APL: A Legacy and Framework for the Concept of Bench-to-Bedside

By Naveen Pemmaraju, MD

In the midst of the pure craziness and rush of the annual meeting, there is something refreshing about taking a moment to ponder the giants of our field and the amazing discoveries that have saved countless lives. No meeting is complete then, without mentioning Dr. Ernest Beutler — an incredible physician-scientist whose research efforts have infinitely improved our knowledge of the genetic basis of hematologic malignancies. Dr. Beutler served as a Professor and Chairman at the Scripps Research Institute from the late 1970s until 2008, and the Ernest Beutler Lecture and Prize, founded in his honor, is presented yearly in recognition of a body of work that has illuminated the underpinnings of an area of hematologic disease.

This year’s recipients, acknowledged during yesterday’s general session, are Dr. Hughes de Thé of University of Paris Hospital Saint-Louis and Dr. Zhu Chen from the Shanghai Institute of Hematology. During this lecture, we contemplate the history and successes of Dr. Hugues de Thé, left, and Dr. Zhu Chen deliver their Ernest Beutler Lecture presentations.

Bone Marrow Maverick

By James S. Blachly, MD

Yesterday at 9:00 a.m., ASH honored Dr. David T. Scadden with one of the Society’s highest honors, the E. Donnall Thomas Lecture and Prize, for his important contributions to the bone marrow hematopoietic microenvironment. This award is named for the late Nobel Prize laureate and ASH Past President, E. Donnall Thomas, MD, who was himself a pioneer of bone marrow transplantation. In conjunction with this acknowledgment, Dr. Scadden delivered the customary lecture, this year titled “Bone Marrow: Structure and Function of the Blood Cell Foundry.”

Dr. Scadden told ASH News Daily that his fascination with science began as a child: From an early age, he loved tinkering with things. Although his parents never attended college, they revered learning and made every effort to ensure their son was well educated. When his father observed his son’s interest in a chemistry set he had gifted him, he built a room in their home’s basement to serve as a lab. The future Dr. Scadden loved spending time there, dissecting and making things blow up, or creating huge wafts of foul-smelling smoke that made his mother both laugh and worry. His mother took him to local companies where chemists would talk to him and offer him old equipment to take home. Amidst his high school chemistry
Vanessa Williams used the imagery of the snow coming down in June and the sun going round the moon to describe the unexpected twists and turns of life. The same could be said of the annual meeting this year, with so many wonderful and unexpected discoveries. Maybe you still haven’t found it though — the abstract…the moment…the one breakthrough made just for you. Well, just when you thought your chance had passed, ASH went and saved the best for last with day-4 events you’ll be glad you stuck around for.

The Best of ASH, being the final general session of the annual meeting, is quite literally the best ASH has to offer in terms of key themes and major breakthroughs presented here in San Diego. The session is being led by the 2016 Annual Meeting Scientific Program Co-Chairs, Drs. Robert Brodsky and Ross Levine, who present a 90-minute dose of super-concentrated knowledge. Although the contents of the Best of ASH are closely guarded until the session unfolds, the program’s co-chairs take great care to select key takeaways from across a variety of topics, therapies, and disease types. The session takes place in Hall AB of the San Diego Convention Center at 11:30 a.m. today.

Year after year, the Presidential Symposium is another one of the most anticipated events, and, as was covered in Monday’s ASH News Daily by Dr. Rakhi Naik, ASH President Dr. Charles Abrams is boldly optimistic in discussing the great possibilities that will unfold during the session: “For the first time in my life,” he said, “I see tremendous progress toward a cure for sickle cell disease. The purpose of this symposium is to present alternate ways to cure sickle cell disease (beyond bone marrow transplantation) and translate these methods toward a cure for other hematologic diseases.” The Presidential Symposium kicks off this morning at 9:45 a.m., also in Hall AB.

If you caught yesterday’s ASH News Daily, you probably saw the interviews with the 2016 Dameshek Prize and Stratton Medal winners. The announcement of these awards is always a day-4 high note, and this year’s inspiring group of awardees offers no exception to that rule. Dr. Charles Mullighan will be awarded the Dameshek Prize in recognition of his leadership in defining the landscape of genetic alterations of acute lymphocytic leukemia. This year’s Stratton Medal winners are Drs. J. Evan Sadler and Ayalvex Tetteri, who are being recognized individually for their pivotal contributions in the areas of basic and clinical/translational hematology research, respectively. Don’t be late, as the award presentations take place from 9:30 to 9:45 a.m. in Hall AB.

