

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

CHAPTER 1

BACKGROUND AND RATIONALE

CHAPTER 1

BACKGROUND AND RATIONALE

1.1 ALLOGENEIC UMBILICAL CORD BLOOD BANKING AND TRANSPLANTATION

1.1.1 Overview

Transplantation of hematopoietic stem cells (HSC) from HLA-identical sibling bone marrow donors has been successfully utilized in the treatment of patients with high-risk or recurrent hematological malignancies, bone marrow failure syndromes, selected hereditary immunodeficiency states and metabolic disorders. However, use of HSC transplant therapy has been limited by a lack of HLA matched donors. While there are currently more than 4 million potential donors in marrow donor registries around the world (approximately 2 million are HLA, B, and DR typed), more than 30% of patients requiring transplant therapy are still unable to find an HLA 0-1 antigen disparate marrow donor, with even less chance of a successful search in patients of non-Northern European descent. Even if a marrow donor is identified and the transplant performed, severe acute and extensive chronic GVHD and increased risk of opportunistic infection limit transplant outcome. The presence of one (or more) HLA antigen mismatches clearly increases the risk of graft-versus-host disease (GVHD) and adversely affects survival.

In an attempt to increase the availability of suitable donors and reduce the morbidity and mortality associated with allogeneic bone marrow transplantation, clinical investigators worldwide have evaluated umbilical cord blood (UCB) as an alternate source of hematopoietic stem and progenitor cells for transplantation (1-18). Laboratory investigators have confirmed the high frequency of primitive hematopoietic stem and progenitor cells in umbilical cord blood (19).

1.1.2 Unrelated Donor UCB Transplantation

As a result of the early successes with umbilical cord blood from sibling donors, pilot programs for the banking of unrelated donor umbilical cord blood began New York, Milan, Dusseldorf, Paris and London. Benefits of using banked umbilical cord blood include: 1) availability of unit on demand, 2) receipt of the unit at the transplant center prior to the start of conditioning, and 3) minimal risk or inconvenience to the donor. Additional advantages which remain to be proven include 1) lower risk of transmissible infectious diseases, such as cytomegalovirus (21) and Epstein-Barr virus (22), 2) a lower risk of acute and chronic GVHD as compared to unrelated-donor marrow transplants, 3) the ability to tolerate HLA mismatched transplants, and 4) shorter interval between search initiation and transplant.

There are also potential disadvantages of umbilical cord blood. Unlike marrow donors who are screened for major medical problems at the time of collection, the newborn cord blood donor does not have a medical history. The newborn's mother is a surrogate for information pertaining to the family medical history and high-risk behaviors. There is often no opportunity to gather additional information about the newborn donor after the cord blood unit (CBU) has been banked and stored. Therefore, it is possible that banked CBUs may be obtained from newborns who subsequently

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

develop hematopoietic or immune system disorders and could transmit the disorder to the recipient. In addition, the limited volume of each CBU results in a nucleated cell dose that is typically 10-fold lower than a bone marrow cell dose. The lower cell dose may account for the delayed neutrophil and platelet engraftment that has been observed in CBU recipients compared to what has been reported for marrow recipients. Although marrow has been used successfully for transplant more than 10 years after cryopreservation, the length of time a frozen cord blood unit retains its engraftment potential is unknown. There are also ethical and legal issues regarding the timing of donor informed consent, subsequent additional testing performed on CBUs, and the ownership of CBUs that remain unresolved (20).

1.1.2.1 The New York Blood Center Placental Blood Program

In 1993 the first unrelated placental cord blood bank was established at the New York Blood Center (NYBC) with grant support from NHLBI. In 1998, Rubinstein et al reported the collection of 7,705 CBUs during a five year period and the performance of 6,497 searches for potential recipients from 290 transplant centers (23). This report described the outcomes for the first 562 consecutive NYBC CBU transplants performed at 98 transplant centers in the United States and abroad. Transplants were performed as part of the treatment of malignant (n=378) and non-malignant disorders (n=184). The majority of patients reported in the study were children and young adults.

