CLINICAL RESEARCH

Ruxolitinib is Potential Corticosteroid-Refractory GVHD Therapy

Allogeneic hematopoietic cell transplantation patients who received ruxolitinib for corticosteroid-refractory (SR) graft-versus-host disease (GVHD) had high overall response and survival rates, as well as low relapse rates, suggesting that the JAK1/2 inhibitor may be a promising new treatment option for patients with SR-GVHD. A new study published in *Leukemia* reports the results of a study that examined outcomes data obtained from 19 stem cell transplant centers in the United States and Europe that used ruxolitinib as salvage therapy for patients with SR-GVHD. Of the 95 patients included in the study, 54 had grades III-IV SR acute (a) GHVD and 41 had moderate or severe chronic (c) GVHD. All of the patients had received a median of three GVHD therapies prior to ruxolitinib, which appeared to be a successful treatment for these patients, based on overall response rates of 85.4% for SR-cGVHD patients and 81.5% for SR-aGVHD patients, including 25 patients who achieved complete response. Of the patients who responded to ruxolitinib therapy, the GVHD relapse rates were only 6.8% for SR-aGVHD patients and 5.7% for SR-cGVHD patients, and six months later, the survival rates were 79% for SR-aGVHD and 97.4% for SR-cGVHD. However, more than half of the SR-aGVHD group developed cytopenia compared to 17.1% of the SR-cGVHD patients. In addition, SR-aGVHD patients were more likely to experience cytomegalovirus reactivation (33.3%) than SR-cGVHD patients (14.6%). The researchers concluded that using ruxolitinib as a treatment option for SR-GVHD should be validated in a prospective trial. More...

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factors that might be predictive of increased donor risks. Their goal was to examine the relationship between donor race/ethnicity, donor socioeconomic status and collection center volumes on the acute toxicities experienced in the first seven days after bone marrow harvest or peripheral blood stem cell collection.

They found that among peripheral blood stem cell donors, female and obese donors had more symptoms with donation; donors older than 40 years of age had less pain with donation, compared with younger donors; and among bone marrow donors, female donors and donors older than 30 years of age had significantly higher toxicity one week after donation. In addition, there was a higher incidence of grades 2–4 skeletal pain in black males on day two after marrow collection. What was very promising, was the lack of correlation between race and socioeconomic status on donor toxicities for either marrow or peripheral blood stem cell collection. However, the authors did identify collection center volume as having significant impact on toxicity: at one week postprocedure, marrow donors from centers performing less than one marrow collection every two months had more toxicity.

So what can we learn from these data? Quality improvement is research in and of itself, and the more data that are available, the more opportunities there are to address what best practice actually looks like. When it comes to stem cell products, there are actually four participants: the operator (who performs the harvest or collection), the donor, the product and the patient. Outcomes can be measured for all. In this regard, a task force comprised of experts from the Foundation for the Accreditation of Cellular Therapy, ASBMT and NMDP will begin to explore best practices for collection. Importantly, it is timely to

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understand both what makes a great donor experience and what identifies the features of a center’s practices that result in high-quality harvests. From this, further education can be provided and specific outcomes measures can be put into place.

The Shaw study is a perfect example of how research can feed back to standards, with the opportunity for positive impact on training and standardization of practices within centers. Collaborative discussion on possible strategies to address issues associated with a decreased number of marrow collections should pave the way for improving overall quality of stem cell products. Furthermore, the data gleaned from the unrelated donor experience have important implications for related donors.

So why, might you ask, is this article entitled, “Giving Thanks?” Consider that without the volunteer donors throughout the world, transplants would not be possible for many of our patients. The real medical issues that our donors face during the process of donating stem cells should give us pause to reflect upon the priceless gift they offer both willingly and proudly, simply because it is the right thing to do.

-Effie P.

