DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Center for Biologics Evaluation and Research
Biological Response Modifiers Advisory Committee

SUMMARY MINUTES
Meeting #34, February 27, 2003
Holiday Inn, Silver Spring, Maryland

COMMITTEE MEMBERS
Daniel R. Salomon, M.D., Chair
Jonathan Allan, D.V.M
Bruce R. Blazar, M.D.*
David M. Harlan, M.D.
Katherine A. High, M.D.
Joanne Kurtzberg, M.D.
Alison F. Lawton
Richard C. Mulligan, Ph.D.

Mahendra S. Rao, M.D., Ph.D.
Anastasios A. Tsiatis, Ph.D.
Alice J. Wolfson, Esq.

NIH REPRESENTATIVE
Lianna Harvath, Ph.D.**

COMMITTEE MANAGEMENT SPECIALIST
Rosanna L. Harvey

EXECUTIVE SECRETARY
Gail M. Dapolito

TEMPORARY VOTING MEMBERS
Mary Horowitz, M.D.
Jeanne V. Linden, M.D.
David F. Stroncek, M.D.

GUEST SPEAKERS
Nelson J. Chao, M.D., M.P.H.
Pablo Rubinstein, M.D.
John E. Wagner, M.D.**

FDA PARTICIPANTS
Philip Noguchi, M.D.
Ruth Solomon, M.D.
Ellen Lazarus, M.D.
Stephen Litwin, M.D.

*not attending
**FDA Consultant

The summary minutes for the February 28, 2003 meeting of the Biological Response Modifiers Advisory Committee were approved on .

I certify that I attended the February 28, 2003 meeting of the Biological Response Modifiers Advisory Committee and that this report accurately reflects what transpired.

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Gail Dapolito, Executive Secretary Daniel R. Salomon, M.D., Chair

FDA BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE
SUMMARY MINUTES
MEETING #34, February 27, 2003

The Biological Response Modifiers Advisory Committee (BRMAC) met on February 27, 2003 at the Holiday Inn, Silver Spring, MD. In open session, the committee discussed issues related to the use of unrelated allogeneic hematopoietic stem/progenitor cells from placental/umbilical cord blood for hematopoietic reconstitution.

Daniel Salomon, M.D., Chair, called the meeting to order and introduced the members, consultants, guests and guest speakers. The executive secretary read the conflict of interest statement into the public record. This statement identified members and consultants of the committee with an appearance of a conflict of interest, who were issued waivers to participate. Copies of the waivers are available from the FDA Freedom of Information Office.

The FDA provided an analysis of clinical outcome data submitted to the FDA regarding the safety and efficacy of cord blood for hematopoietic reconstitution. Guest experts provided the most recent data on clinical studies of unrelated donor umbilical cord blood transplantation in children and adults.

The Chair commenced the Open Public Hearing. During the Open Public Hearing, patients, parents and families of patients addressed the committee regarding their experiences and views on cord blood transplantation to treat oncologic, genetic and metabolic disorders. The comments highlighted concerns related to licensing, ethnic/racial distributions, time to procedure, impact on families and patients, age of recipients and informed consent. The committee also heard comments from the St. Louis Cord Blood Bank and the International Bone Marrow Registry.

The committee deliberations focused on 1) factors the agency should consider in determining the safety and effectiveness for the use of placental/umbilical cord blood (UCB) transplantations for hematopoietic reconstitution, 2) the role of CD 34^+ cell count in selection of UCB and 3) other measures of quality that should be considered.

1) Factors to consider

Specific disease indications:

The committee agreed that umbilical cord blood transplantation is an accepted approach in a variety of diseases. The committee agreed that current available outcome data for bone marrow (BMT), peripheral blood stem cell (PBSC) and umbilical cord blood (UCB) transplantation do not support recommendations for the preferential use of BMT vs UCB for particular disease indications, rather the decision should depend on medical judgment and availability.

The committee agreed that, in general, results of cord blood transplantation are very similar to results of bone marrow/peripheral blood transplantation. The most significant differences concern current cord blood transplantation protocols that operate at the limits of cell dose and a more extensive experience with outcomes of multiply mismatched cord blood transplants vs. bone marrow transplants.

The committee also stated that criteria for obtaining cord blood should be equally as stringent as the criteria for obtaining donor marrow, including a requirement to report outcome data.

Maximum number of HLA mismatches permitted for UCB transplantation:
The committee stated there are insufficient data to evaluate UCB transplants HLA mismatched by 3 or more antigens. Therefore, the committee recommended UCB transplants be limited to 2 or less HLA mismatches - as defined by current standard low-intermediate level resolution HLA typing for class I and high resolution typing for Class II. The committee also stated research needs to continue to provide further data on transplants of 3 or more HLA mismatches.

Incidence of graft vs. host disease:
The committee generally agreed that the incidence of acute GVHD in UCB transplant recipients is no worse than GVHD in BMT recipients, and could be better, but that this comparison is difficult due to inter-center variability in grading of GVHD.

Time to engraftment:
The committee agreed that time to engraftment (neutrophil and platelet recovery) is longer for cord blood than for other sources of hematopoietic stem/progenitor cells, regardless of cell dose. However, engraftment after cord blood transplantation is durable (low risk of secondary graft failure) and the delayed engraftment does not appear to affect overall survival. The committee also recognized that some data indicate a dramatic difference in time to recovery and ultimate engraftment when cell dose (TNC or $CD34^+$ dose) is a factor.

Age of patients to be transplanted:
The committee stated age does not differentially impact BMT or UCB transplantation provided the cell dose is adequate.

Cell Dose
In general the committee agreed on a recommended post-processing (pre-thaw) target dose of 25M total nucleated cells (TNC)/kg, with the provision that the individual transplant centers validate 70% or greater cell recovery post-thaw.

Additional comments from the committee on this point included:

A recommendation that informed consent include information on cell dose to provide patients with the information necessary to make an informed choice about accepting a lower cell dose, than the target dose, if no other suitable hematopoietic stem cell product is available.

A recommendation for development of a thawing procedure certification program for transplant centers.

A recommendation that FDA mandate collection of outcome data for retrospective assessment of product efficacy and quality assurance.

Recommendations for additional outcome data to collect prospectively in future trials

The committee agreed general outcome parameters recommended for other types of hematopoietic stem cell transplantation trials are suitable for UCB trials with the addition of routine chimerism studies in experimental UCB trials. Individual committee members listed several outcome parameters of interest including survival, disease-free survival, time to engraftment, time to hematopoietic recovery, immune reconstitution.

2) Role of $CD34^+$ cell count in selection of UCB

This parameter is an effective predictor of engraftment. However, the committee agreed that TNC also predicts engraftment and it is not necessary to also know the number of $CD34^+$ cells in the unit for purposes of selection of a unit for transplantation.

Minimum number of $CD34^+$ cells below which a product should not be considered for transplantation

The committee issued no consensus statement on this point. Some committee members commented that there are no standardized enumeration assays to assess CD34+ cell number.

3) Other parameters of quality that should be considered

The committee discussed confirmatory HLA typing pre-transplant. Some committee members recommended confirmation of HLA typing at either cord bank or transplant center prior to release of product for transplantation. The committee also recommended that this testing be done on a sample from a contiguously attached segment, whenever possible, as a measure to detect errors in product labeling and thus prevent inadvertent transplant of incompatible units