ASH Announces $9 Million Bridge Grant Program to Combat the Reduction in NIH Funding

Commits to 30 one-year grants of $100,000 each year for the next three years totaling $90 awards

Lenalidomide Maintenance Therapy in Multiple Myeloma

Three recently published studies support the use of lenalidomide maintenance therapy in multiple myeloma (MM). The first, a clinical trial from Palumbo and colleagues compared melphalan prednisone (MP) versus MP lenalidomide (MPR) versus MPR plus R maintenance therapy. At a median follow-up of 30 months, progression-free survival (PFS) was significantly prolonged after MPR-R (31 months) versus MPR (14 months, p < 0.001) or MP (13 months, p < 0.001). Importantly, the PFS benefit occurred in patients 65 to 75 years old, but not in older patients. To date, there is no overall survival (OS) difference. Landmark analysis showed a 68 percent reduction in progressive disease after MPR-R treatment. The incidence of secondary cancers at three years was 7 percent in patients receiving MPR-R; 7 percent for those receiving MPR, and 3 percent for those receiving MP. The other two studies evaluated lenalidomide maintenance post high-dose therapy supported by autologous stem cell rescue. The study by McCarthy et al. was unblinded when an interim analysis revealed that 20 percent of patients on lenalidomide versus 44 percent of patients on placebo (p < 0.001) treatment died or had progressive disease. Moreover, 86 of 128 patients receiving placebo who had not yet progressed then elected to begin lenalidomide maintenance. In spite of this high percentage of crossover, the median time to progression, post-transplant, was 46 months with lenalidomide maintenance versus 27 months in the placebo group (p < 0.001). Additionally, more deaths were noted in the placebo arm (35, 23%) compared with the lenalidomide arm (35, 15%) (p = 0.03). Secondary cancers were noted in 18 (8%) and six (3%) of patients who received lenalidomide and placebo maintenance, respectively. The third trial by Attal and colleagues in the Intergroupe Francophone du Myelome (IFM) also evaluated lenalidomide maintenance therapy post-transplant. PFS was 41 months and 23 months with lenalidomide and placebo maintenance, respectively (p < 0.001), but there was no significant difference in OS. The incidence of secondary malignancies was 3.1 versus 1.2 per 100 patient-years in the lenalidomide and placebo maintenance cohorts, respectively (p = 0.002). Moreover, median event-free survival, including secondary cancers, was prolonged in the lenalidomide cohort at 40 months compared with 23 months in the placebo cohort (p < 0.001).

These three studies provide a strong rationale for the use of lenalidomide as maintenance therapy in MM. For many years, there have been efforts to identify effective maintenance therapies to prolong response to initial treatment in MM. Although is interferon prolonged responses by several months, its toxic adverse effect profile precluded broad clinical use. Corticosteroids were also explored in early trials, but efficacy was unconfirmed. In the era of novel therapies, low-dose thalidomide has been evaluated in both patients ineligible for transplant and those undergoing transplant. Benefit was observed in both groups, but neuropathy attendant to prolonged use of even low-dose thalidomide limits its utility. Intravenous bortezomib at several doses and schedules has also shown activity in prolonging PFS and even OS in both patients ineligible for transplant and patients who are post-transplant. Further evaluation of proteasome inhibitor therapy as a maintenance strategy is warranted as bortezomib given subcutaneously has the advantage of ease of administration and better tolerability compared with the intravenous form, and next-generation, oral proteasome inhibitors promise an even more patient-friendly delivery system. At present, however, the three randomized trials cited above provide the strongest evidence for use of lenalidomide maintenance treatment to prolong response in MM.

What have we learned? In all three studies, the PFS was markedly prolonged with use of lenalidomide maintenance. For many years we have understood the heterogeneity of MM, and recent studies have confirmed its genetic complexity at diagnosis as well as the molecular mechanisms that underlie treatment failure due to drug resistance. Although relapsed MM may be effectively treated with novel agents, it is not curable. Therefore, current strategies include combinations of targeted and conventional therapies to address
If It’s a Benign Disease, Why Is the Patient So Sick?

CHARLES PARKER, MD,* KEITH HOOKS, MD,* ARMAND KEATING, MD*

1. Professor of Medicine, Division of Hematology and Hematologic Malignancies, University of Utah School of Medicine
2. Director, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute
3. ASH President, Professor of Medicine, Director, Division of Hematology, Epstein Chair in Cell Therapy and Transplantation, Professor, Institute of Biomaterials and Biomedical Engineering, University of Toronto

*In “benign hematology” in the United States a subspecialty that deals with diagnosis and management of a loose collection of uncommon/rare diseases (e.g., thalassemias, hemoglobinopathies, and inherited bleeding disorders), or one that covers those diseases together with some of the country’s most common disorders (e.g., complications of arterial and venous thrombosis and anemia)? This is one of many questions that was addressed at a workshop convened by the National Heart, Lung, and Blood Institute (NHLBI) on June 8, 2012. The title of the workshop was “Planning for the Training Future of the Workforce in Hematology.” The roster was composed of 28 health professionals from throughout the United States (both pediatric and adult hematology were represented) and 19 National Institutes of Health (NIH) participants. Dr. Keith Hooks, director, Division of Blood Diseases and Resources (DBDR), NHLBI, and Dr. Donna DiMichele, deputy director, DBDR, hosted the meeting that was held on the NIH campus. Dr. Armand Keating, ASH president, Martha Liggett, Esq., ASH executive director, and Mila Becker, Esq., ASH senior director, Government Relations, Practice, and Scientific Affairs, dutifully represented the Society.

The impetus for the meeting is the perception that the number of physicians whose clinical and research focus is non-malignant hematology is declining. In his introductory remarks, Dr. Hooks presented data in support of that perception. In addition to the problems that plague all areas of academic medicine (the steady decline in NIH appropriations since 2003, the low success rate of grant funding, the high burden of educational debt), Dr. Hooks showed that the number of principal investigators funded through DBDR has declined by more than 50 percent over the past 10 years (Figure 1). What accounts for this precipitous decline in funded

The graph shows discreet individual principal investigators funded by the National Heart, Lung, and Blood Institute (NHLBI) beginning in fiscal year 2000 and ending September 30, 2011 (FY 2011). Each funded principal investigator (PI) is included only in the first year during which he or she is funded. Inclusion in a given year represents individuals appearing for the first time in the 12-year time period. This includes new and established PIs who were funded prior to October 1, 1999, by an NIH Institute other than NHLBI (without concurrent NHLBI funding) who then achieved new funding from NHLBI. The only way a PI could be counted on more than one occasion is if he or she had a hiatus in NHLBI funding for one or more years after being funded in the early part of the FY2000-FY2011 time period and then subsequently was funded as an NHLBI PI before September 30, 2011 (a very infrequent event). Accordingly, the graph may be said to represent the “steady-state” of hematologic PIs funded by NHLBI over the time period.

The Hematologist welcomes letters of up to 200 words. Please include a postal address, email 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:
Karen Learner, Managing Editor
The Hematologist: ASH News and Reports
2021 1st Street, NW, Suite 900
Washington, DC 20036
klearner@hematology.org

Multiple Myeloma

(Cont. from page 1)

The graph shows discreet individual principal investigators funded by the National Heart, Lung, and Blood Institute (NHLBI) beginning in fiscal year 2000 and ending September 30, 2011 (FY 2011). Each funded principal investigator (PI) is included only in the first year during which he or she is funded. Inclusion in a given year represents individuals appearing for the first time in the 12-year time period. This includes new and established PIs who were funded prior to October 1, 1999, by an NIH Institute other than NHLBI (without concurrent NHLBI funding) who then achieved new funding from NHLBI. The only way a PI could be counted on more than one occasion is if he or she had a hiatus in NHLBI funding for one or more years after being funded in the early part of the FY2000-FY2011 time period and then subsequently was funded as an NHLBI PI before September 30, 2011 (a very infrequent event). Accordingly, the graph may be said to represent the “steady-state” of hematologic PIs funded by NHLBI over the time period.
Corrections:

In the July/August issue, Dr. David Scadden’s title on page 3 was incorrect. His correct title is:

David T. Scadden, MD
Gerald and Darlene Jordan Professor of Medicine
Co-Director, Harvard Stem Cell Institute
Co-Chair and Professor, Department of Stem Cell
and Regenerative Biology, Harvard University
Director, Center for Regenerative Medicine
Massachusetts General Hospital

In the July/August issue, we inadvertently switched the faculty for the 2012 State of the Art Symposium and the 2012 Consultative Hematology Course. The online issue is correct; go to www.hematology.org/Publications/Hematologist/issues/8612.aspx.