ASSOCIATION NEWS

Potential Directions for ABIM Certification and MOC Programs

In response to concerns about the Certification and Maintenance of Certification (MOC) programs, the American Board of Internal Medicine (ABIM) launched the Assessment 2020 initiative to explore the future of assessment in internal medicine and its various subspecialties. A task force made up of a wide range of participants was convened to investigate the underlying issues and guide the redesign of ABIM programs. A report released in September 2015, A Vision for Certification in Internal Medicine in 2020, includes key recommendations such as:

- **Change the MOC exam.** The task force recommends replacing the 10-year MOC exam with more meaningful, less burdensome assessments.

- **Focus assessments on cognitive and technical skills.** Assessment of cognitive skills assures the public that physicians are staying current with the clinical knowledge relevant to patient care. Assessment of technical skills ensures that physicians can apply that knowledge to adequately perform the technical procedures appropriate to the discipline.

- **Recognize specialization.** The task force recommends exploring the need for certification in specialized areas, without the requirement to maintain underlying certificates, while being transparent about specialization to the public.

“The Assessment 2020 Task Force members provided useful insights and recommendations that will be instrumental as we reshape certification to meet physicians’ and society’s changing needs,” said Clarence H. Braddock III, M.D., chair of the ABIM board of directors.

“We now need to hear constructive feedback from the internal medicine community on these recommendations, begin to determine their feasibility and develop implementation plans where needed.”

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ASSOCIATION NEWS (CONTINUED FROM PAGE 3)

Fourth BMT Winter Workshop Dec. 4
On the eve of the American Society of Hematology Annual Meeting, leaders in blood and marrow transplantation (BMT) will review their latest new findings in a dynamic workshop.

The BMT Winter Workshop was created by co-chairs Marcel van den Brink, M.D., head of the Division of Hematologic Oncology at Memorial Sloan Kettering Cancer Center, and Edmund K. Waller, M.D., director of Emory University’s Bone Marrow and Stem Cell Transplant Center.

Since its inception in 2012, the annual workshop has provided a catalytic forum that has helped facilitate the application of new technologies to old and new BMT challenges. The program features fast-paced talks by 18 experts, addressing recent unpublished data on high-impact clinical and pre-clinical studies, with this year’s topics including Microbiota, chimeric antigen receptors and T-cell receptor sequencing.

The fourth BMT Winter Workshop is hosted by Moffitt Cancer Center of Tampa, Florida, under the direction of Claudio Anasetti, M.D., senior member and chair of Blood and Marrow Transplantation at Moffitt Cancer Center. The event will be held on Friday, Dec. 4, from 3 p.m.–8:30 p.m. at the University of Central Florida (UCF) Rosen College of Hospitality Management within miles of the Orlando convention center. Shuttle service will be available between the Orlando convention center and Rosen College. Registration is now open. For more information, contact Marsha.Moyer@Moffitt.org or Janet.Young@Moffitt.org or visit MOFFITT.org/BMTworkshop2015.

King Abdullah International Medical Research Center First Saudi Arabia Cord Blood Bank to Earn FACT Accreditation
The King Abdullah International Medical Research Center (KAIMRC) Cord Blood Bank in Saudi Arabia received internationally recognized accreditation by the Foundation for the Accreditation of Cellular Therapy (FACT) at the University of Nebraska Medical Center. The KAIMRC program is the first and only one in Saudi Arabia to be recognized by FACT. The KAIMRC Cord Blood Bank, directed by Dunia Jawdat, Ph.D., received accreditation on Sept. 15 and is accredited for banking cord blood for both public and private family use.

“The bridge of trust between our bank and patients is based on the quality of service we provide,” said Dr. Jawdat. “Achieving FACT accreditation validates the continuous hard work given by our staff to provide high quality products. Being internationally recognized as a high quality service provider will continuously drive us to aim for excellence and quality improvement and further discover advancement in cord blood stem cell therapy.”

Worldwide, FACT has accredited cord blood banks in 21 countries. Phyllis Warkentin, M.D., FACT chief medical officer, is pleased to see that number continue to rise.

“Accreditation is important outside the United States since best-matched donors can be in a different part of the world,” she said. “Availability of high-quality matched cells depends on international consensus and collaboration.”