And now, as is tradition each year, we have previewed today’s Late-Breaking Abstracts, which bring us much-anticipated findings across the complete spectrum of malignant hematology, from optimal therapy of myelofibrosis and multiple myeloma, to understanding of genetic predisposition to acute lymphoblastic leukemia (ALL) and of stem cell dormancy, to the activity of chimeric antigen receptor (CAR) T-cells in diffuse large B-cell lymphoma. The session begins at 7:30 a.m. sharp, in Hall AB.

Leading off, Dr. Edward Stadtmauer will be presenting, on behalf of the BMT Clinical Trial Network, the results of the StaMINA Trial, an ambitious attempt to improve upon the standard of a single up-front autologous stem cell transplant with melphalan and post-transplant maintenance lenalidomide. Investigators randomized more than 750 patients equally among a standard arm and two experimental arms: one administering tandem autologous transplants and maintenance lenalidomide, and one administering a single transplant and four cycles of consolidative treatment with lenalidomide, bortezomib, and dexamethasone, again followed by maintenance lenalidomide. We will see data demonstrating that no arm led to superior results, reaffirming the standard of a single transplant and maintenance lenalidomide.

Expanding our understanding of genetic predisposition to pediatric ALL, Dr. Churchman will be presenting data on the role of germline alterations of IKZF1, which encodes a zinc finger transcription factor known to play a critical role in lymphoid development. Make haste to this session so as not to miss the details regarding: 1) the 28 germline variants in this gene identified by sequencing more than 5,000 children with newly diagnosed ALL, 2) the effects that perturbation of this gene have on cellular function in preclinical models, and 3) the impact that mutations have on sensitivity to dasatinib, an inhibitor of the BCR-ABL tyrosine kinase.

Next up will be Dr. David Miklos, presenting phase II data on the use of the irbritinib in managing chronic graft-versus-host disease (cGVHD). Forty-two patients with steroid-refractory cGVHD were treated on protocol, and irbritinib achieved an overall response rate of 67 percent, with the majority of responders being able to reduce or eliminate corticosteroid use. Dr. Miklos will certainly save time for discussion of the drug’s toxicity, which was substantial: 40 percent of patients experienced toxicity of at least grade 3 in severity, and there were two treatment-related deaths, including a case of invasive aspergillosis. These data nonetheless are promising and have led to...
NEW TREATMENTS

CD33, 7+3, and Platelets: Old Dogs Doing New Tricks!

By Shruti Chaturvedi, MBBS and R. Frank Cornell, MD

Among the outstanding abstracts presented at this meeting, many highlighted the notable therapeutic advances made by repackaging or restructuring familiar agents. The old dogs have learned some new tricks and are changing the daunting landscape of poor-risk acute myeloid leukemia (AML) and hemophilia with inhibitors.

Targeting CD33 in AML is no new concept by any stretch of the imagination. Many are familiar with the provocative story of gemtuzumab ozogamicin, a CD33 monoclonal antibody conjugated with calicheamicin. It made history in 2000 when it received accelerated FDA approval for older patients with AML, but then was withdrawn from the market in 2010 after confirmatory studies with negative results. Gemtuzumab’s withdrawal was controversial, and since then, additional studies have demonstrated its efficacy, resulting in CD33 reemerging at a potential therapeutic target. Enter vadastuzumab talirine (33A), a new CD33 antibody-drug conjugate, featured in four abstracts at the annual meeting.

On Monday, Dr. Amir Fathi reported results of a phase I trial of 33A in combination with azacitidine in older, treatment-naïve patients with AML (abstract #591). The combination was well-tolerated, and of the 49 evaluable patients, 73 percent achieved complete response (CR+CRI). In the same session, Dr. Anjali Advani reported a 53 percent CR+CRI rate in older AML patients treated with 33A monotherapy in a phase I study (abstract #590), which is twice the rate historically seen with standard hypomethylating agents or cytarabine therapy alone. On Saturday, Dr. Harry Erba shared the results of a phase IIb study evaluating 33A given along with standard 7+3 induction for newly diagnosed AML (abstract #211). Dr. Erba noted that 76 percent of patients had a response and most of these were complete remissions. He concluded that a randomized clinical trial of 7+3 with or without 33A is planned to start next year. Dr. Jay Yang reported that 33A can be administered safely along with high-dose cytarabine consolidation, or as single agent maintenance, in patients who have achieved first remission (abstract #340). Collectively, none of these studies showed an increased rate of hepatotoxicity including hepatic veno-occlusive disease, even in patients who went on to transplant.