In the July/August issue, we incorrectly identified the year of a previous article in The Hematologist in the article titled "A Post-Modern View of Women in Hematology: A Focus on Work/Life Balance." The article, "Women in Hematology – Where Are We Today" was published in May 2007, not May 2005.

YOU SPOKE UP; ASH LISTENED

Programming Changes for Annual Meeting Attendees Interested in Hemostasis and Thrombosis

The leadership of ASH wants to ensure that the annual meeting addresses the needs of researchers and practitioners across the entire field of hematology, including those with interests in the fields of hemostasis and thrombosis. In an effort to make the annual meeting a more valuable experience for members of the hemostasis and thrombosis community, some changes in the programming of the annual meeting sessions will be piloted at the 2012 ASH meeting in Atlanta.

Based on the recommendations of the ASH Task Force on Hemostasis and Thrombosis, ASH will make every effort to group hemostasis and thrombosis presentations in one geographical location. The schedule will be reviewed to ensure maximum adherence to this principle, including evaluation by the ASH Committee on Scientific Affairs and the ASH Program Committee before being finalized in September. ASH will also provide wireless Internet connectivity, comfortable seating, and concessions and refreshment stands during the breaks in close proximity to thematically grouped sessions. The goal is to provide an atmosphere conducive to networking and interaction among meeting participants with shared interests.

In addition, the format of the "Special Symposium on the Basic Science of Hemostasis and Thrombosis" will be changed. While the symposium will still be held on Tuesday, the simultaneous sessions will not be held in the afternoon as in past years. Instead, the morning session will be extended by 30 minutes to take place from 7:15 to 9:15 a.m. and will include a 30-minute overview of "Best of ASH in Hemostasis and Thrombosis." The overview will highlight the key abstracts presented at this year’s meeting.

ASH Clinical Practice Webinar Series

ASH continues to host a series of webinars on issues practicing hematologists frequently confront. These sessions will feature presentation by experts in the field, provide time for questions and answers, and cover the most current information on how to best diagnose and care for patients.

The next webinar will be held Thursday, September 20, 2012, at 8:00 p.m. Eastern Time. Registration is free and available to ASH members and non-members. Visit www.hematology.org/webinars for more information on registration.

Autoimmune Hemolytic Anemia Webinar

Idiopathic autoimmune hemolytic anemia (AIHA) is an acquired disease that occurs when antibodies form against a person’s own red blood cells. One of the most important issues associated with the early diagnosis and acute management of AIHA is the communication between blood bank personnel and the hematologist. Diagnosis, followed by acute and chronic management of AIHA involves the thoughtful use of an array of clinical and laboratory analytical tools and a familiarity with a complex therapeutic armamentarium.

Moderator:
Samuel M. Silver, MD, PhD, University of Michigan Medical School

Speakers:
Marc Kahn, MD, Tulane University School of Medicine, New Orleans, LA
Leslie E. Silberstein, MD, Boston Children’s Hospital, Boston, MA

ASH is grateful to The Henry Loring Masters Foundation for building awareness among caregivers, patients, and families of the critical path and timelines for treatment of Autoimmune Hemolytic Anemia (AIHA) in young people and for providing support for the development and distribution of this valuable webinar.
The Clinical Research Training Institute – How It Began

One of ASH’s most important goals is to facilitate the career development of trainees in hematology. During the ASH strategic planning meeting of 2000, insufficient opportunity to obtain formal training was recognized as an obstacle for those fellows and junior faculty who were interested in careers in patient-oriented clinical research. To address this problem, the Society’s Executive Committee established the Clinical Research Training Institute (CRTI) in 2001. An organizing committee consisting of Drs. Ron Hoffman, Mount Sinai School of Medicine; George Dover, Johns Hopkins Children’s Center; Robert Todd III, Baylor College of Medicine; and Douglas Rizzo, Medical College of Wisconsin, formulated the outline of what was to be a 1-weeklong, intensive training course focused on clinical investigation. Dr. Jim George, past ASH president, then counselor, was asked to lead the program, and he recruited Dr. Beverly Mitchell, 2001 ASH president, to share director responsibilities. Together with Drs. Gary Raskob and Sara Vesely, both of the University of Oklahoma Health Sciences Center, the organizing committee formulated a program that included lectures and, most importantly, small group discussions aimed at refining clinical research protocols developed by the participants. Additionally, ASH leaders were brought in to participate in informal evening discussions during which they provided the participants with insights from their own career development paths. A cornerstone of the program was the selection of participants who were highly motivated to pursue careers in clinical research and who had the appropriate mentorship at their home institutions. The program started with 20 participants and 20 faculty, and this 1:1 participant-to-faculty ratio has been maintained over the life of the program.

The opportunity for both structured and informal collegial interactions among the faculty and participants has fostered durable relationships. For example, Dr. George recently wrote letters to support the promotion and award of tenure to two former participants with whom he has corresponded since 2003. As documented in Dr. Gitlin’s article, the academic progress of CRTI participants has been notable. Having former participants return as CRTI faculty has been particularly rewarding, and we are looking forward to the circle being completed when (or more of) the graduates return as CRTI director.

~James N. George, MD, and Beverly S. Mitchell, MD
First Co-Directors of CRTI

State of the Program

As the Clinical Research Training Institute (CRTI) celebrates its 10th anniversary, it is an opportunity time to reflect on the current state of the program. Initially, admission to the CRTI was restricted to members from North America. Two years ago, eligibility criteria were modified to allow ASH members (North American or International) in good standing who meet other eligibility criteria to apply for and be accepted into CRTI. A competitive selection process leads to acceptance of 20 well-qualified participants each year.

What makes this program unique is the 1:1 faculty-to-participant ratio, a feature that has been carefully protected over the life time of the program. Participants are paired with faculty mentors, and this relationship is maintained over the course of the year and often beyond. The goal of the program is to provide exceptional training in order to conduct rigorous patient-oriented clinical research. To achieve this goal, CRTI participants attend a series of didactic lectures presented during the weeklong summer workshop; revise and refine their research projects in small-group sessions, both at the workshop and over the course of the year; and draw on the special skills of the faculty that include expertise in biostatistics, bioinformatics, and clinical trial design.

Collaboration with CRTI faculty often continues after the program is completed. For example, with CRTI faculty, CRTI graduates co-author evidence-based mini-reviews (www.hematology.org/Patients/Other-Resources/Education-Book/6708.aspx) for Hematology, the ASH Education Program Book. In addition to the intense focus on teaching participants how to conduct patient-oriented clinical research, the overarching aim of CRTI is to create an environment that encourages scholarship, career development, networking, and fosters long-term mentoring relationships.

CRTI costs approximately $400,000 per year to operate, with the bulk of the expenditures going to support the summer workshop. The program is funded principally by the Society but also receives support from NIH conference grants, individual member contributions, and an endowment. Looking to the future, ongoing support from ASH members through the newly formed ASH Foundation will be critical to the continued success of CRTI.

Future goals of the program are to develop a stronger, more sustainable mentoring program; to support the program with faculty largely composed of CRTI graduates who have gone on to achieve successful careers as clinical researchers and are now mentoring others; and to critically analyze and disseminate to the membership the outcomes of the CRTI program. CRTI allows faculty to teach and mentor others while they are engaged in clinical practice, building collaborative networks, and celebrating the success of junior colleagues who are at the inception of their careers.

~Julie Panepinto, MD, MSPH, and Mark Crowther, MD
2012 Co-Directors of CRTI

ASH is in the midst of celebrating the 10-year anniversary of the Clinical Research Training Institute (CRTI). This intense, longitudinal, mentored educational and training experience is designed to accelerate the development of early-career hematologists interested in pursuing patient-oriented clinical research (POCR). The 10th class of participants recently completed the weeklong workshop in La Jolla, CA.

Among the obstacles that interfere with the successful recruitment and retention of trainees into careers focused on POCR, paucity of clinical research-specific training programs and effective mentorship appears paramount.1 Productive development and implementation of POCR projects has been shown to correlate with mentor involvement in an area specific to hematology/oncology trainees.2 To encourage POCR careers in hematology, the Society has invested both capital and human resources in programs that support clinical investigation, including the CRTI.

The program consists of a weeklong workshop in the summer that includes didactic, interactive large-group, small-group, and one-on-one experiences that cover a variety of topics that are important for conducting POCR and for academic career development. Following the workshop, participants are expected to use the CRTI experience to guide further development and implementation of their research projects under the auspices of their “home mentor” and with the advice of a “CRTI mentor.” Participants reconvene with their CRTI small groups at the ASH annual meeting in December to review project progress and ongoing career-development activities. Networking opportunities with other CRTI participants and faculty are provided at the annual meeting. At the end of the CRTI program year, participants meet once again to review progress on both research aims and career development.

