HEMATOPOIETIC STEM/PROGENITOR CELL PRODUCTS: DISCUSSION OF UNRELATED ALLOGENEIC PLACENTAL/UMBILICAL CORD BLOOD AND PERIPHERAL BLOOD CELL BANKING AND TRANSPLANTATION

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Sponsored by

Center for Biologics Evaluation and Research, FDA
and
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WORKSHOP OBJECTIVES

- Overview the Federal Register notice published by FDA, January 20th 1998, entitled "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical cord Blood Hematopoietic Stem/ Progenitor Cell Products: Request for Comments".

- Discuss issues regarding the administration of cytokines to normal donors for mobilization of peripheral blood hematopoietic stem/progenitor cells

- Discuss the current status of related and unrelated allogeneic peripheral blood hematopoietic stem/ progenitor cell collection and transplantation

- Discuss the current status of unrelated allogeneic placental/ umbilical cord blood banking and transplantation

- Discuss the status of professional voluntary standards development

WORKSHOP SPEAKERS AND TOPICS

SESSION I - Moderator: Giovanna Tosato, M.D.

Purpose of Conference and Overview of the Federal Register Notice FR Vol 63, No 12, Jan 20, 1998:2985-2988	Liana Harvath, Ph.D. CBER, FDA
Transplant Registry Data-International Bone Marrow Transplant Registry	Mary Horowitz, M.D. IBMTR

Normal Donors and Cytokine Administration	Paolo Anderlini, M.D. M.D. Anderson Cancer Ctr.
SESSION II - Moderator: David Stroncek, M.D.	
Related Allogeneic PBSC Transplants: M.D. Anderson Experience	Richard Champlin, M.D. M.D. Anderson Cancer Ctr.
Related Allogeneic PBSC Transplants: Washington University Experience	John DiPersio, M.D., Ph.D. Washington University
Unrelated Allogeneic PBSC Transplants: National Marrow Donor Program Experience	Dennis Confer, M.D. NMDP
SESSION III - Moderator: John Wagner, M.D.	
The NHLBI Multicenter Cord Blood Banking and Transplantation Study	Mitchell Cairo, M.D. Georgetown University
Banking Issues in Cord Blood Transplantation- The NY Placental Blood Program Experience	Pablo Rubinstein, M.D. NY Blood Center
Unrelated Cord Blood Transplants- The U.S. Experience	Joanne Kurtzberg, M.D. Duke University
The St. Louis Cord Blood Bank Experience	Donna Wall, M.D. Cardinal Glennon Children's Hospital
SESSION IV - Moderator: Liana Harvath, Ph.D.	
Professional Standards—American Association of Blood Banks Approach	N. Rebecca Haley, M.D. AABB
Professional Standards—Foundation for the Accreditation of Hematopoietic Cell Therapy Approach	Elizabeth J. Shpall, M.D. FAHCT Scott Rowley, M.D. ISHAGE Fred LeMaistre, M.D. ASBMT

SUMMARY

The workshop began with an overview presentation of the January 20th 1998 FDA Federal Register Notice entitled "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/

Progenitor Cell Products: Request for Comments". The FDA approach described in this Federal Register Notice indicates that for minimally manipulated unrelated allogeneic peripheral and placental/umbilical cord blood stem/progenitor cells intended for hematopoietic reconstitution, it may be possible to:

- develop product standards, establishment controls and processing controls from existing scientific and clinical data,
- issue guidance for establishment controls, processing controls and product standards, and
- grant licensure for products certified as meeting issued standards.

If FDA determines that data are available to support the development of standards, FDA intends to publicly announce such standards and licensure may be granted for products certified as meeting promulgated standards. If sufficient data are not available to develop standards, then after a specified period of time, unrelated allogeneic stem cell products would be subject to IND and marketing application requirements. The Federal Register Notice is posted on the CBER web site at http://www.fda.gov/cber/genadmin/cord.txt

Peripheral Blood Hematopoietic Stem/Progenitor Cells (PBHSPC)

Presentations regarding PBHSPC included discussions of clinical approaches taken in the related and unrelated allogeneic transplant setting. PBHSPC are mobilized in normal donors who are treated over a 5 to 6 day period with daily injections of Granulocyte-Colony Stimulating Factor or Granulocyte Macrophage-Colony Stimulating Factor prior to apheresis collections. The majority of PBHSPC transplants have thus far occurred with human leukocyte antigen (HLA)-identical sibling donor/recipient pairs.

Transplant outcomes in the HLA-identical sibling donor/recipient setting were described for PBHSPC grafts and were contrasted with HLA-identical sibling bone marrow transplant outcomes of the first 100 days post transplant. The reported advantages of PBHSPC appear to be a decreased time to an absolute neutrophil count $\geq$500 neutrophils/μL (4-5 days), and decreased inpatient days, pharmacy costs and blood product support. The data presented regarding graft versus host disease (GVHD) indicated that the incidence of acute GVHD does not appear to be different, however, the incidence of chronic GVHD is increased in PBHSPC recipients. The International Bone Marrow Transplant Registry data analysis of a one year post transplant period indicates a chronic GVHD trend toward a 75% incidence in PBHSPC recipients as compared to a 45% incidence in bone marrow recipients. The Washington University data, collected over a two-year post transplant period, indicate a 90% actuarial incidence of chronic GVHD in PBHSPC recipients in contrast to a 40-60% incidence in bone marrow recipients. In the related allogeneic PBHSPC donor/sibling setting, PBHSPC grafts that were mismatched at one HLA antigen resulted in a 100% incidence of chronic GVHD (40% of the GVHD is Grade 3-4). The increased incidence in chronic GVHD is associated with high CD34+ cell and lymphocyte doses of these grafts. Studies are underway to quantify the effects of lower cell doses ($<8x10^6$ CD34+ cells/kg) and different conditioning regimens on the incidence of GVHD.