CPX-351 is a liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio. This repackaging of the “old faithful” 7+3 has already shown a signal for survival benefit in older patients with AML in a phase III trial. On Monday, the study investigators presented two pre-planned subgroup analyses from this study.

ASH’s New School Has Some Old School Style

By Rashi Naik, MD, MHS

We all remember the first elementary school teacher who inspired us during childhood, teaching us with such tremendous passion, fervor, and attention that it opened our eyes to a whole new world. Oddly, however, we are not always met with such enthusiasm for teaching as we progress through higher education. Those who desire to become master educators for medical schools, residencies, and fellowship programs are often glaringly neglected, falling prey to the more traditional academic pathways. However, in a first-of-its-kind effort, aСH is turning this on its head. Modeled after the highly successful ASH Clinical Research Training Institute (CRTI), ASH has just introduced the Medical Educator’s Institute (MEI), a 12-month bootcamp for junior faculty pursuing careers in medical education. Hematology trainees can now finally expect the same emphasis on teaching and education that they encountered in elementary school, old school style.

The inaugural class of ASH MEI was announced in September and included 20 junior faculty from academic institutions throughout the United States and Canada. The program involves an intensive fall workshop, webinar series, and mentorship support with the goal of training the next generation of hematology educators. “It is always thrilling to launch a brand new program and see the thing you worked so hard on ‘in theory’ become a reality,” remarked Dr. Jennifer Kesselheim, a co-director of the 2016 ASH MEI. Dr. Marc Kahn, MEI co-founder, reflected on the unique opportunity that the institute provides for applicants, “Many junior faculty find themselves in the role of an educator without specific training. ASH MEI provides such training.”

The fall workshop, which was held from October 17 to 20 at ASH Headquarters in Washington, DC, focused on topics such as effective teaching strategies and test question development. For curriculum development, the course highlighted techniques to maximize student participation, including active learning and technology-based education. Although these evidence-based strategies could be considered newer and hipper than the long-revered traditional chalk talk, the underlying goal of the sessions remained refreshingly “old school” to connect with students and teach them the love of hematology.

The focus of ASH MEI was not only to teach effective teaching methods, but also to help cultivate successful careers in medical education within academic hematology. Each participant is required to design an educational-focused scholarly project that will be executed throughout the year. Example of this year’s projects included designing a tool to teach residents how to read blood smears and developing a translational research training course.

If you love the art of teaching, but missed the October workshop, know that ASH MEI is not the only way ASH is showcasing its unwavering commitment to education. From Trainee Day and events for hematology program directors, to abstracts on curriculum development, this year’s annual meeting also highlighted a renewed emphasis on hematology education. Sunday’s oral abstract #314 presented by Dr. Chenchen Hou, and poster abstracts #3537 and #3538 presented by Erik Levinsohn and Dr. Natalie Wallace, respectively, also gave a glimpse into some of this year’s fervor for education.

Eager to be a part of the next generation of hematological medical educators? If so, don’t just sit there … do something — apply for ASH MEI! The 2017 application cycle is open from February 1, 2017, until March 31, 2017.

Dr. Naik indicated no relevant conflicts of interest.
By R. Frank Cornell, MD

n lymphomas, the spotlight shone on potentially practice-changing randomized phase III trials taking on long-festering questions and difficult-to-treat lymphomas, as well as expanding the indications of our old friends rituximab, lenalidomide, and brentuximab.

Jordan versus Bird, Manning versus Brady, Graf versus Seles. R-CHOP versus EPOCH-R has the hype of a bright lights, big-time rivalry. On Sunday, Dr. Nancy Bartlett showed us initial results of the eagerly awaited phase III CALGB/Alliance 50033 trial pitting R-CHOP versus DA-EPOCH-R in an unselected group of patients with diffuse large B-cell lymphoma (DLBCL; abstract #469). At a median follow-up of 4.9 years, there was no difference in progression-free survival and overall survival (OS) between the two arms, but DA-EPOCH-R had increased toxicity and rates of treatment discontinuation. According to Dr. Brad Kahl, “this was a very important study that needed to be done. The question that remains: are there subgroups of patients for which R-CHOP is better like the double hits, double expressors, or a certain cell of origin?” Dr. Bartlett emphasized that the study had few patients with primary mediastinal DLBCL and myeloid-precursor DLBCL. Unless data emerge to contradict its use, DA-EPOCH-R will likely remain a mainstay of therapy for these patients based on promising phase II data.