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A review and assessment of CRTI participants from the program’s first seven years was recently completed by ASH volunteers and staff. Participant racial and gender characteristics were diverse. Sixty-seven percent (67%) of trainees were white, and 33 percent were from other racial/ethnic groups. Fifty-nine percent (55%) of trainees were female. Although the majority of participants were in their fellowship while participating in CRTI, 32 percent had previously completed their fellowship training and were in early-career positions. The majority of participants have been from the United States with 8 percent from Canada. (Initially, eligibility was limited to applicants from institutions in the United States and Canada. Beginning two years ago, individuals from anywhere in the world became eligible to apply to the program.)

Both non-malignant and malignant diseases were the focus of wide-ranging areas of investigation during the program’s first 10 years. More than one-half of these projects were either completed or ongoing at the time of the survey. An emphasis of CRTI is development of collaborative research teams. Collaborations with other participants and/or program faculty continue today. As part of the ongoing 10-year anniversary coverage, look for an article in the November/December issue of The Hematologist that focuses on a past participant and how she used the CRTI experience productively to obtain funding and catapult her career to the next level.
ASH President Applauds the Success of CRTI

The ASH leadership is delighted with CRTI’s success. CRTI has become an ASH flagship program as reflected by the passion displayed by the Executive Committee, the faculty, and the participants. As documented in Dr. Gitlin’s article, the metrics show that CRTI is an exemplary model that should be adopted by many specialty societies and has already been emulated by at least one.

I applaud the outstanding contributions of the CRTI co-directors and faculty who have contributed their time and energy over the past decade and encourage anyone called to participate in the program to treat the invitation like the true honor it is.

There are several key features to its success, including the enviable and distinctive 1:1 ratio of faculty to participants. Another feature, one that I have had the privilege to witness, is the ongoing networking among CRTI graduates. I believe that the benefits of the interactions among the participants will continue to accrue in the years to come.

The success of the program is also a tribute to the individual ASH members who have contributed monetarily to the program. I recently spoke with one such donor who said his support for the program is based on his conviction that it provides young hematologists with an outstanding start in a career in clinical research. I also want to recognize the Wallace H. Coulter Foundation both for their generous support of the program’s start-up and for their continued interest to this day.

As with many aspects of clinical research currently, the future of CRTI will have an international focus. We began welcoming participants from outside North America in 2011 and hope to attract more international applicants to the program through our outreach efforts around the globe. We have already been able to build on the program’s success through our partnership with the European Hematology Association in establishing the Translational Research Training in Hematology program. I am also very pleased to share that ASH will be hosting a research skills workshop for hematology faculty in Latin America in advance of the Highlights of ASH® meeting in Santiago, Chile, in 2013.

Bravo CRTI! We congratulate the CRTI participants and faculty on the program’s 10th anniversary, and we look forward to your continued success over the next decade.

~Armand Keating, MD
ASH President

2012 CRTI Participants

Staci D. Arnold, MD, MBA, Columbia University Medical Center, New York, NY
Vinai C. Bhagrath, MD, McMaster University, Hamilton, Ontario, Canada
Danielle M. Brande, MD, Duke University, Durham, NC
Tyler W. Buckner, MD, University of North Carolina, Chapel Hill, NC
Jonathan B. Cohen, MD, The Ohio State University-James Cancer Center, Columbus, OH
Kevin J. Curran, MD, Memorial Sloan-Kettering Cancer Center, New York, NY
Alexey V. Danilov, MD, Dartmouth-Hitchcock Medical Center, Lebanon, NH
Adam J. Esbenshade, MD, Vanderbilt University, Nashville, TN
Michael W. Evans, MD, MPH, Penn State Hershey College of Medicine, Hershey, PA
Saar I. Gill, MD, University of Pennsylvania Health System, Philadelphia, PA
Saulius K. Girmus, MD, Boston University School of Medicine, Boston, MA
Patrick T. McGann, MD, Baylor College of Medicine, Houston, TX
Keri Nottage, MD, St. Jude Children’s Research Hospital, Memphis, TN
Christine Phillips, MD, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH
Reajeev Rajendra, MD, PhD, Fred Hutchinson Cancer Research Center, Seattle, WA
Kristen M. Santillipo, MD, Washington University, St. Louis, MO
Edward Allan Sison, MD, The Johns Hopkins University, Baltimore, MD
Kendra L. Sweet, MD, H. Lee Moffitt Cancer Center, Tampa, FL
Rachel M. Thienprayoon, MD, The University of Texas Southwestern, Dallas, TX
Kitsada Wudikarn, MD, University of Iowa, Iowa City, IA

The Hematologist: ASH NEWS AND REPORTS
Congressional Pressure Builds on Spending as New Fiscal Year Approaches

October marks the beginning of the new fiscal year and the date by which spending bills must be completed by Congress. If Congress cannot reach a decision about spending bills by that date, it has two options: pass a temporary continuing resolution that extends federal agency and program funding from the prior year or shut down the government until it can come to an agreement on spending. As this issue of The Hematologist went to press, it appeared that the leadership in the House and Senate had reached an agreement to fund the government for six months—a move that would avert an October 1 shutdown and keep the federal government operating through March 2013. The continuing resolution would keep the government funding at the same levels as last year, and it would prevent a pre-election showdown over shutting down the government, something neither Democrats nor Republicans want. However, many issues need to be resolved, including how to deal with the automatic across-the-board spending cuts (sequestration) that arose as a consequence of the failure of the Super Committee to agree upon a plan to curtail spending.

Sequestration: What Is It and Is It Going to Happen?

“Sequestration” is often in the news and is dominating the budget debate in Congress, but what exactly does it mean? Originally sequestration was a legal term referring to the act of seizing property by an agent of the court to prevent that property from being disposed of or misused before a dispute over its ownership could be resolved. But recently the term has been appropriated by Congress to describe a fiscal policy procedure. If the 13 appropriation bills passed separately by the legislature provide for total government spending in excess of the limits of the Budget Control Act, and if Congress cannot agree on ways to cut back the total or if a higher Budget Resolution is not passed, an automatic reduction in spending goes into effect. This automatic spending cut is called sequestration, and in this case, the U.S. Treasury Department will sequester the money that was appropriated in excess of that prescribed by the Budget Control Act. To avoid sequestration, Congress must identify more than $100 billion in savings or across-the-board cuts in funding of domestic and defense programs will be enacted on January 2, 2013.

The budget of every agency could have been equally affected by sequestration. However, Congress chose to exempt some programs (for example, Social Security and certain parts of Medicare and Medicaid). The fallout from this decision is that sequestration of a higher proportion of the budgets of the nonexempt programs would be required to meet the prescribed spending reduction mandate. The exact impact on programs that would be subject to sequestration has not been made available, but NIH leadership has been instructed to plan for sequester cuts of 7 to 9 percent.

Sequestration was intended to be so catastrophic that Congress would find means to avoid such a draconian process, but so far Congress has not been able to come to an agreement on how to resolve the deficit (remember the failure of the Super Committee?). With sequestration pressures mounting, some in Congress have begun discussing the possibility of delaying the process by a year while other members are proposing alternative spending and revenue strategies. Consequently, the outlook is unclear.

ASH is anxious about the impact of sequestration on federal agencies and programs relevant to hematology, particularly the impact on hematology research funded by NIH. As noted in this issue’s cover story, the Society has taken steps to address the NIH budget crisis, including enhanced advocacy focused on protecting NIH. All ASH members are encouraged to participate in ASH’s advocacy campaign and to contact your Representative and Senators. Please visit http://grassroots.hematology.org to get involved.

Medicare Proposes 2013 Physician Fee Schedule Regulation

The Centers for Medicare & Medicaid Services (CMS) announced the proposed 2013 Physician Fee Schedule rule on July 7. The proposed rule assumes that physician payment will be reduced by 25 percent as a result of the flawed physician payment formula. On the other hand, payments to family physicians would be increased by approximately 7 percent and by 3 to 5 percent for other primary care practitioners. Among the many aspects of health care that are dealt with in this broad-reaching legislation are the following: care transition codes, telehealth, advanced molecular pathology services, preventive services, multiple procedure payment reductions, face-to-face requirement for high-cost durable medical equipment, the Physician Compare Program, the Physician Quality Reporting System, e-prescribing, and the value-based modifier. ASH will be submitting comments to CMS by the September 4 deadline.