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ASSOCIATION NEWS (CONTINUED FROM PAGE 4)

FACT 2015-2016 Education Calendar Available Online
The 2015-2016 education calendar is posted on the Foundation for the Accreditation of Cellular Therapy (FACT) website with several events open for registration. This year’s calendar boasts a wide variety of events. In addition to inspection and accreditation workshops, take advantage of events currently open for registration, addressing such topics as pharmacy requirements, quality management, navigating FACT standards and more. View the education calendar.

NetCord and the Foundation for the Accreditation of Cellular Therapy (FACT) have published the draft sixth edition NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration for review and comment by the cellular therapy community and the public at large. The standards apply to all phases of cord blood collection, banking and release for administration, including donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release and distribution to clinical programs. Comments will be accepted through Nov. 30. For more details about the draft and instructions for submitting comments, visit http://www.factwebsite.org/publiccomments.

Asia-Pacific Blood and Marrow Transplantation (APBMT) Group Annual Congress
The 20th Congress of the Asia-Pacific Blood and Marrow Transplantation Group (APBMT), Oct. 30-Nov. 1 in Okinawa, Japan, is being hosted by the Japan Society for Hematopoietic Cell Transplantation and supported by its domestic and international colleagues. The APBMT meetings provide an international focus on the science and practice of hematopoietic stem cell therapy. APBMT provides the forum for the exchange of information between participants, an opportunity to establish and renew personal relationships and stimulate the interest and ambition of participants from all Asia-Pacific countries/regions to make hematopoietic stem cell therapy an ideal treatment for a variety of diseases. Please stop by the ASBMT booth in Okinawa for information on membership, Society initiatives and more. More...

Membership Dues
The ASBMT appreciates your support in 2015 and looks forward to a productive 2016, helping you as you help your patients. Keep an eye on your inbox as you will be receiving your 2016 membership dues invoice in the coming weeks.
ASBMT President’s Symposium, HCT as Precision Medicine: Historical Reflection and Future Potential

The importance of precision medicine was articulated by President Obama during his State of the Union address in January 2015 with the unveiling of the Precision Medicine Initiative (PMI). It should come as no surprise that hematopoietic cell transplantation (HCT) is well-positioned to capitalize on this initiative if we embrace the accompanying opportunities and challenges.

HCT has had targeted therapy from its earliest days with the identification of the importance of donor and recipient HLA matching for successful outcomes. Similarly, our selection of donors and conditioning regimens for specific patients has been a bedside approach of targeted therapy. The PMI offers us the potential to push our patient-specific planning of therapies beyond our currently improving, but limited, applications of molecular characterization of acute leukemia and the unfulfilled promise of genetic profiles to predict graft-versus-host disease or transplant-related mortality.

If we are to reach our potential, however, we must do three things that form the basis of our symposium: First, we must look back at the seeds planted in the mid-1980s with the inception of the Human Genome Project and see what lessons were learned to inform the vision of the PMI. We are pleased to have Kathy L. Hudson, Ph.D., deputy director for Science, Outreach and Policy, National Institutes of Health, use the historical context to identify key issues we as transplant physicians must consider if we are to successfully meet the challenges inherent in the president’s PMI.

Second, we need to consider the profound ethical questions that are raised by the strategy being taken in the PMI: uploading of individuals’ clinical history, behaviors and genomic information into a database to be used by widely distributed researchers. Rebecca Pentz, Ph.D., professor of research ethics, Emory School of Medicine, is going to help us shape the ethical questions and issues we will have to grapple with as we develop basic science and translational and clinical interventions that are patient-specific in a public arena.

Third, and perhaps most difficult, we must consider the potential of this initiative and how it will transform HCT in the context of other developments and movements. For example, developments in “big data,” the interaction of genomics and lifestyle or environment, economics, geography and competing non-HCT innovations. The eye of the futurist must be keen and survey a broad horizon. Alois Gratwohl, M.D., Ph.D., Division of Hematology, Department of Medicine, University Hospital Basel, is going to be our futurist, looking down the road to see where HCT may be in a decade in light of all the potential of precision medicine amidst the other developments and considerations outlined above.

