation tools that guide physicians through chart abstraction, patient survey, and practice system inventory to establish a practice performance assessment for a chronic condition or preventive service. Initially, the physician abstracts data from the charts of at least 10 patients and compares his/her management of a specific clinical condition to guidelines set forth by national accrediting agencies or medical societies. Areas of deficiency are noted, and a plan is put in place to correct these deficiencies. The PIM is completed when the effect of the plan has been measured and the diplomate reports the results to the ABIM. In addition, Maintenance of Certification credit physicians who complete a PIM earn 20 CME credits.

Many large group practices already use this approach to evaluate their practice’s performance adherence to national guidelines for the treatment of chronic diseases. Previously, multiple guidelines were available for physicians to use, particularly for patients with chronic illnesses such as hypertension, diabetes mellitus, or asthma, or for the assessment of procedural-based competence. However, completing a PIM in a subspecialty such as hematology for an academician is a requirement and the physician was difficult in the past, as it required either querying patients or colleagues via a questionnaire, communication skills or a self-directed module that the physician had to generate on his/her own for a specific area of hematology. I’m happy to report that this is no longer the situation.

To assist hematologists, ASH has generated PIMs that assess the management of patients with multiple myeloma, idiopathic thrombocytopenic purpura, and myelodysplastic syndromes. I recently completed the PIM in multiple myeloma. It focused on multiple areas in the management of patients with multiple myeloma — whether or not one’s practice always obtains markers predictive of response to treatment such as beta 2-microglobulin prior to therapy; whether any patient is given bisphosphonates using accepted guidelines for efficacy and safety. The questions for this PIM take about two to three hours to complete for the minimum number of patients (10) that are queried. However, the entire process took me seven months to complete, as it required implementing and reporting the effect of the changes mandated for completion of the PIM. For our group, this centered on the nursing system for all of our investigators and a consistent approach to treatment based on that system. In the future, this should allow for more uniform management of patients with multiple myeloma by the physicians at our center.

These ASH PIMs allow hematologists the ability to compare their practice performance with national guidelines and to correct areas of deficiency. However, please remember that the PIM is not completed until a report is generated describing how the changes implemented affected care. I recommend that physicians who need to recertify make sure that they start the PIM at least one year prior to the expiration of their certificates.

CONTROL YOUR DESTINY WITH THE ASH ITP PIM

KENNETH ADLER, MD, FACP

Dr. Adler is Assistant Clinical Professor at the University of Medicine and Dentistry of New Jersey. He is also a member of the ASH Pay-For-Performance Task Force, for which he was awarded the ASH Outstanding Service Award in 2006.

The practice of medicine continues to change dramatically and we as hematologists must maintain control of our destiny as best we can. Recertification is a fact of life for practicing hematologists who were certified after 1990 and are subject to a time-consuming exam, it can be daunting to try to fulfill the American Board of Internal Medicine’s (ABIM) self-evaluation requirements as well. In order to ease this process and ensure that the practice community is provided with fair and relevant criteria to measure performance, ASH has created hematologyspecific practice improvement modules (PIMs). Now, the Society is pleased to announce the creation of its newest module, the ASH idiopathic thrombocytopenic purpura (ITP) PIM. This benign hematologic module joins the malignant hematology ASH PIMs for myelodysplastic syndromes and multiple myeloma. The voice of hematologists, on the ASH PayForPerformance Task Force of which I am a member, are hopeful that the ITP PIM will be the first of several common benign hematologic conditions such as anemia, thrombophilic disorders, and bleeding disorders that may serve as future PIMs.

As Dr. Serody details in the adjacent piece, requirements for hematologists enrolled in the ABIM Maintenance of Certification (MOC) program have changed. The new recertification requirements for physicians include the need to secure 100 self-evaluation points with 20 points earned in routine knowledge, 20 points gained through an evaluation of practice performance improvement, and 60 elective points. We the members of ASH are looking forward to demonstrating to the ABIM the high quality of our care our members strive to achieve.

Each ASH PIM awards 20 practice improvement points, the number required for recertification as well as 20 AMA category 1 credits. Each set of measures on the ASH Web site is accompanied by physician resources and educational materials. Visit the ASH Web site at www.hematology.org/education/recertification/pim.cfm to access these web-based self-evaluation tools. I must admit that even with my prehistoric computer skills I found the PIM Web site highly user-friendly and wish all our post-1990 members the best of luck.

NEWS AND REPORTS

The Hematologist: ASH News and Reports
Female Leadership in ASH

The program for the 13th Annual Meeting in 1970 included a “Ladies’ Program” which featured a “Luncheon-Fashion Show by a leading San Juan fashion designer,” and promised that “other activities for the ladies will be announced later.” The registration form also included a line for “wife’s first name if accompanying.” Female members of ASH have made great progress since then. Four years later, ASH elected its first female president, Dr. Helen Ranney (pictured, top left). There have been three other female presidents since, with another to come when Dr. Nancy Berliner (pictured, bottom right) assumes the title in 2009.