Supreme Court Upholds Health-Care Law in 5-4 Decision

MILA BECKER, ESQ.
Senior Director, Government Relations, Practice, and Scientific Affairs

As soon as President Obama signed the Patient Protection and Affordable Care Act (PPACA) into law in March 2010, opponents called for its repeal and challenged the law’s constitutionality. The new law phases in, over a period of years, several reforms, including eliminating limits on annual and lifetime coverage; removing restrictions for pre-existing conditions; requiring that large insurers spend 85 percent of the premium dollar on direct patient care (80% for small market insurers); guaranteeing essential benefits; expanding Medicaid; providing no-cost preventive benefits; eliminating the Medicare Part D “doughnut” hole; increasing Medicare and Medicaid payments and funding of programs to support primary care; testing new, patient-centered payment and delivery models; and funding research on the effectiveness of different treatments. The core concern, however, was a provision known as the individual mandate, requiring most U.S. citizens and legal residents to have health insurance (or pay a fee) by 2014. Critics argued that the law’s requirement that people have a minimum level of health insurance coverage exceeded congressional powers under the Commerce Clause of the Constitution.

On June 28, in a five-to-four decision, the U.S. Supreme Court decided that the individual mandate was constitutional. The majority decision, drafted by Chief Justice John Roberts, held that the indispensability of delaying and penalty fee are constitutional as an exercise of Congress’ taxing power. The Court also ruled that the PPACA’s Medicaid expansion provisions are constitutional, but the penalty for a state’s failure to expand is not. Under the PPACA, states were given federal subsidies and required to accept an expansion in Medicaid recipient eligibility to cover all individuals under age 65 with incomes below 133 percent of the Federal Poverty Level and a minimum benefits package, or lose all of their existing Medicaid funding. The Court ruled that Congress can offer states the option to accept expansion under the PPACA but cannot put their existing Medicaid funding at risk.

What does the Supreme Court’s decision mean, and what is the expected fallout?

The decision means that the law’s complex framework remains intact. Employees will be required to provide health insurance or pay penalties. Provisions of the law already implemented will continue, such as not allowing insurers to discriminate against sick people and allowing young adults to remain on their parents’ health insurance policies. Additional provisions will continue to move forward, such as testing new delivery and payment methods and extending coverage of insurance.
investigation in the field? This question generated a wide-ranging discussion, but there was a consensus that the field’s growth has been stymied by a paucity of career opportunities for those who invest in training in benign hematology.

According to the model envisioned by Dr. Gil White of the BloodCenter of Wisconsin (Figure 2), entry into the training “pipeline” is discouraged, because, at the other end, career opportunities in benign hematology are limited almost exclusively to academic positions, and those positions must be leveraged through acquisition of highly competitive extramural funding as clinical revenue alone is insufficient to support those positions. But most of those who enter hematology/oncology training programs eventually take jobs in private practice, and, currently, positions in the private sector devoted exclusively or even predominately to benign hematology are rare. The idea that this shortage of career opportunities constrained growth in the field resonated with the group and produced a number of suggestions aimed at addressing this critical issue. Much of the discussion focused on how to create job opportunities in the private sector. This issue has been championed by ASH, and Dr. Keating presented a vision of how the unique skills of an expertly trained benign hematologist could be utilized by hospitals to improve patient care while reducing costs through improved efficiency. The position of a “systems hematologist” is seen as somewhat analogous to that of the hospital-based infectious disease specialist who acts in a number of capacities that utilize his/her special skills, including being the infection control officer and infectious disease epidemiologist and providing oversight on the use of antimicrobial agents. Similarly, the systems hematologist would provide expertise in the use of anticoagulant drugs, oversee the utilization of recombinant prohemostatic drugs; interface with the pathologist in transfusion medicine, laboratory medicine, and bone marrow analysis; and provide support in fetal/maternal hematology and critical care hematology in intensive care units and emergency rooms.

Looking to the future, one can easily imagine the systems hematologist providing expertise in the interpretation of the results of whole-genome and whole-exome sequencing, in implementation of cell and gene therapy, and in appropriate reimbursement for services.

The Hematologist: looking to the future, one can easily imagine the systems hematologist providing expertise in the interpretation of the results of whole-genome and whole-exome sequencing, in implementation of cell and gene therapy, and in appropriate reimbursement for services.

For states, the ruling means that those who have been sitting on the fence will be under pressure to get to work on implementing the main portion of the law—setting up health benefit exchanges. At least a third of the states have made little progress developing these new marketplaces, which means either the federal government will run their health exchanges or they will take part in a state-federal partnership. States face a November 16 deadline to file for federal approval of their health exchanges, which will serve the individual and small-group markets.

On the Medicaid front, without the power to pressure states into expanding their Medicaid programs, some states may choose not to comply with the federal government provisions. Consequently, fewer people than expected may be able to obtain insurance coverage through Medicaid. It is unclear, however, how many states will ultimately turn down the expansion for which the federal government has agreed to pay 90 percent.

Even with the Supreme Court’s ruling, the political debate over the health-care law continues and its future will be an issue in the 2012 elections. Initially, the ruling should be a victory for President Obama’s signature accomplishment in office and for congressional Democrats, even with the swipe at the Medicaid provision. However, some supporters of the law are concerned that the allusion to taxes in the decision could cause the President to lose political points as Republicans will frame it as “the greatest tax ever.”

Campaign analysts expect that the decision will fade quickly from the presidential election debates, but it will figure more prominently in contested congressional races.

Meanwhile, Republican leadership in the House of Representatives responded that they will continue to schedule votes for bills to repeal the health-care reform law. On July 10, for example, the House of Representatives voted for the 33rd time to pass a bill that would repeal PPACA, but, without a majority in the Senate and with the veto pen at the ready of President Obama, this legislation is not moving forward before the November elections.

The American Society of Hematology will continue to work with Congress and the Obama administration on implementation, but we will also advocate for changes or refinements that we think could improve the law. Such modifications include supporting reforms that will benefit the practice of hematology and the patients our members treat. For more information about the Society’s work on health reform, please visit www.ash.org.
OTT1: A New Link Between Stem Cell Self-Renewal, Leukemia, and Aging


The findings of this study from the laboratory of Glen Raffel at the University of Massachusetts Medical School provide new insights into the regulation of hematopoietic stem cell (HSC) self-renewal, transformation to leukemia, and stem cell aging.

One-Twenty-Two-1 (OTT1) was first identified as a fusion partner with MKL1 in the t(1;22) translocation acute megakaryocytic leukemia (AMKL). (OTT is also called RBM15, as it was the 15th RNA binding motif protein to be named.) To understand the role of OTT1 in the OTT1-MKL1 fusion protein, investigators needed to study the function of OTT in normal hematopoiesis. Previous studies had shown that Ott1 in murine cells is differentially expressed during hematopoiesis and may act to inhibit myeloid differentiation. It is expressed at the highest levels in hematopoietic stem cells and at progressively decreased levels during myeloid differentiation. When Ott1 levels are artificially decreased using RNA interference, there is increased differentiation. Conversely, enforced expression inhibits differentiation.

The investigators assessed the effects of knocking out Ott1 in cells of the mouse hematopoietic system. Under steady-state conditions, deletion of the Ott1 gene had no significant effect on peripheral blood counts or bone marrow cellularity. In contrast, under stress conditions that require HSC self-renewal, lack of Ott1 led to increased cycling and rapid loss of HSCs (Figure). For example, in contrast to wild-type mice, mice lacking Ott1 had impaired hematopoietic recovery following treatment with 5FU and died after 10 to 14 days. Also, BM cells from Ott1 knockout mice failed to engraft into lethally irradiated, wild-type recipients, an even more demanding test of HSC expansion capacity.

Potential mechanisms leading to stem cell exhaustion were examined. While there was no apparent increase in apoptosis or senescence of Ott1 KO cells, there was evidence of loss of quiescence, DNA damage, and increased reactive oxygen species (ROS). However, inhibition of ROS production by anti-oxidant treatment did not rescue the HSC defect.

When the investigators compared the gene expression pattern of Ott1 KO with that of wild-type HSCs, they found that many genes were differentially expressed. What did this list look like? It was amazing! There was a very high degree of similarity between this list and the list of genes that are differentially expressed in aged versus young mice. How aging affects the function of adult stem cells, which regenerate our tissues, is not yet known. Therefore, it is very illuminating that loss of Ott1 seems to molecularly mimic aging of HSCs. Also, like Ott1 knockout cells, HSCs from old mice are less effective at engrafting the bone marrow of lethally irradiated recipients and have a higher likelihood of being in the cell cycle (decreased quiescence).