To assess the safety and effectiveness of unrelated allogeneic PBHSPC transplants, the National Marrow Donor Program (NMDP) is conducting a study of PBHSPC from unrelated allogeneic donors for a second transplant subsequent to an initial bone marrow donation. The results of an Investigational New Drug protocol that began February 1997 were presented. The protocol design extensively studies both the donors and recipients. The NMDP intends to develop a similar study for unrelated PBHSPC for first donation transplants.

There are several potential disadvantages of PBHSPC. They include more frequent CMV viremia, unknown risks of increased chronic GVHD, unknown survival advantage, and risks for the normal PBHSPC donor. A presentation regarding cytokine administration to normal donors outlined a variety of short-term safety issues for normal donors. These include:

- bone pain, headache, fatigue, nausea,
- transient elevations in alkaline phosphatase and lactate dehydrogenase,
- infrequent episodes of chest pain, fluid retention,
- central venous catheter placement,
- electrolyte and fluid shifts,
- leukocytosis, and
- thrombocytopenia

The long-term safety issues for normal donors remain unknown at present. Many participants agreed that long-term follow-up of normal donors is important.

Areas Proposed by Speakers for Future PBHSPC Research

Numerous areas in need of future research were identified by the speakers and included:

- normal donor registry to monitor long term (10 years) follow-up of normal donors receiving cytokines for mobilization of cell products,
- further studies of the biological and clinical effects of cytokines and apheresis procedures in normal donors,
- approaches to control GVHD,
- assess the stability of PBHSPC engraftment,
- assess the functional effects of T cell depletion,
- standardization of CD34+ cell assays, and
- standardization of tumor cell assays.

Unrelated Allogeneic Placental/Umbilical Cord Blood Banking & Transplantation

An overview of the National Heart Lung and Blood Institute (NHLBI) multi-center cord blood banking and transplantation study was presented. The study includes three banks (Duke University, University of California at Los Angeles, Georgetown University) and six transplant centers (Duke University, University of Minnesota, University of California at Los Angeles, Fred Hutchinson Cancer Research Center, Indiana University,

and Dana-Farber Cancer Institute). The project is a five-year study that utilizes uniform protocols and is intended to characterize the cord blood product and transplant outcome results. The protocols will be published in December 1998 and will also be available on a web site.

The experience of New York Placental Blood Program was presented. This program was established in 1992 as the first placental/umbilical cord blood bank for unrelated allogeneic transplantation. It has banked and characterized more than 7700 units and provided 700 units of placental blood for transplantation. The results of the first 562 consecutive transplants are to be reported in the New England Journal of Medicine in 1998. The experience reported indicates that the time to myeloid engraftment is primarily associated with the graft cell dose. The transplant-related events are associated with the patient's underlying disease, age, graft cell dose, HLA disparity, and location of transplant center (U.S. versus foreign).

The approach of the St. Louis Cord Blood Bank was presented. This community-based unrelated allogeneic cord blood bank differs from the NHLBI and New York Placental Blood Program banks in that obstetricians or nurse midwives, rather than dedicated collection staff, perform the cord blood collections. It was reported that 30% of cord blood units collected were determined to be suitable for banking.

Areas Proposed by Speakers for Future Placental/Cord Blood Research

A variety of areas in need of future research were identified and included:

- *ex vivo* expansion of cord blood,
- adoptive cellular therapies,
- haplo-identical related cord blood transplants,
- the use of cord blood with gene therapy, and
- immunological vaccine development.

Voluntary Professional Standards Update

Professional organizations have developed voluntary standards and accreditation programs for hematopoietic stem/progenitor cell programs. Presentations were made by representatives of American Association of Blood Banks (AABB) and the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT).

The AABB was established in 1947 and currently represents 8500 individual and 2200 institutional members. The AABB has published standards for hematopoietic progenitor cells since 1991. In developing and revising its standards, the AABB has included the participation of representatives from AABB, American Society for Apheresis, FDA, FAHCT, and NMDP. The AABB standards development committee also includes two public members, an ethicist and a patient who has received hematopoietic progenitor cells as therapy. The AABB is revising its 1996 published standards to incorporate the

International Standards Organization 9000 model for prospective comprehensive quality management programs.

The FAHCT was founded in 1996 by American Society for Blood and Marrow Transplantation (ASBMT; 900 individual members) and the International Society for Hematotherapy and Graft Engineering (ISHAGE; 1000 individual members). The goals of FAHCT are to establish standards for medical and laboratory practice and develop and implement voluntary inspection and accreditation. In developing its standards, the FAHCT standards committee has included the participation of representatives from ASBMT, ISHAGE, and FAHCT. The FAHCT collection center standards include recording clinical outcome data and donor health screening including genetic diseases.

The panel discussion of this session indicated the importance of developing a single set of standards that are acceptable to all interested professionals in this field.