In addition to the Scientific Plenary Session, maintenance therapy remained in the spotlight throughout the weekend and was featured in abstracts presented by Dr. Steven Le Gouill, Dr. Anna Maria Fink, and Dr. Catharine Thieblemont. However, mature data, including OS results, are needed before any consensus can be reached regarding these maintenance strategies in chronic lymphocytic leukemia and DLBCL. Given the extended duration and costs of maintenance therapy, safety and value-based care have huge implications. It will be crucial to identify patients who will get the most mileage out of maintenance.

Central nervous system (CNS) lymphoma was also onstage at the meeting. Yesterday, Dr. Carol Soussain also presented results of the PRECISI trial (abstract #762) comparing whole-brain radiation therapy (WBRT) versus intensive chemotherapy (IC) and autologous hematopoietic cell transplantation as consolidation after standard chemoimmunotherapy in primary central nervous system lymphoma (PCNSL). Overall response rate (ORR) at the end of therapy was 71 percent with WBRT and 67 percent with IC + ASCT. Dr. Soussain said that although IC + ASCT had better efficacy outcomes, neurocognitive evaluation results are pending and it remains to be answered whether IC + ASCT should be recommended as standard treatment. Abstracts presented by Drs. Andres J.M. Ferrerri and Dr. Benjamin Kasenda similarly emphasized the balance between efficacy and toxicity in treating CNS lymphomas with intensive treatments.

Studies with ibrutinib in CNS lymphoma are beginning to see results and were reported here in San Diego. Dr. Christian Grommes presented the results of a phase I/II single arm study of ibrutinib in patients with recurrent or refractory CNS lymphoma. Ibrutinib was found to be safe, meaningful CSF concentrations of ibrutinib were reached, and there was a 75 percent overall response rate (ORR) (CR 40 percent, PR 35 percent) by the international PCNSL Collaborative Group criteria. Median FFS was 5.4 months with a median OS of 15 months. Dr. Carol Soussain also reported disease control in 83 percent of 18 evaluable patients with refractory or relapsed PCNSL or primary vitreoretinal lymphoma treated with ibrutinib monotherapy in the open label phase II iLOC study (abstract 89). Ibrutinib is clearly going to play an important role in PCNSL. It raises the question of how ibrutinib will be positioned with regard to other effective treatments in PCNSL.

On Saturday, the ALCANZA investigators (abstract #1182) reported the results of the first randomized phase III trial in previously treated cutaneous T-cell lymphoma (CTCL) comparing the efficacy and safety of brentuximab vedotin versus physician’s choice (methotrexate or brentuximab). Brentuximab vedotin, physician’s choice in ORR (67 vs. 20 percent) PFS (16.7 vs. 3.5 months), symptom burden, and OS. Brentuximab’s remarkably strong performance in terms of ORR and PFS compared to standard of care could well push it to the forefront of therapy for CD30 positive CTCL, a disorder for which there are otherwise few good options.

Dr. Cornell indicated no relevant conflicts of interest.

Beutler

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our field and, in effect, the vast history of modern medicine. As Dr. William Osler best summarized it, “the good physician treats the disease; the great physician treats the patient who has the disease.” The field of acute promyelocytic leukemia (APL) biology and treatment has reflected this highest of Oslerian ideals, in a true bench-to-bedside approach that has taken basic biological breakthroughs and remarkably converted them into highly curative approaches to a once universally deadly cancer.

Dr. de Thé’s deep fascination with medicine began in high school, and even now he expresses fascination with the actual biological basis for therapeutic drugs: “I always wanted to understand the human body, its alterations by disease, and perhaps even more, the basis for its restoration by drugs.” He was also inspired by his father to pursue a career in medicine and science. He mentioned that his late father was a very creative scientist who taught him a great deal, especially to “look for the real problems and their putative solutions, out of the box.” This dedication to research and learning about new drugs has provided for a fruitful career in cellular and molecular oncology and hematology. He recalled his reaction when he learned he had been awarded the 2016 Ernest Beutler Lecture and Prize by ASH, saying that he was so surprised he went for a long walk along the canals of Milan, where he was speaking the day before a meeting, to process the big news.