How, then, does loss of Ott1 reveal clues about leukemogenesis? For one thing, the risk of leukemia increases with aging, and the leukemic transformation in this case may be at least in part due to more frequent mitotic cycling. In the case of AMKL associated longer able to make normal OTT1, which means that the leukemia cells may have half of the normal amount of OTT1. Also, it is not yet known whether the OTT1-MKL1 fusion protein blocks the function of normal OTT1. It will be interesting to find out the hematopoietic phenotype of OTT1 mice in which OTT1MKL1 is expressed.

In summary, there is a significant phenotypic overlap between Ott1-deficient and aging hematopoiesis, including impaired HSC self-renewal and decreased stress response. Whether loss of Ott1 function and aging contribute to leukemogenesis via analogous mechanisms remains to be shown.
An Inflammatory Paradox: Oxidation Promotes Infection

Hematologists understand the critical role that inflammatory cells play in killing microbes and their role in infections. Many of the oxidants are catalyzed by iron, yet iron is also an excellent nutrient for microbes. Patients with iron overload have a propensity for opportunistic infections such as Yersinia or mycobacteriosis. Murray suggested that hyperferremia associated with refeeding individuals in Central Africa led to rapid multiplication of parasites leading to attacks of malaria. In Chagas disease, caused by Trypanosoma cruzi (T. cruzi), the acute phase is characterized by intense parasitemia and H-ferritin expression, both of which decrease free iron in macrophages. Iron in infection, gp91phox (Nox1)-deficient macrophages and mice had reduced reactive oxygen species. The inflammatory response damages the heart but does not kill the bug. Pavia and colleagues in Brazil address this paradox experimentally and suggested that oxidative stress contributes to parasite persistence in host tissues and suggest that the process may be exploited as a target for novel therapies.


Somatic Mosaicism: It’s Tough Getting Older

Somatic mosaicism, the co-existence of genetically distinct cell populations in a single individual as a result of post-zygotic genetic events that can occur at any time in the life cycle from fertilization to death, can be meaningless and clinically silent, but mosaicism is also potentially dangerous, contributing to a range of maladies from birth defects to cancer.1 Somatic mosaicism can result from errors in replication of segments of chromosomes or of whole chromosomes, leading to chromosomal aneuploidy. In addition, copy-neutral reciprocal gains and losses may result in acquired uniparental disomy or loss of heterozygosity (LOH), and somatic mosaicism can also be as simple as an acquired point mutation. The prevalence of somatic mosaicism in tissues in the general population is unclear.

In order to better estimate the prevalence of somatic mosaicism and explore a link to neoplasia risk, more than 100 investigators led by a team from the U.S. National Cancer Institute (NCI) analyzed blood or buccal cell-derived autosomes from 31,717 patients with cancer and 26,136 cancer-free controls. These 57,853 samples had been obtained during 13 genome-wide association studies from 48 epidemiologic analyses previously conducted by various groups in collaboration with the NCI’s Division of Cancer Epidemiology and Genetics (DCEG) and Core Genotyping Facility (CGF). In the current study, the investigators used a 2 megabase pair (2 Mb)-size cutoff to define mosaicism in order to be conservative and to minimize “false discovery” of germline variants.

The major finding of the NCI analysis was that mosaic aberrations > 2 Mb in size were found in 0.89 percent of study subjects overall, and the frequency of detectable somatic mosaicism increased with age, ranging from 0.23 percent in individuals under age 50 to 1.91 percent in patients between 75 and 79 years old. Mosaic abnormalities were also more common in the cancer cases (0.97%) compared with cancer-free persons (0.74%). The most frequent class of anomaly detected was copy-neutral LOH, representing 48 percent of mosaic events — most commonly LOH of chromosomes 9p (where JAK2 is located) or of chromosome 14. Trisomies 8, 12, and 15 were also observed recurrently, as were deletions of chromosomes 13q and 20q; these are frequent findings in neoplastic cells from patients with hematologic malignancies.

A recent Swedish analysis of somatic alterations in 318 monozygotic twins and 296 single-born subjects also described age-related accumulation of copy number variation, suggesting a mechanism for age-associated reduction in the diversity of blood cells and for accumulation of hematopoietic clones with structural abnormalities. Such clonal changes could lead to myelodysplasia, monoclonal B-cell lymphocytosis, or other aging-related blood dyscrasias. In fact, the Swedish study detected somatic aberrations characteristic of patients with myelodysplastic syndromes in three apparently healthy persons, who are likely to be at considerable risk for subsequent development of clinical disease.

Since cancer is an example of somatic mosaicism, one implication of these findings is that specific types of clonal mosaicism that randomly arise in a time-dependent fashion and confer a cellular survival advantage likely contribute to an increased risk of subsequent clonal shifts and eventually development of frank malignancy. Supporting this idea is the observation that among 43 individuals in the NCI study who subsequently developed a hematologic malignancy > 1 year after their DNA was obtained for analysis, clonal mosaicism was present in a whopping 20 percent of those who were ultimately diagnosed with myeloid leukemias and 22 percent with lymphocytic leukemias.

The most immediate application of the NCI-led consortium’s results is as a point of caution for molecular epidemiology studies comparing blood or buccal cells with tumor cells, but surveillance for age-related somatic mosaicism might one day serve as a biomarker for individuals at increased risk for subsequent development of hematologic malignancies of or other cancers.

patients who have experienced an episode of unprovoked venous thromboembolism (VTE), recurrence is observed in as many as 20 percent following discontinuation of anticoagulant therapy. Yet, extending anticoagulation longer than the recommended six months would increase cost, inconvenience patients, and put them at risk for bleeding complications. Thus, the need for uncomplicated, safe, inexpensive therapy for long-term VTE prevention is apparent.

What is the role of aspirin in VTE prevention? From a biologic standpoint, the question is the need for uncomplicated, safe, inexpensive therapy for long-term VTE prevention is apparent. Further, while anticoagulants reduce the incidence of major bleeding (one episode in each arm, 0.5%), non-major bleeding, (three episodes in each arm, 1.5%), or deaths (1.4% vs. 1.3% per year, treatment arm vs. placebo arm, respectively). By providing evidence that, following standard oral anticoagulation, low-dose aspirin safely and significantly reduces the incidence of thrombosis recurrence, the current study suggests a new standard of care for patients who experience a first-time, unprovoked VTE event. Further, the results of the study by Becattini can be seen as verification of the hypothesis that platelets contribute to the pathobiology of VTE.

Patients with cancer or a thrombophilic condition were excluded from the study. Whether the findings of Becattini and colleagues apply to such patients and other groups requires further investigation.

How do these findings using low-dose aspirin compare with extended use of oral anticoagulant therapy or with extended use of one of the new oral anticoagulants (the thrombin inhibitor [dabigatran] or the Xa inhibitor [rivaroxaban])? Continuing oral vitamin K antagonists with warfarin is associated with modest risk reduction, but such therapy necessitates monitoring and increases the incidence of bleeding. The oral thrombin and Xa inhibitors reduce the risk of VTE recurrence by 80 percent, but treatment is expensive, and, importantly, the relatively long half-life of these agents increases the risk of mortality for patients transfused with RBCs stored for longer than the recommended six months 1 would result in unacceptable risk of mortality for patients transfused with RBCs stored for longer than the recommended six months.

To study the pathophysiology of the red cell storage lesion in vivo, Baek et al. developed a guinea pig exchange transfusion model. Guinea pig RBCs had similar deformabilities at two days of storage (new blood) as did human RBCs. However, guinea pig RBCs had accelerated loss of deformability such that at four weeks of storage (defined as old blood) they were as fragile as human RBCs stored for six weeks. Compared with animals transfused with new blood, those transfused with old blood were found to have significantly more intravascular hemolysis that was accompanied by an increase in mean arterial pressure and development of renal failure within one day. Infused human hemoglobin did not induce the vascular and renal effects that old blood transfusion did, and washed, old blood RBCs retained their vascular and renal toxicities despite loss of the most fragile RBCs during the washing procedure. The fact that bolus infusion did not reproduce the adverse effects of transfused old blood suggests that brief exposure to isolated hemoglobin (as might occur during transfusion) is insufficient to account for the red cell storage lesion.

