ASBMT eNews

American Society For Blood and Marrow Transplantation

September 2011

Clinical Research

Abnormal Endothelial Cells Play Role in GVHD Treatment Resistance

Investigators have discovered that weak and abnormal endothelial cells may play a role in resistance to high-dose steroid treatment of graft-versus-host disease (GVHD) rather than refractory T-cell activity. The study published in *Blood* compares the kinetics of T-cell activation markers with impaired endothelial markers in the serum of sensitive and refractory GVHD. Patients with steroid-refractory acute GVHD were not exposed to unchecked activation by T cells but had rising thrombomodulin levels and high angiopoietin-2 (ANG2)/vascular endothelial-derived growth factor ratios unlike steroid-responsive GVHD. Refractory patients even had elevated ANG2 before transplant. More...

Risk Factors for Secondary Autoimmune Disorders Following Transplant

According to a new study appearing in *Blood*, lupus erythematosus and antithymocyte globulins use plus CD34 graft selection are risk factors for the development of secondary autoimmune diseases following a hematopoietic stem cell transplant (HSCT) for a primary autoimmune disease. The European Group for Blood and Marrow Transplantation (EBMT) studied data it received from 1995 to 2009 on patients who did and did not develop a secondary autoimmune disease after their transplants. They discovered that 29 out of 347 autologous HSCT patients and 3 out of 16 allogeneic HSCT patients developed at least one secondary autoimmune disease within less than two years of the transplant. In addition, the occurrence of a secondary autoimmune disease was approximately 10% five years after autologous HSCT. More...

Rituximab Safe and Effective for Thrombotic Thrombocytopenic Purpura Treatment

A phase 2 clinical trial of rituximab indicates that it is a safe and effective treatment for acute thrombotic thrombocytopenic purpura in addition to standard therapy, reports a new study in *Blood*. Researchers found that rituximab-treated patients experienced reduced hospital stays and lower relapse rates compared with historical controls who had received only standard therapy without rituximab. More...

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A Word from President Daniel Weisdorf, MD

Equipoise vs. Enthusiasm: How Much Do We Want To Learn?

Allogeneic transplant cures hematologic malignancies by capitalizing on two effective tools: conditioning regimen-induced tumor cytoreduction and the immunologically based graft vs. leukemia/tumor (GVL or GVT) effect.

Since the first studies of transplantation decades ago, there have been conditioning regimen tinkerers who have tailored combination therapies for maximum tumor cell depletion, yet with still tolerable toxicity. The other camp (sometimes the same investigators) focused on limiting GVHD while preserving the immunologically based GVL effect. In 2011, both groups remain alive and well.

But are these really distinct antineoplastic entities? Conditioning regimens designed for specific tumors can no doubt yield tumor debulking. This can create the minimal disease state conducive for donor cell engraftment and immunologic reconstitution and are at least permissive of GVL. Yet various observations demonstrated that excess tissue toxicity can augment risks of GVHD. It was postulated that excessively damaged tissues looked foreign to the donor immune system or that toxicity compromised effective delivery of GVH prophylactic medications, and though unknown in earlier times, conditioning toxicity might have altered the relative balance between T cell effectors that mediate GVHD (and GVL) and regulatory T cells or myeloid-derived suppressor cells (or as yet unknown regulatory elements) that limit the potency of GVL. Conditioning intensity is thus intertwined with the clinical manifestations of GVH along with the functional expression of GVL.

Each center's investigative bent chooses emphasis on one or another tactic for specific populations of patients. For our most common indication for allotransplantation, acute myeloid leukemia, we now recognize a myriad of cytogenetically and molecularly defined subsets with differing risks of achieving remission, getting to a minimal residual disease (MRD) state, and responding to the allogeneic GVL of a transplant. But do "favorable" subsets of AML really need less conditioning or does the availability of reduced intensity conditioning (RIC) merely make the transplants seem appealing because early toxicities are diminished? In these favorable subsets do we really need less tumor cytoreduction? Alternatively, are the higher risk cytogenetic phenotypes really in need of more intensive tumor cell depletion plus potent GVL? Perhaps other strategies including posttransplant maintenance therapy, adoptive immunotherapy or anti-tumor vaccines could better limit risks of relapse? Reminding ourselves that the choice of conditioning agents or intensity could also influence the potency of GVL or the setting for effective adoptive immunotherapy highlights the interrelationship of these two antitumor components and the limits of our knowledge in choosing the best two-pronged attack.