Yesterday, Dr. de Thé, in his lecture on the basic science of APL, gave a thorough overview of the breath-taking developments in the field — from the discovery of the most common translocation that leads to APL, to the joining of chromosomes 15 and 17 in a so-called translocation, to the ins and outs of the fusion protein product that it gives rise to, PML-RAR alpha. From this platform, he described the seminal achievements made by groups worldwide in better understanding the pathobiology of APL cells, the mysterious granules they contain, and approaches on how best to take away the block on their haled differentiation to more mature cells. One take-away from Dr. De Thé’s incredible bench-to-bedside story was his very own lesson learned, that “targeted therapies can be curative.” He also stressed the important role of international collaboration in establishing successful pathways to APL therapy.

Dr. Chen underscored how deeply moved and grateful he was upon learning he would receive the Beutler award, especially given its namesake. Dr. Beutler was a respected mentor and good friend to Dr. Chen, who recalled Dr. Beutler’s visit to the Shanghai Institute of Hematology in 2001, where he encouraged Dr. Chen and his colleagues to continue their research work. “His look, expression, and voice remain fresh in my memory and encourage me to always do my best to make a humble contribution to the development of hematology.” While both his parents were doctors, Dr. Chen dreamed of being an engineer as a teenager. However, during his time in the countryside of the Jiangxi Province at the age of 16, after witnessing the severe shortage of doctors and drugs, he became determined to study medicine. He chose hematology, which he perceived to be a challenging but promising discipline. This is where his journey began, and he never looked back. This experience as a “barefoot doctor” has a special significance as it opened the door to the basic concept and practice of public health and equipped him with knowledge about the combination of western and traditional medicine for the treatment of common diseases in rural areas; it also fostered his spirit of humanity.

In his lecture, Dr. Chen reviewed the astonishing clinical developments in the field of APL that have converted a deadly disease into now one of the most highly curable forms of cancer known to human-kind, with upwards of 90 percent remission rates. These improvements in therapy have largely been based around the development and use of all-trans retinoic acid (ATRA) and arsenic tri-oxide (ATO) therapy. Dr. Chen nicely detailed the historical origins of these agents from their first applications in China, through clinical trials in the United States and Europe, to their place as the worldwide standard-of-care agents for the treatment of APL.

With a nod to our rich history as hematologists, the practice-changing story of the evolution of optimal treatment of patients with APL serves as a beautiful framework as we move forward in an attempt to apply these basic principles and to replicate this story of curative therapy in other blood cancers.

Dr. Penmuru indicated no relevant conflicts of interest.
Above – Dr. María I. Juárez presents her work during the session featuring the 2016 ASH Choosing Wisely® Champions.

Left – As the sun rises, ASH annual meeting attendees make their way into the San Diego Convention Center.

Dr. George Daley (from left), EHA President Dr. Anthony Green, ASH President Dr. Charles Abrams, and Dr. Oliver Brustle discuss pluripotent stem cells during the ASH/EHA Joint Symposium.

Dr. Mengya Zhou snaps an early morning photo of the artwork “Flame of Friendship,” by Leonardo Nierman, on her way into the San Diego Convention Center.

Annual meeting attendees pack the room for the E. Donnall Thomas Lecture.

The ASH logo is showcased at the end of a tunnel highlighted by neon lights at night, reflected in the architecture of the San Diego Convention Center.
A Roundup of Randomized Trials in Transplantation

By R. Frank Cornell, MD

In this year’s ASH meeting, investigators from two sides of the Atlantic worked to answer two critically important questions regarding multiple myeloma and autologous hematopoietic cell transplantation (AHCT): 1) What is the role of tandem AHCT in patients with newly diagnosed myeloma? 2) Is AHCT needed when bortezomib-based induction therapy is used?

To answer the first question, two large, randomized phase III trials were conducted. The first will be presented this morning in a late-breaking abstract session in Hall AB from 7:30-9:00 a.m., where Dr. Edward Storb will report the results from the BMT CTN 0702, StAmina Trial. Second, results from the EMN02/H095 MM trial were presented by Dr. Michele Cavo on Monday (abstract #991).

In summary, these two very important studies are reported with differing results. In one study, tandem AHCT is not superior to single transplant, and in the other, tandem AHCT is superior to single transplant. To help reconcile these differences, I spoke with Dr. Parameswaran Hari. Per Dr. Hari, “The difference in induction regimens between the two studies could most likely explain these outcomes. There was a specified induction in the EMN02 study while it was open in the BMT CTN study. In the United States, upfront RVD (PI and IMiD combo) is commonly used and the use of a better induction regimen may explain the lack of benefit from the additional transplant.”