The pathologic effects of old blood transfusion included necrotic damage affecting the luminal and medial layers of the aortic root and the epithelium of renal tubules. The renal tubules also accumulated large amounts of stainable iron. A role for intravascular-free hemoglobin in the pathologic process was suggested when co-administration of haptoglobin, the physiological scavenger of free hemoglobin in the plasma, was found to ameliorate the adverse events associated with fresh blood transfusion. Proteomics of kidneys from guinea pigs transfused with old blood showed increased expression of proteins associated with hemoglobin catabolism and oxidative stress, suggesting that renal damage was an oxidative process induced by free hemoglobin and heme. Haptoglobin co-administration significantly reduced the pathologic changes affecting vessels and renal tubules through binding and sequestration of free hemoglobin with subsequent delivery to macrophages where hemoglobin is catabolized.2 Pathologic vascular and renal effects intermediate between guinea pigs transfused with new blood versus old blood were observed in animals transfused with a three-week-old blood, indicating a time-dependent worsening of the toxic effects of blood storage.

The study from Baek and colleagues provides a plausible explanation for some of the adverse events observed in patients who undergo massive RBC transfusions. In patients with pre-existing vascular lesions and in those having undergone a recent surgical procedure, lesser volumes of transfused old blood may have similar adverse effects. Amelioration of the pathologic effects of chronic storage-related intravascular hemolysis by co-administration of haptoglobin, the plasma protein that binds free hemoglobin but is present in limited quantities, provides a potential therapeutic approach to preventing the clinical disease induced by the red cell storage lesion.


MARK J. KOURY, MD
Dr. Koury indicated no relevant conflicts of interest.
Inhibition of thrombin and/or factor Xa is the mechanism of action of several antithrombotic agents. For example, standard heparin catalyzes the rate of inactivation of thrombin and factor Xa by antithrombin. Antithrombin undergoes a conformational change when it binds to a specific sequence in heparin that facilitates its interaction with factor Xa. In contrast, thrombin binds indiscriminately along the linear heparin polysaccharide molecule, which facilitates its diffusion to bind to and be inhibited by antithrombin. Low-molecular-weight heparins and fondaparinux, which retain the antithrombin binding site but are not long enough to facilitate the diffusion of thrombin, selectively enhance inhibition of factor Xa by antithrombin. Additionally, thrombin can be selectively targeted by specific inhibitors, including bivalirudin and argatroban. There is a fine line between the degree of anticoagulation necessary for inhibition of coagulation for antithrombotic purposes and that which pathologically disrupts hemostatic function. Thus, the option to reverse the anticoagulant activity of an antithrombotic agent is desirable, as in the case with reversal of heparin activity by protamine.

In a phase 2 clinical trial, EP217609 is being tested as a reversible antithrombotic in patients undergoing cardiopulmonary bypass surgery. The drug contains three functional sites: a fondaparinux analog for factor Xa inhibition, an active-site directed thrombin inhibitor, and a biotin tag that provides a mechanism for reversal of anticoagulant activity through binding to avidin (Figure). The dual inhibition of thrombin and factor Xa, together with the antithrombin dependence of the factor Xa component, present a challenging task to investigators attempting to establish the basis of the antithrombotic properties of EP217609. Steven Olson and colleagues at the University of Illinois at Chicago have developed elegant biophysical methods to characterize the inhibition of coagulation enzymes by antithrombin and the mechanism of action of heparin.1,2 and now, in a Plenary Paper in Blood, this group reports delineation of the biochemical and structural basis of the potency and selectivity of EP217609. Based on the intrinsic fluorescence of antithrombin that occurs when the molecule interacts with EP217609, they found that antithrombin binds EP217609 with high affinity (30 nM). Additionally, kinetic modeling revealed that the rate of inhibition of factor Xa by the EP217609-antithrombin complex was more than 20-fold higher than that of other proteases. EP217609 competitively inhibited small substrate hydrolysis by thrombin, a property that allowed the authors to determine that EP217609 binds thrombin rapidly (k∞ = 10^6 M^-1 s^-1) and with very high affinity (30-40 pM). In contrast, affinity of EP217609 for other coagulation enzymes was over two orders of magnitude lower than for thrombin.

The binding of EP217609 to antithrombin could affect its interaction with thrombin and vice versa. The inhibition by EP217609 of thrombin-catalyzed small substrate hydrolysis revealed a modest decrease in affinity of the EP217609-antithrombin complex for thrombin compared with uncomplexed EP217609. The reciprocal experiment in which the kinetics of inhibition of factor Xa by the EP217609-antithrombin complex were analyzed in the presence and absence of thrombin revealed a similar modest decrease in inhibition when thrombin was present in the reaction mixture. Together, these results indicate that the two inhibitor moieties of EP217609 (Figure) act nearly independently.

Although the biotin tag was designed to provide a mechanism for rapid in vivo clearance of EP217609 through binding to avidin, the authors found that avidin weakened the direct inhibitory effect of EP217609 on thrombin by over two orders of magnitude. Avidin also reduced the rate constant for EP217609-antithrombin inhibition five-fold and decreased the affinity of EP217609 for antithrombin 20- to 30-fold.

The study by Olson et al. provides a rigorous thermodynamic and kinetic analysis of the mechanism of action of EP217609, a complex antithrombotic agent that is undergoing clinical evaluation. It builds on a broad foundation of work involving the study of coagulation enzymes, antithrombin, and heparin by many groups over many years and provides a rational underpinning for the development of novel antithrombotic agents.

Tumor metastasis is a hallmark of aggressive disease and is usually associated with an unfavorable prognosis. The mechanism by which a tumor develops metastatic potential is thought to result primarily from acquisition of cell-autonomous (intrinsic) properties and not from the selection and outgrowth of a clone capable of vascular dissemination. According to this hypothesis, accumulation of somatic mutations that affect the genetic and epigenetic properties of the cell underlies clonal evolution. However, metastatic properties could be acquired through other mechanisms. For example, cell-cell fusion between tumor cells and bone marrow macrophages has been proposed as an extrinsic mechanism for acquiring the pathologic properties necessary to induce metastasis, and now, a study from the laboratory of David Lyden of Weill Cornell Medical College in New York suggests another mechanism by which an extrinsic process may contribute to the development of metastatic disease. Tumor cells are known to release membrane-bound nano-sized vesicles (30-100 nm) called exosomes that traffic protein and RNA between cells (Figure). Tumor exosomes are readily detected in body fluids including serum, saliva, urine, and breast milk. The current study presents evidence of cellular reprogramming of bone marrow cells by tumor-derived exosomes.

Peinado et al. demonstrate that exosomal transfer of the oncoprotein MET from melanoma cells to bone marrow progenitor cells induces release of bone-marrow-derived progenitor cells. This process contributes to the switch from localized disease to disseminated disease because the pro-angiogenic and pro-vasculogenic properties of the released bone marrow cells provide a niche for expansion of disseminated melanoma cells (Figure). To decipher the molecular and cellular events involved in this process, the authors used a murine model. Cell-free exosomes were derived from the highly metastatic mouse melanoma cell line, B16-F10. Exosome infusion followed by injection of melanoma cells resulted in an increase in the burden of pulmonary metastases. Further experiments showed that exosome injection of exosomes increased the proportion of c-kit+/Tie-2+ progenitors in the bone marrow and induced their release into the circulation. Based on increased MET protein and MET phospho-protein expression in the bone marrow cells, these events appeared to be mediated by direct transfer of MET (a receptor tyrosine kinase) from the tumor exosomes to bone marrow cells. Intriguingly, these alterations in MET expression were durable as the bone marrow cells retained their “educated” metastatic phenotype after adoptive transfer to a naive host. Finally, the authors showed that knockdown of Rab27a, a protein important for exosome biogenesis, decreased exosome secretion by mouse and human cell lines and consequently blunted the metastatic potential of the malignant cells.

The murine studies were complemented by a correlative analysis of patient specimens that showed the presence of characteristic melanoma markers, TYRP2 and MET, in serum-derived exosomes from patients with regional and distant metastatic disease. Analogous to the murine studies, patients with stage 3 and 4 melanomas also demonstrated higher levels of activated phospho-MET in tumor exosomes, and circulating bone marrow progenitor cells from patients had higher expression of phospho-MET when compared with cells from healthy volunteers. A direct correlation was observed between MET expression in tumor exosomes and subsequent development of metastasis in patients, suggesting that quantitation of MET expression in serum exosomes might serve as a predictive marker of metastatic disease.

While the specifics are intriguing, more broadly, the study hints at the complexity of the cargo carried by tumor exosomes, suggesting an enormous potential to directly influence the biology of the tumor microenvironment. The experiments also identify another part of the multi-compartmental physiology of metastatic cancer by demonstrating that exosome trafficking alters the malignant phenotype and transmits conventional paracrine signaling by direct cytoplasmic transfer of a receptor tyrosine kinase. Even though experimentally feasible, global interference with exosome release as a constitutive cellular function is too broad a therapeutic target. Going forward, we can anticipate that discovery-driven proteomic or transcriptomic analyses will dissect the molecular events that result from vesicle trafficking in the tumor and bone marrow microenvironment and lead to the identification of more suitable therapeutic targets.