Since reports of RIC allotransplantation are published fast and furiously, it seems that two themes have appeared. First, with a longer view (six-24 months posttransplant), RIC is not always associated with lesser non-relapse mortality (NRM) as GVHD and immunocompetence, and the older population receiving reduced intensity regimens still succumb to NRM. But equally important, for the broad population of patients with AML, more intense conditioning has only modest incremental impact in reducing risks of relapse.

So what should we do? Should we tailor the intensity to our pretransplant perceived risk of relapse and use more intense, yet tolerable myeloablative conditioning for those with high-risk cytogenetics, advanced remission or measurable MRD? And, conversely, should we limit conditioning with hopes of reduced NRM for those with standard risk AML?

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Association News

eNews Editor

In August, James W. Young, MD, from Memorial Sloan-Kettering Cancer Center was installed as the new editor for the eNews. Prior to this, Stephanie J. Lee, MD, MPH, from the Fred Hutchinson Cancer Research Center served as editor for three years. On behalf of ASBMT, we thank Dr. Lee for her commitment and support.

Transplant Reimbursement Resource Center

The ASBMT and the NMDP work together to pursue improvements in transplant coverage, benefits and reimbursement. Visit www.marrow.org/reimbursement to find resources related to financial topics.

Free ASBMT Membership for Trainees

Postdoctoral fellows and physicians-in-training for blood and marrow transplantation are eligible for free membership in the American Society for Blood and Marrow Transplantation. Through October, annual dues are waived for new trainees who apply for membership in the Society. The program is made possible through a grant from Otsuka America Pharmaceuticals, Inc. More...

Oct. 1 Deadline for New Investigator Awards

New investigator awards of $60,000 each, to be presented at the 2012 BMT Tandem Meetings, are being supported by Amgen, Genentech, Millennium, Otsuka and ASBMT. The deadline for applications is Oct. 1. More...

NHLBI/PACT Workshop Announcement

The NHLBI/PACT Workshop "Cell Therapy for Pediatric Diseases: A Growing Frontier" will take place Sept. 14-15 at the Lister Hill Center Auditorium of the National Library of Medicine in Bethesda, Md. This workshop will address strategies to overcome the barriers to advancing the development and delivery of cell-based therapies for pediatric patients, in particular, those with rare and life-threatening diseases. The clinical applications of cellular therapies and regenerative medicine, including the ethical considerations and models of clinical trial design, will be examined with intent to optimize overall processes for the future. Visit www.pactgroup.net for workshop details.

Call for Clinical Trial Contributions

The Federation of Clinical Immunology Societies (FOCIS) has created an opportunity for collaboration with their member societies in building an interdisciplinary clinical trial listing in the new ePublication, *Translational Immunology Update*. The section will include phase 1 and 2 studies using novel or standard immunotherapeutics in new diseases or new ways. The trials will be formatted in a table with key variables including the drug name, disease, N, overall study design, primary outcome variables and results. The goal is for readers to have a better understanding of the application of clinical immunology outside of their field. To participate, submit trials that you are aware of to http://translationalimmunology.pbworks.com/Clinical-Trial-Contributions.

Summit on Cell Therapy for Cancer

The Summit on Cell Therapy for Cancer is a 1½-day program that will be held on the National Institutes of Health (NIH) campus in Bethesda, Md., and will feature dynamic discussions and lectures by leaders in the field to provide an in-depth review of the state of the art of cell therapy as a cancer immunotherapy. The Summit is sponsored by the Society for Immunotherapy of Cancer (SITC) in collaboration with AABB (formerly the American Association of Blood Banks), the American Society for Blood and Marrow Transplantation (ASBMT), the American Society of Gene & Cell Therapy (ASGCT), the Cancer Immunotherapy Trials Network (CITN), and the NIH, Clinical Center Department of Transfusion Medicine. For more information on the program, speakers and registration, please visit http://www.sitcancer.org/meetings/am11/summit11/

Basic Science Studies

Major Histocompatibility Complex Barrier in Allogeniec Transplantation Overcome

By expanding purified hematopoietic stem cells (HSCs) from mice ex vivo, scientists were able to overcome poor engraftment while maintaining a low risk of GVHD in allogeniec transplantation. The researchers discovered that expanding the cells in a culture for eight days led to a 40-fold increase in the ability of the cells to be used successfully for allografts. Keys to the success of the *Cell Stem Cell* study were a greater number of hematopoietic stem cells and a culture-induced increase of the cell surface expression of the immune inhibitor CD274 (B7-H1 or PD-L1). More...