To answer the second question regarding the need for AHCT when bortezomib-based induction is used, Dr. Cavo again presented data from the EMN02/H095 trial (abstract #673). Outcomes in patients receiving CVd induction and VMP consolidation with no AHCT versus CVd induction followed by AHCT (single or tandem) were presented. Patients randomized to AHCT had significantly improved PFS compared with those not receiving AHCT (HR 0.67; 95% CI, 0.53-0.85; p=0.01). This difference was highlighted in patients with high-risk features. The authors concluded that in the era of modern therapies, AHCT should remain the standard of care when bortezomib-based induction is used, particularly in high-risk patients.

At the annual meeting this year, readouts from randomized trials were not exclusive to autologous transplantation. A study led by Dr. Robert J. Soiffer included the first ever double blind prospective randomized trial to determine the efficacy of anti-T lymphocyte globulin (ATLG) in combination with methotrexate and dexamethasone in reducing chronic graft versus-host-disease (cGVHD) after myeloablative conditioning for allogeneic stem cell transplantation (alloHCT; abstract #505). The authors randomized 260 patients, and the addition of ATLG reduced grades 2-4 acute, as well as moderate to severe, cGVHD. However, OS was higher in the placebo arm and ATLG did not affect cGVHD relapse-free survival. Further research is needed to determine the precise role of ATLG in the setting of allogeneic stem cell transplantation.

Bone Marrow

and biology courses he figured that he could never become a scientist, and later studied history and literature in college. Despite his parents’ encouragement, Dr. Scadden proved to have a rebellious streak, and although he was recruited to several colleges, he was bothered greatly by the recruiters’ focus on “status,” and he decided not to attend. Finally convinced by a family friend to give college a try, he attended briefly, but his rebelliousness struck again and he went off to work on the railroad. Dr. Scadden did ultimately graduate but observed, “I’ve done that repeatedly in my life. Rebel, resist, repeat. It’s not a good formula, but it keeps things interesting and has taught me a bit about what matters...There is no single path.”

Dr. Scadden began his career aspiring to be a clinician. During residency, a family member was diagnosed with cancer, solidifying his choice. However, he was driven toward research owing to a lack of effective tools and therapies that could in his words, “really make a difference to people.” Yesterday, ASH recognized Dr. Scadden for his contributions to hematopoietic biology, including his recent work that provides insights into the mechanisms underlying hematopoietic malignancy. But just as his path to college and medicine was marked by detours and rebelliousness, his route to hematopoiesis, the microenvironment, and myeloid malignancy took a circuitous and surprising route.

At the beginning of Dr. Scadden’s research career, the most tractable disease models were mouse retroviral model systems. Meanwhile, “the AIDS epidemic was going full bore,” he explained. Putting this together, he realized the potential to study both HIV and blood cancers, and thereby help patients with either condition. Unfortunately, no single center was at that time seeing enough patients to answer big questions, so Dr. Scadden saw an opportunity and helped to form the AIDS Malignancy Consortium.

Ultimately his work with gene treatments on blood stem cells related to HIV led him to stem cells and hematopoietic biology. Around this time, treatment for AIDS came along, and the need for clinical work decreased, and he dedicated more time to the lab. Thinking of hematopoietic stem cells, Dr. Scadden connected with Doug Melton, an embryonic stem cell expert studying diabetes just down the hall. Dr. Scadden describes this as a foundation of his work in stem cell biology and the source of a long-lasting and productive collaboration. He was understandably excited about understanding normal stem cells: “In the blood system, normal cells are such an important part of treatment. By understanding normal cells, we can improve stem cell transplantation.”

Dr. Scadden used his lecture to remind us of the importance of stem cell biology on the path to understanding disease: “A better understanding of basic cellular mechanisms leads to clinical insights.” With this in mind, he described his philosophy as the prioritization of projects with a path to the clinic, but not limiting his work solely to translational projects, because surprising insights often come from basic discoveries. He described to ASH News Daily a practice of giving his postdocs free reign to be adventurous in the lab: “Because creativity is such an important part of advancing our field, it should be celebrated and encouraged.” This was clearly evident during his talk, during which he described a variety of creative approaches taken by his postdocs to answer profound questions about stem cells and their niche.

The chances Dr. Scadden has taken and the support he has received throughout his life have provided differences in OS. This study highlights the importance of performing prospective, double-blind, phase III randomized trials.