Peinado and colleagues provide persuasive evidence that tumor-derived exosomes promote melanoma metastasis by activating cells in the bone marrow and prompting the formation of a “pre-metastatic” niche. Questions remain unanswered about the mechanism by which c-kit+/Tie-2+ expressing cells shape the microenvironment in the metastatic target tissue and about other cellular processes that are affected by the exosome transfer process. Nevertheless, this imaginative study has both diagnostic and therapeutic implications and deserves further research into the role of exosomes and their cellular targets in the bone marrow during the evolution and progression of cancer.

Pharmacogenetics on Trial: The Utility of Genotyping in Warfarin Management

STUDY TITLES: Clarification of Optimal Anticoagulation Through Genetics (COAG); Genetics Informatics Trial (GIFT) of Warfarin to Prevent DVT

Clinical Trials.gov identifier: COAG – NCT00839657; GIFT– NCT01066733

STUDY SPONSOR: COAG – National Heart, Lung, and Blood Institute (NHLBI); GIFT – Washington University School of Medicine

Collaborators: COAG – Bristol-Myers Squibb; GIFT – Intermountain Health Care, Inc., University of Utah, Hospital for Special Surgery, New York, and NHLBI

Participant centers: COAG – 16 centers throughout the United States; GIFT – Washington University School of Medicine (MO); Hospital for Special Surgery (NY); University of Utah, Intermountain Medical Center (UT)

Principal investigator: COAG – Stephen E. Kimmel, MD, MSCE, University of Pennsylvania; GIFT – Ryan E. Gage, MD, MSc, Washington University School of Medicine

Accrual goal: COAG – 1,600; GIFT – 1,238

Study design: COAG is a phase 3, double-blind, randomized trial to compare the efficacy of a warfarin-dosing algorithm based on genotype and clinical data with a dosing algorithm based on clinical data only. Patients in the experimental arm will receive initial dosing of warfarin for the first three to four days of treatment, as determined by an algorithm that uses clinical data and evaluation of vitamin K epoxide reductase complex-1 gene (VKORC1) and cytochrome P450 2C9 gene (CYP2C9) polymorphisms. A dose adjustment will be made after three and/or four doses of warfarin using a dose revision algorithm that incorporates both clinical and genetic variant information. Warfarin dosing for the comparator arm will be guided by an algorithm that only includes clinical information. The primary objective is the percentage of time patients spend in the therapeutic INR range (2.0-3.0) during the first four weeks of therapy. Secondary outcomes include the occurrence of an INR < 2.0 or a serious adverse clinical event during the first four weeks.

GIFT is a phase 3, double-blind, randomized trial designed to evaluate whether the addition of genotyping will reduce the risk of VTE and severe bleeding associated with warfarin management in patients 65 years old receiving warfarin prophylaxis after hip or knee arthroplasty. The study contains two arms with different target INRs: 1.8 and 2.5. Within each arm, warfarin dosing guided by genotyping and clinical information will be compared with dosing guided by clinical information alone. Dosing algorithms are available at www.WarfarinDosing.org. Primary outcomes will be evaluated over a four- to six-week time frame and include a non-fatal venous thromboembolic event, non-fatal hemorrhage, death from any cause, or INR < 4. Secondary outcomes include percent of time in therapeutic INR range, or time to first laboratory event (INR > 4 or target INR). Rationale: The challenge of dosing warfarin to achieve an INR of 2.3 is well-known to most hematologists. Accurately predicting the maintenance dose could improve the time within therapeutic range and potentially lead to safer administration of warfarin. A substantial body of literature demonstrates that polymorphisms in the VKORC1 and the (CYP2C9) affect warfarin dose requirements. Polymorphisms in these genes account for approximately 50 percent of the variance in dose requirements. These observations suggest that prediction of maintenance dosage could be improved by testing VKORC1 and CYP2C9 genetic variants. This hope has been buttressed by relatively small studies indicating increased time in therapeutic range and reduced episodes of bleeding with the use of VKORC1 and CYP2C9 genotyping. COAG and GIFT will test the hypothesis that guiding warfarin management using algorithms that incorporate genotyping information will improve the efficacy and safety of warfarin.

Comments: There is considerable interest in demonstrating tangible health-care benefits from the substantial investment made in deciphering the human genome. Pharmacogenetics is viewed as an area in which this objective may be achieved, and warfarin genotyping has been dubbed the poster child of pharmacogenetics. Warfarin is commonly used, inexpensive, effective, and has few side effects. Its Achilles’ heel, however, is its narrow effective and safe therapeutic range and the problem of severe bleeding associated with overdosing. The data that polymorphisms in VKORC1 and CYP2C9 influence response to warfarin are compelling and raise the possibility that systematic patient genotyping will inform improved warfarin management. COAG and GIFT are designed to address this possibility. As with any trial testing algorithms of warfarin dosing, results from these tightly controlled studies may not be reproduced in the real world. The cost-effectiveness of genotype-guided warfarin management and the willingness of insurers to pay for testing are also uncertain. In addition to these hypothetical concerns, skeptics have raised two criticisms with regard to the approach itself. The first is a logistical argument: By the time the genotyping information becomes available for a particular patient, the INR response will have captured the relevant information on warfarin sensitivity. The second argument is that even if genotyping improves the initial time in therapeutic range, it may not have a significant impact on bleeding outcomes. COAG will directly address the first criticism, and GIFT will address the second criticism. The outcome of these trials will likely determine whether genotyping has an important role in the future of warfarin management, and it may have broader implications for the nascent field of pharmacogenetics.

Robert Flamenhaft, MD, PhD

Follicular Lymphoma: The Environment as the Target

STUDY TITLE: Combined Rituximab and Lenalidomide Treatment for Untreated Patients with Follicular Lymphoma (RELEVANCE)

Sponsor: Celgene Corporation, USA, and GELARC, France

ClinicalTrials.gov identifier: NCT01476787

Participating centers: 30 centers throughout the United States

Accrual goal: 1,000 patients

Rationale: The challenge of dosing warfarin to achieve an INR of 2.3 is well-known to most hematologists. Accurately predicting the maintenance dose could improve the time within therapeutic range and potentially lead to safer administration of warfarin. A substantial body of literature demonstrates that polymorphisms in the VKORC1 and the (CYP2C9) affect warfarin dose requirements. Polymorphisms in these genes account for approximately therapy and lenalidomide plus rituximab. Standard therapy can be one of the following, selected prior to randomization by the investigator: R-CHOP, R-CVP (both given every 21 days for 8 cycles) or R-bendamustine (every 28 days for 6 cycles). The experimental arm comprises rituximab 375 mg/m² on day one and lenalidomide 20 mg daily on days 2 to 22 of a 28-day cycle, for six cycles. Patients with an objective response to initial therapy go on to receive maintenance treatment. Those in the standard arm receive maintenance therapy for two years with rituximab alone, while those on the experimental arm have lenalidomide for one year and rituximab for two years. The maintenance dose of lenalidomide is determined by the initial response. Patients with a CR or CRu (complete response or unconfirmed complete response) take 10 mg, while those with PR continue to take 20 mg for 3 to 6 cycles until CRu (CR or unconfirmed CR) is reached, and then they continue to take 10 mg.

The primary endpoints are CR/CRu (complete response and progression-free survival (PFS), with secondary outcome measures such as time to treatment failure, time to next anti-lymphoma treatment, and overall survival. Quality-of-life measurements will also be recorded using EORTC QLQ-C30 questionnaires. The target for recruitment is 1,000 patients, and the aim is to detect a 30 percent improvement in PFS.


Comment: The possibility of using a non-cytotoxic regimen for the initial therapy of advanced FL has great appeal, but until recently the only option for this was to use rituximab alone, which does not appear to have sufficient potency and durability of effect for patients with high-risk disease. If the combination of rituximab and lenalidomide performs as well in the phase 3 study as the pilot, it may provide an important new option for the standard of care. Some question remain concerning the long-term safety of lenalidomide, particularly regarding the incidence of second primary malignancies in studies of myeloma, so long-term follow-up will be important in this trial, as will careful analysis of the quality-of-life endpoints.