After we have heard from each of our three speakers, they will come together for a panel discussion of the issues raised and to answer questions from the audience. We hope to see all of you on Sunday, Feb. 21, in Honolulu, Hawaii, for this important and exciting discussion.

Chris Bredeson
ASBMT President-Elect
Chair, ASBMT President’s Symposium

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The first trial to publish results of a study using a combination of lenalidomide and vorinostat as maintenance therapy following autologous hematopoietic cell transplantation reports that the regimen was well-tolerated by patients. Researchers of the study appearing in the British Journal of Haematology used a standard 3x3 dose escalation phase 1 design. For the study, 16 multiple myeloma patients were given vorinostat starting at least 90 days after transplantation on days one through seven and 15-21 and 10 mg. of lenalidomide on days one through 21. The oral regimen was administered on a 28-day cycle. All of the patients tolerated the combination maintenance therapy, and seven of the patients had improved transplant responses after starting the treatment. The most common side effects included cytopenias, gastrointestinal issues and fatigue. As of the study publication date, the median progression-free survival and overall survival had yet to be reached, but researchers concluded that the early results of the study support continued research into the combination therapy.

Patients who received an allogeneic hematopoietic cell transplantation (HCT) from an HLA-10/10-match unrelated donor with mismatched DRB4 had a shorter median survival time than the other patients included in a study published in a recent issue of Bone Marrow Transplantation. Researchers conducted a retrospective study to determine the effect of HLA-DRB3/B4/B5 allele mismatching after HLA-10/10-matched unrelated HCT. Of the 251 patients included in the study, 14 of the patients receiving HCT from a fully matched unrelated donor had a mismatched DRB4 donor, 23 had a mismatched DRB3 donor and 214 had neither a DRB3- nor DRB4-mismatched donor. After comparing the 37 patients with DRB3 or DRB4 mismatches to the other patients, researchers discovered that the median survival for patients without one of the DRB3/4 mismatches was 18 months, with DRB3-mismatch was 32 months and with DRB4-mismatch was seven months. In addition, a multivariate analysis showed that DRB4 mismatching had a significant negative impact on survival, acute graft-versus-host disease and transplant-related mortality. Researchers recommended that a prospective study be performed to confirm the effects of DRB4-mismatch on patient outcomes following HCT from an unrelated donor.
**TRANSLATIONAL SCIENCE STUDIES**

**Tc17 Cells Linked to GVHD, Not GVL**

Researchers have discovered that after allogeneic stem cell transplantation, Tc17 cells from a donor differentiate early and are extremely plastic and inflammatory, inducing graft-versus-host disease (GVHD) without graft-versus-leukemia (GVL) effects. The study from *Blood* demonstrated that a CD8+ Tc17 population developed quickly after transplantation but failed to maintain its lineage. Tc17 differentiation occurred in response to IL-6 and alloantigen presentation by host dendritic cells, and Tc17 cells expressed elevated levels of prototypic lineage-defining transcription factors and cytokines. Targeted depletion of Tc17 soon after transplantation provided protection from fatal acute GVHD but since Tc17 cells are noncytolytic, they failed to facilitate GVL effects. As a result, the Tc17 cells led to inflammatory iTc17 (iTc17) during GVHD. The researchers concluded that preventing iTc17 from developing may be a viable option for separating GVHD and GVL in a clinical setting. [More...]

**Conditioning and Inflammation Cause MDSC Suppressor Function Loss**

A study appearing in *Blood* reports that a conditioning regimen and inflammation from graft-versus-host disease (GVHD) caused myeloid-derived suppressor cells (MDSCs) to lose their suppressor function, affecting their ability to minimize life-threatening GVHD. For this study, researchers transferred MDSCs to lethally irradiated recipients of allogeneic hematopoietic grafts. They discovered that MDSCs exposed to an inflammatory setting associated with acute GVHD for even a brief period had limited suppressor efficacy. In addition, MDSCs lacking the adaptor apoptosis-associated speck-like protein containing a CARD, which assembles inflammasome complexes, improved survival of mice developing GVHD compared with wild-type donor MDSCs. The researchers concluded that MDSCs can be used as a treatment to prevent GVHD and other inflammatory conditions by limiting in vivo MDSC inflammasome activation to maintain the suppressive ability of MDSCs. [More...]