In a phase III trial, sirolimus was combined with mycophenolate mofetil (MMF) and cyclosporine (CSP) to reduce the incidence of acute GVHD (aGVHD) after reduced intensity conditioning for unrelated alloHCT (abstract #506). The study was closed at the pre-planned interim analysis after 158 patients enrolled due to efficacy improvement with the study arm (sirolimus/MMF/CSP) compared with the control arm (MMF/CSP). There was a reduction in grades 2-4 and 2-4 aGVHD and nonrelapse mortality without increasing relapsing risk. It will be of interest to see if these data result in more routine use of this uncommon combination of agents in the future.

HCT often suffers from a lack of randomized controlled data. It is refreshing to see these large randomized trials being conducted to answer challenging and practice-changing questions.

Dr. Cornell indicated no relevant conflicts of interest.
hematopoietic cell transplantation (abstract # 906).

Factor VIII inhibitory autoantibodies have dogged the steps of factor replacement therapy in hemophilia. For several decades, the only solutions have been costly, inconvenient, and marginally successful immune tolerance induction or expensive bypassing agents. The solution to this problem may reside in a blood product available for many decades: platelets. On Saturday, Dr. Caroline E. Hansen delivered an approach that cleverly uses platelets to bring the factor to where it is needed (abstract #81). This first-of-its-kind approach uses factor VIII, packaged into microcapsules composed of multiple polyelectrolyte layers on a calcium carbonate core, and piggybacked onto platelets by binding through fibrinogen incorporated into the outermost layer. Along with platelets, these microcapsules incorporate into nascent clots at the site of vascular injury and rupture due to the contractile changes from platelet aggregation, thereby releasing factor VIII. The encapsulated factor VIII is protected from circulating inhibitory autoantibodies and can augment hemostasis at sites of active clot formation.

The microcapsules are somewhat porous, releasing about 80 percent of the contained factor VIII in two days. Still, this doesn’t affect the first two hours, which are most crucial in the context of injury. Dr. Hansen said that future work will look into more in vitro models, including addition of von Willebrand factor along with factor VIII to improve efficacy, and testing in a hemophilia mouse model. Certainly, this packaged and carried factor VIII may prove to be a viable strategy for therapy for hemophilia A, especially in the setting of inhibitors. Harnessing the biological properties of platelets to serve as the carrier, sensor, and actuator of delivery may well herald a new era in targeted drug delivery.

Hitting an old target, repackaging an old treatment, and using a common blood product to deliver treatment — these old dogs are showing us that you don’t have to be new to “novel.”

Dr. Chaturvedi and Dr. Cornell indicated no relevant conflicts of interest.

Abstracts

breakthrough designation for ibritinib in the treatment of cGVHD, making this presentation at the ASH annual meeting all the more timely.

Following this, it will be time to gain new insights into hematopoietic stem cell (HSC) biology. Data from single-cell RNA sequencing will help delineate the processes by which HSCs transition from dormancy to activation. As part of this work, Dr. Cabezas-Wallscheid will explain the all-trades approach: a cancer drug can “stop the clock” on HSC activation, and how vitamin A deficiency can affect the regulation of cell cycle-mediated stem cell plasticity.

Next, the pendulum will swing back to clinical trials with the last two late-breaking abstracts. We will hear data from the PERSIST-2 trial, evaluating the use of pacritinib, an oral kinase inhibitor targeting JAK2, FLT3, IRAK1, and CSF1R, in patients with myelofibrosis and thrombocytope尼亚. This trial, too, was a 1:1:1 randomization, comparing two dosing schedules (200 mg twice daily and 400 mg once daily) to “best available therapy,” including ruxolitinib. Dr. Mascarenhas will explain the group’s results, demonstrating improvement in splenic volume and symptoms with ruxolitinib (particularly the twice-daily dosing) and balance this against a higher risk of significant bleeding with this treatment approach.

And, before time runs out, Dr. Neelapu will present the first results of Zuma-1, the phase II clinical trial of Kte-C19 chimeric antigen receptor T cells in the treatment of refractory diffuse large B-cell lymphoma. We will be presented the results of 51 evaluable patients of this 111-patient protocol. Kte-19 clocked in with an overall response rate of 76 percent, and a complete response rate of 47 percent, though the response rate at three months had already dropped to 39 percent. We’ll learn more about the toxicity of treatment, including cytokine release syndrome, neurotoxicity, and hemophagocytic lymphohistiocytosis. So make sure to save time to attend the Late-Breaking Abstracts session (Tuesday 7:30 a.m.-9:00 a.m., SDCC Hall AB). Tempus fugit!