Tumor Necrosis Factor Receptors Involved in Cell Function

Two distinct tumor necrosis factor (TNF) receptors play a role in inhibiting hematopoietic stem cell (HSC) activity, reports a study published in *The Journal of Experimental Medicine*. While positive regulators of HSC numbers have been identified, this study identifies TNF as a potent inhibitor of normal HSC activity in mice, with important implications for bone marrow failure syndromes in humans. More...

BMT Tandem Meetings

Registration Open for 2012 BMT Tandem Meetings in San Diego

Online registration and housing is now open for the 2012 BMT Tandem Meetings Feb. 1-5 in San Diego. Links to meeting registration, housing reservations, a preliminary program, abstract submission and parallel conferences can all be found in one convenient location. More...

Abstract Submission Deadline is Oct. 13 for Tandem Meetings

Abstracts for the BMT Tandem Meetings in San Diego will be accepted through Oct. 13. Invitations for oral presentations will be offered to more than 100 authors whose abstracts received the highest scores from the review committees. Many others will be accepted for poster presentations. More...

President's Message (continued from page 2)

One approach might be to trade our uncertainty for equipoise and address the question in prospective fashion. The BMT CTN protocol 0901 offers just that opportunity to prospectively study patients with AML in remission (or MDS) having either sibling or well-matched unrelated donors randomized between fuller intensity versus lesser intensity conditioning regimens (Flu big Bu or Bu Cy or Cy TBI versus Flu little Bu or Flu Mel). This trial gives us a chance to stop playing our hunches and substitute this well-designed study to prospectively address the importance of conditioning regimen intensity.

While we all hope to know the answers and choose our best for each patient, for the individually unanswerable question, I suggest we lean toward equipoise and use the power of a group-wide study to improve outcomes for all of our patients. Intellectual enthusiasm is to be applauded but sometimes a group effort is the smartest of all. -Daniel

Calendar of Events

•September

2ND Donor Outcome Workshop
September 1-2
Leiden, The Netherlands

BMT InfoNet
4th National Survivorship Conference
September 10-11
Atlanta, Georgia

ISCT North American Regional Meeting
September 15-16
Charlottesville, Virginia

ESH-ICMLF 13th International Conference on Chronic Myeloid Leukemia – Biological Basis of Therapy
September 22-25
Estoril, Portugal

European Society for Medical Oncology
The European Multidisciplinary Cancer Congress
September 23-27
Stockholm, Sweden

REACT/TS 5th International Symposium
September 27-29
Miami, Florida

•October

Radiation Injury Treatment Network
State of the Science Workshop
October 11
Chicago, Illinois

•October (cont.)

American Society for Histocompatibility and Immunogenetics
37th Annual Meeting
October 17-21
New Orleans, Louisiana

American Association of Blood Banks
2011 Annual Meeting
October 22-25
San Diego, California

World Cord Blood Congress
October 27-29
Rome, Italy

European Society of Gene & Cell Therapy
19th Annual Congress
October 27-31
Brighton, United Kingdom

ISCT Australasia Regional Meeting
October 30-November 2
Bunker Bay, Australia

•November

2011 World Conference on Regenerative Medicine
November 2-4
Leipzig, Germany

National Marrow Donor Program
2011 Council Meeting
November 3-5
Minneapolis, Minnesota

•December

American Society of Hematology
53rd Annual Meeting
December 10-13
San Diego, California

•January

Phacilitate Cell & Gene Therapy Forum 2012
January 30-February 1
Washington, D.C.

•February

BMT Tandem Meetings
Combined ASBMT and CIBMTR Annual Meetings
February 1-5
San Diego, California

Canadian Society of Transplantation
Annual Scientific Conference
February 23-25
Quebec City, Quebec

• 2013

BMT Tandem Meetings
Combined ASBMT and CIBMTR Annual Meetings
February 13-17
Salt Lake City, Utah

• 2014

BMT Tandem Meetings
Combined ASBMT and CIBMTR Annual Meetings
February 19-23
Orlando, Florida

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Do you have news, responses or opinions to share with us?
Please e-mail the association office at enews@asbmt.org.