**Virus-Specific T Cells Prevent Dendritic Cell Defects**

Dendritic cell (DC) defects caused by acute graft-versus-host disease (GVHD) prevented virus-specific T cells from priming, but polyclonal T cells transferred from immune donors provided antiviral immunity, despite the presence of GVHD, according to a study published in *Blood*. Using cytomegalovirus (CMV) as the pathogen for this study, researchers discovered that CMV was self-limiting after syngeneic bone marrow transplantation (BMT) but that when GVHD was present after allogeneic BMT, CMV induced a cytopathy, leading to fulminant necrotizing hepatitis and universal death. GVHD caused a DC defect, resulting in failure of the CMV-specific CD8+ T cells to respond, and an antiviral CD8+ T-cell defect. Together, these defects limited antiviral T-cell responses. When virus-specific cells were transferred, DC defects were avoided and protective immunity was provided, even though GVHD was present. The researchers indicated that the results of this study support the importance of avoiding GVHD when reconstructing antiviral immunity after BMT and highlight how adoptive transfer of virus-specific T cells overcome priming defects triggered by GVHD. [More...]

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### Calendar of Events

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<td>Society for Immunotherapy of Cancer</td>
<td>Annual Meeting November 4-8 National Harbor, Maryland</td>
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<td>National Marrow Donor Program/Be The Match</td>
<td>Council Meeting November 5-7 Minneapolis, Minnesota</td>
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<td>European Society for Medical Oncology</td>
<td>Summit Americas November 6-8 Miami, Florida</td>
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<td></td>
<td>European Society for Medical Oncology</td>
<td>Symposium on Immuno-Oncology November 20-21 Lausanne, Switzerland</td>
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<tr>
<td><strong>December</strong></td>
<td>European Society for Medical Oncology</td>
<td>Asia Congress December 18-21 Singapore</td>
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<td>Bioleaders Forum</td>
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<td>BMT Tandem Meetings</td>
<td>Combined ASBMT and CIBMTR Annual Meetings February 18-22 Honolulu, Hawaii</td>
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<td>Association of Community Cancer Centers</td>
<td>42nd Annual Meeting March 2-4 Washington, D.C.</td>
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<td>National Comprehensive Cancer Network</td>
<td>21st Annual Conference: Advancing the Standard of Cancer Care March 31-April 2 Hollywood, Florida</td>
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<td><strong>January</strong></td>
<td>European Society for Blood and Marrow Transplantation</td>
<td>42nd Annual Meeting April 3-6 Valencia, Spain</td>
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<td><strong>February</strong></td>
<td>European School of Haematology</td>
<td>5th International Conference on Myelodysplastic Syndromes April 14-16 Estoril, Portugal</td>
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<td>American Association for Cancer Research</td>
<td>Annual Meeting April 16-20 New Orleans, Louisiana</td>
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<td>British Society for Haematology</td>
<td>Annual Scientific Meeting April 18-21 Glasgow, Scotland</td>
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<td>Oncology Nursing Society</td>
<td>41st Annual Congress April 28-May 1 San Antonio, Texas</td>
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<tr>
<td><strong>March</strong></td>
<td>Moffitt Cancer Center</td>
<td>4th Annual BMT Winter Workshop December 4 Orlando, Florida</td>
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<td></td>
<td>American Society of Hematology</td>
<td>57th Annual Meeting and Exposition December 5-8 Orlando, Florida</td>
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<td></td>
<td>European Society for Blood and Marrow Transplantation</td>
<td>42nd Annual Meeting February 21-25 Salt Lake City, Utah</td>
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[Seattle Genetics](#)