Dr. Matasar indicated no relevant conflicts of interest.

CML

Exploring the Unknown Unknowns

BY NAVEEN PENMARAJU, MD

Former U.S. Secretary of Defense Donald Rumsfeld attempting to explain the inherent complexities of foreign policy and diplomatic engagement, once famously quipped, “... there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say, we know there are some things we do not know. But there are also unknown unknowns — the ones we don’t know we don’t know.”

No longer are the chronic myeloid leukemia (CML) oral and poster presentations dominated by the five- to seven-year updates of front-line imatinib therapy. The field of CML research has moved into several new, patient-centric areas, topped by tyrosine kinase inhibitor (TKI) discontinuation. That’s right. Discontinuation. Well alas, in 2016, Rumsfeld’s famous idiom might be applied to the field of CML.

A “known known” and fundamental concept of CML therapy has been that all patients should be taking TKIs without stopping. However, a new “known known” has emerged, as many groups worldwide have identified that there is a subset of patients with CML who may be able to stop taking TKIs (after a period of molecular remission), with the reasonable expectation that in a percentage of these patients, the disease will never recur. However, the “known unknowns” of this clinical question include the fact that we cannot thus far identify 100 percent of the time, a priori, who those patients are. Many “unknown unknowns” abound in this novel area, but of course, since we don’t know what they are, I cannot write anymore about them!

At this year’s annual meeting, there will be a host of abstracts to sift through on the topic of TKI discontinuation for patients with CML. Abstract #3066, “Patient-Reported Quality of Life before and after Stopping Treatment in the ENESTFreedom Trial of Treatment-Free Remission for Patients with Chronic Myeloid Leukemia in Chronic Phase,” will present a analysis by Dr. Andreas Hochhaus and colleagues that focuses on two important aspects of patient care in CML. These aspects are quality of life and stopping TKI therapy. The abstract looks at little-discussed, but very clinically relevant, occurrences of adverse events such as musculoskeletal events seen with TKI therapy during the course of a front-line nilotinib clinical trial (ENEST freedom). The second abstract to highlight is #787, “Cessation of Tyrosine Kinase Inhibitors Treatment in Chronic Myeloid Leukemia Patients with Deep Molecular Response: Results of the Euro-Ski Trial.” Dr. Francois-Xavier Mahon and colleagues conducted the large-scale European Stop TKI (EURO-SKI) trial (ClinicalTrials.gov number NCT01996114) in which the investigators enrolled more than 800 patients (750 of whom had molecular data available for full assessments) from 11 European countries. Patients with CML in the chronic phase without prior TKI failure who received imatinib, nilotinib, or dasatinib, and who were in deep molecular remission (defined as BCR-ABL < 0.01 percent on the international scale, MR4) for at least one year were put forward to stop TKI treatment on this study. Remarkably, investigators demonstrated that the molecular remission-free survival was 62 percent at six months, the majority of patients regained their deep molecular remission, and no patients had advanced to blast phase.

Rounding things out, abstract #938, “Chronic Myeloid Leukemia Patients with Stable Molecu lar Responses (at least MR3) May Safely Decrease the Dose of Their Tyrosine Kinase Inhibitor: Data from the British Destiny Study,” helps validate the theme of “less is more.” Dr. Richard Clark and colleagues conducted the “British escalation study” and found that among 174 patients from throughout the United Kingdom, patients with at least stable MR3 (on the international scale) initially decreased their TKI to half the standard dose for one year, followed by stoppage of the TKI. They showed that among the patients who had molecular recurrence of disease (n=12), all returned to MR3 by four months of restarting their TKI.

Therefore, while there are more “unknown unknowns” at this time than “known knowns,” 2016 may well be remembered as the year for the era of exploration for “less is more” in the realm of therapy for CML, with many more studies warranted to investigate this area over the next decade.

Dr. Pennmaraju indicated no relevant conflicts of interest.

Errata:

On page A-1 of Sunday’s edition, ASH News Daily mistakenly referenced the “Norwegian Nobel Committee,” however, the committee is Swedish. The article has been corrected online.

On page A-1 of Monday’s edition, ASH News Daily mistakenly captioned a photo of Dr. Martin Schrappe as “Dr. Stephen Hunger.” Apologies to Drs. Schrappe and Hunger. The article has been corrected online.
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