Peter Johnson, MD

Dr. Johnson is a remunerated member of the Data Safety Monitoring Committee of a different GELARC study using lenalidomide, the REMARC trial.
My story begins in a tiny, three-room apartment in New York’s infamous South Bronx. As a six-year-old child with recurrent fever and constant sore throats, I can recall regular visits to the home of my immigrant parents from a short, well-dressed doctor. Though he could not do much, I always felt better afterward, and I wanted to be like him.

In school, I loved biology, and I enjoyed reading dramatized medical science like Paul De Kruif’s Microbe Hunters and technical books on forensic pathology. At 10, I tried On the Origin of Species, but I found it difficult to get through. My mother, understanding my love of science, encouraged me to go to Bronx High School of Science; I was admitted in 1943. I continued my education at New York University, but having spent a summer with relatives in Denver, I fell in love with the West where I could fish, hunt, and hike in the Rockies. I transferred to the University of Colorado in Boulder before my junior year. I graduated in 1949, but despite good grades and test scores, I was hindered by the 10 percent Jewish quota (or maximum) and denied admission into medical school.

Attempting to find an alternative plan, I took an environmental science job with the U.S. Public Health Service (USPHS) and met a charismatic cardiologist, Dr. Allan Riemer, who encouraged me and helped me apply to Johns Hopkins University School of Medicine. I was accepted into the freshman class of 1950. Cash-strapped, I traveled three days by bus from Denver to Baltimore and was grateful to receive a scholarship for $500, which was a significant amount of money at that time. On arrival, I learned that each Hopkins class of 70 students had exactly seven Jewish students and four women, a remarkable coincidence. Still, my medical education at Hopkins was everything I had hoped for.

So why did I choose hematology? A highlight of the Hopkins week was the Clinical Pathologic Conference where Dr. Rich, professor of pathology, assumed he had the final word until he clashed with Chief Hematologist Dr. C. Lockard Conley. They both used morphology, but Dr. Conley gave me a great role model when he added environmental science to his alma mater, Johns Hopkins University School of Medicine. I was accepted into the freshman class of 1950. Cash-strapped, I traveled three days by bus from Denver to Baltimore and was grateful to receive a scholarship for $500, which was a significant amount of money at that time. On arrival, I learned that each Hopkins class of 70 students had exactly seven Jewish students and four women, a remarkable coincidence. Still, my medical education at Hopkins was everything I had hoped for.

Later on, as a medical resident in Ann Arbor, about to be drafted into the Army Medical Corps, I received an unanticipated phone call from Dr. All S. Alving, professor of nephrology at the University of Chicago, asking if I would rather serve my military time as a member of the Commissioned Corps of the USPHS stationed at the maximum security Stateville Penitentiary in Joliet, IL. In the summer of 1956, I moved with my wife Peggy and our daughter and went to work at the jail. As a senior assistant surgeon, I learned quickly that mentoring teachers, saw how they each differently identified what creativity. I chaired the Stanford Hematology Division for almost 27 years. When I started, I had teaching assignments, which at first did not come naturally to me. I tracked three excellent teachers, saw how they each differently identified what the students needed to understand, and from there developed my own style. I learned quickly that mentoring is a satisfying form of education but differs in that it requires a more personal relationship.

I won most of the major teaching awards at Stanford and put my experience to use when I chaired the ASH Educational Affairs Committee and also when I became the first hematologist editor-in-chief at UpToDate.

My research interests in red cell biology led me to a 20-plus-year effort to understand the pathophysiology of the thalassemias; that, in turn, led to projects in Israel, Italy, and Thailand, where there is a high rate of thalassemia and where I found expert, enthusiastic collaborators. Perhaps because of the experience of working at these sites, I am involved in ASH’s outreach programs such as the ASH-sponsored International Consortium on Acute Promyelocytic Leukemia (ICAPL), now the International Consortium on Acute Leukemia (ICAL), and in the Health Volunteers Overseas (HVO) programs in Uganda, Peru, and Cambodia. ASH has been a very important part of my professional life for many years. In every substantive issue in which I was directly involved, ASH was always on the side of the angels.

I am sometimes asked what in my career gives me the most pleasure. It is evaluating a complex patient illness, with a fellow, and together coming up with a formulation that improves the patient’s quality of life. That’s what that six-year-old kid growing up in the South Bronx wanted. An unexpected joy is to see the enthusiastic new and diverse medical residents and to realize that the quotas that were once my roadblock have vanished. I am now 83 years old and classified by Stanford as Active Emeritus. I currently have research grants on anemia of the elderly and amyloidosis, two weekly teaching sessions with medical students and house staff, and a burgeoning practice in consultative hematology.

I am grateful for my supportive family, wife Barbara, my blended family of five children, their mates, five grandchildren, friends, students, and great colleagues.
Thoughts From a Former Protégé

JASON GOTOUB, MD, MS
Associate Professor of Medicine (Hematology); Director, Hematology Fellowship Training Program, Stanford Cancer Institute/Stanford University School of Medicine

Since his arrival at Stanford in 1959, and during his 27 years as chief of the division of hematology (1968-1995), Stan mentored two generations of hematologists in his triple role of physician, educator, and scientist — the latter focused on the pathophysiology of the thalassemias. I met Stan while he was attending on the inpatient hematology service in 1994; I was a green medical student on the first year of clinical rotations. My experience then, which remains true today, is that Stan’s starting assumption is that everyone should be captivated by hematology. He believes that the romance between hematology and the doctor-in-training should be love at first sight. If Stan senses that his audience is not immediately enamored with hematology, he will work hard to nurture this bond, and if medical students or residents don’t choose hematology for subspecialty training, they will have at least learned a great deal along the way. Stan knows that short of a love affair, a friend of hematology is still a relationship worth cultivating.

At age 83, Stan maintains a busy weekly clinic and an unflinching presence at all of our educational conferences, including his lead of microscope rounds. When I arrive at these venues, it is a warm and comfortable feeling to see Stan waiting for us to start. The quality and durability of his tenure at Stanford will us to remember the historical roots of the division and to preserve his commitment to teaching and scholarship. His clinical acumen is of immeasurable value to our trainees — and yes, to faculty members as well — who still may lack Stan’s vast arc of experience. At the conclusion of such conferences, Stan often verbalizes that it was a “fascinating conference,” “great cases,” or “I didn’t know that.” He’s a master teacher who always savors an opportunity to learn.

Stan relayed to me a story about how he matriculated in a class titled “Speech” while attending college in New York. Although he expected it would be a boring waste of time, he remembers it today as a seminal experience. The teacher took Stan and his classmates on trips to Union City’s Hudson Theatre in New Jersey. This inspired curriculum introduced Stan to burlesque-era comedians, dancers, and other stage performers. The experience taught him how to gauge the temperament of the audience and to appreciate how the animated performance of the artist could help relay the essential meaning of a subject. Stan has adopted this dynamic teaching style, punctuated with his unique sarcasm. This method accentuates his core teaching objectives and would never be mistaken for style over substance. Stan will question trainees as part of this banter; in the content of dialogue.

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As technology and the Web have evolved, so too have ASH’s online offerings. Now, beyond the ASH website, you can download ASH apps for your smartphone or tablet, follow ASH on Twitter (www.twitter.com/ASH_hematology), and find ASH videos on YouTube (www.youtube.com/user/ASHWebmaster). Our newest offering is ASH on Facebook.

WHAT’S ON THE WEB

September

5  Deadline to submit application for Translational Research Training in Hematology
Washington, DC  www.hematology.org

7  Application available for ASH Bridge Grant Program
Washington, DC  www.hematology.org

12-13  ASH Advocacy Leadership Institute
Washington, DC  www.hematology.org

20  ASH Webinar on Autoimmune Hemolytic Anemia
Washington, DC  www.hematology.org

28  Consultative Hematology Course
Chicago, IL  www.hematology.org

28-29  ASH State-of-the-Art Symposium
Chicago, IL  www.hematology.org

October

5  Group room block request and cancellation deadline for the ASH annual meeting
Atlanta, GA  www.hematology.org

12-13  ASH State-of-the-Art Symposium
Los Angeles, CA  www.hematology.org

22  ASH annual meeting late-breaking abstracts submission site opens
Atlanta, GA  www.hematology.org

29  Deadline to submit late-breaking abstracts for the ASH annual meeting
Atlanta, GA  www.hematology.org

November

5-6  2nd International Workshop on The Biology, Prevention, and Treatment of Relapse After Hematopoietic Stem Cell Transplantation
Bethesda, MD  http://ncifredneck.cancer.gov/events/relapse2012

December

8-11  54th ASH Annual Meeting and Exposition
Atlanta, GA  www.hematology.org

14  Deadline to submit letter of intent for Research Training Award for Fellows
Washington, DC  www.hematology.org