Women in Hematology — Where Are We Today?
LANIE KASDAN FRANCIS, MD

As ASH prepares to mark its 50th anniversary, in a mood of introspection and optimism I’d like to examine where we’ve been and where we are as women in the field of hematology. The most recent ASH statistics show that 26 percent of ASH members are women. In the last 50 years, there have been four female ASH presidents, making up approximately 10 percent of these leaders in our field.

Looking around at the other fellows in my program and on the ASH Trainee Council, such numbers do not seem representative. A random sampling of fellowship programs represented on the Trainee Council shows that in some of the largest and most prestigious programs, women are catching up with and overtaking their male counterparts in numbers. At the Dana-Farber Cancer Institute, the incoming class of 2006 had 10 women and four men as compared to an even seven and seven in 2000 and five men and three women in 1990. At the University of Michigan, the incoming class of 2006 had eight women and seven men. In 2000, there were seven men and six women and, in 1990, six men and two women. Participants in ASH’s Clinical Research Training Institute over the past five years total 80 and include 46 (57 percent) female fellows and junior faculty. There are women represented on every ASH standing committee, making up a range of 17-50 percent of each committee, and chairing four out of 12. And that speaks only of numbers. Clearly, women hematologists are a growing and formidable force.

Historically, women have made an impact on hematology not through sheer numbers, but through drive, intelligence, and compassion. A review of the National Library of Medicine’s exhibition on Women in Medicine highlights some of our most impressive and inspiring female hematologists. Helen Ranney, born in 1920, was not just a landmark researcher in the field of sickle cell anemia, but also the first woman president of the Association of American Physicians and the first woman to chair the department of medicine at the University of San Diego. Incidentally, she served as ASH president in 1974. Jane Desforges, born in 1921, also served as ASH president (in 1985) in addition to serving as the Associate Editor of the New England Journal of Medicine from 1960-1993.

The climate today was built upon the fortitude of female hematologists like Drs. Ranney and Desforges and is nurtured by a group of women that make contributions to basic and translational science while simultaneously providing trainees with academic mentorship and life lessons. Dr. Margaret Ragni, Professor of Medicine at the University of Pittsburgh and an ASH member since 1985, has served on several standing committees for ASH and co-chaired this year’s special symposium at the annual meeting highlighting hematologic problems in women. It was one of the most well attended sessions at the annual meeting.

Dr. Ragni tells me that she has always approached her academic career as a level playing field, feeling that she has just as much to give as the man or woman next to her. Her advice to trainees is not to believe in the word no, instead to persevere toward your goal. She advises, “Don’t focus on perceived inadequacies and insecurities; everyone has them. Even if you feel like you’re not good enough, act like you are.”

In terms of generalizations, real or imagined, of women being more sensitive or taking work personally, her advice is both wise and practical. She says, “Learn to act and present yourself professionally, learn to manage stress and not get flustered.” Her overriding advice in facing obstacles is to humanize those that you disagree with, working toward common goals becomes easy when you make adversaries into friends.

Barbara Alving, Director of the National Center for Research Resources at the NIH, has a cv. that is as impressive as it is diverse. In addition to co-holding two patents, editing three books, and publishing over 100 papers in the field of thrombosis and hemostasis, she has worked for the FDA and as a member of the hematology subcommittee at the ABIM, and serves as Professor of Medicine at the Uniformed Services University of the Health Sciences in Bethesda.

Dr. Alving feels that she is constantly in the state of becoming and evolving. Her flexibility and intellectual curiosity, characteristics she feels are integral to personal and academic success, help propel her forward in her endeavors. Her advice to trainees is to “never burn bridges; instead build networks” and she notes that women have particular communication and socializing skills that move projects and collaborations along. She warns against crumbling in the face of rejection and urges women in the field to “pick yourself up, keep showing up, and keep publishing papers.” Dr. Alving is clear that the challenges and stresses of family have an impact on women in hematology. She stresses the importance of nurturing a strong family; in order to do this, she advises women to think strategically about their time commitments, to obtain help with tasks not essential to their careers and family lives, and to always provide time for themselves.

So the question remains: women in hematology — where are we today? Our numbers and presence are growing and we are finding ways into leadership positions. We look for advice from those who went before us and work to encourage and mentor those who follow behind us. We think and feel deeply — about our patients, our research, and our families. In the end, we continue to evolve and adapt to a new world where we still struggle to have it all.

The Hematologist: ASH News and Reports
With the creation of the Hematology Library, ASH has improved accessibility and expanded the functionality of its publications online. The Hematology Library, available at www.hematologylibrary.org, provides access to the wealth of information available from ASH. The site features quick links to every ASH publication, including *Blood*, the annual meeting abstracts, the ASH Image Bank, and *Hematology*, the ASH Education Program Book.

The results are impressive. For example, typing “thrombosis” into the search field yields an issue of *Blood* from October 1998, an entry from the latest copy of *Hematology*, and several photos of necrotic lesions from the ASH Image Bank, along with over 5,000 other responses.

Visit the new ASH Hematology Library today to easily access the vast amount of information available through the ASH publications online.