The report suggested that the time to myeloid engraftment was associated with the CBU nucleated cell dose. Of 562 patients, myeloid engraftment, defined as reaching an ANC $\geq 5 \times 10^8/L$ of donor origin, did not occur in 160; 102 died before engrafting, 13 had autologous reconstitution, 29 received a second transplant, and 16 relapsed. The median time to neutrophil recovery was 28 days for all patients and 25 days for those who engrafted. The median time to platelet recovery (platelet count $\geq 5 \times 10^8/L$ without transfusion for 7 days) was 90 days for all patients and 71 days for patients who reached this endpoint.

Severe acute GVHD (grade III-IV) occurred in 23% of patients and chronic GVHD occurred in 25%. Notably, the incidence of grade III-IV acute GVHD was lower in recipients of six of six antigen matched grafts, but did not otherwise correlate with the number of mismatches. Transplant-related events (death, autologous recovery and second transplant) were associated with the patient's underlying disease, age, CBU cell dose, HLA disparity, and location of transplant center (U.S. versus foreign).

Although the reports by Rubinstein et al demonstrated the feasibility of cord blood transplants, many questions remain unanswered. Specifically, what is the lowest cell dose that reliably results in engraftment? What is the maximal degree of HLA disparity that can be tolerated without GVHD or compromised immune function? Do the outcomes differ in adult recipients compared to pediatric patients? Are there specific graft, demographic or treatment parameters that predict a good or poor outcome? What is the composition of the optimal graft? Are there specific groups of patients who should not be treated with UCB transplants either because of increased risk of graft failure or disease relapse (e.g. Fanconi Anemia and CML).

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

1.1.2.2 Combined Clinical Results from Duke University and the University of Minnesota

Nearly 375 unrelated donor UCB transplants have been performed at Duke University and University of Minnesota. In July 2000, a detailed analysis of their combined data sets was performed to determine the potential influence of various factors (e.g., graft cell dose and donor/recipient HLA disparity) on rate of hematopoietic recovery and probabilities of engraftment, acute GVHD, chronic GVHD, non relapse mortality, relapse and overall survival. In comparison to prior reports on unrelated donor UCB transplantation, the present study benefits from standardized HLA typing with high resolution typing of HLA-DR, greater homogeneity in supportive care treatments between two centers, and the ability to internally verify data accuracy.

At these centers, patients with acute leukemia, bone marrow failure syndromes, immunodeficiency states or inborn errors of metabolism were eligible for unrelated donor UCB transplantation if: 1) an HLA-compatible related or unrelated bone marrow donor was not immediately available at the time needed, and 2) the subject/parent(s) consented to the transplant procedure. At the University of Minnesota, patients were preferentially offered BMT. Protocols for myeloablative therapy and use of unrelated donor UCB for transplantation were reviewed and approved by the respective institutional review boards.

Patients

Between August 1993 and April 15, 2000, 312 patients were transplanted with unmanipulated, banked unrelated donor UCB at Duke University and the University of Minnesota (excluding COBLT study transplants). Cord blood units were primarily obtained from the Placental Blood Program of the New York Blood Center and St. Louis Cord Blood Bank. For this analysis, patients with <100 days follow-up post transplant (n=27) or who had a history of prior allogeneic HSC transplantation (n=24), an HLA 4 antigen mismatched UCB donor (n=2), or who required less than conventional myeloablative therapy (n=2) were excluded. Therefore, 257 patients treated for various malignant and non-malignant disorders were evaluable. The univariate analyses described below refer to the sample of 257 patients. The multivariate results are from an analysis of the first 146 patients performed in July 1999. Multivariate analyses are pending for this group of 257 patients. Median age of the patients was 8.1 years (range, 0.2-58) and median weight was 24.5 kg (range, 3.9-102.8).

Preparative regimen and GVHD prophylaxis

Pre-transplant conditioning varied according to the patient's disease, disease status and institution. At the University of Minnesota, 94% patients received a total body irradiation (TBI)-containing regimen and at Duke University, 56% patients received TBI. Most patients received anti-thymocyte globulin (ATG) prior to unrelated donor UCB transplantation. Prophylaxis for acute GVHD primarily consisted of cyclosporine A (CsA) or CsA and methylprednisolone (MP). MP dosing and CsA taper varied slightly between institutions. Of note, some early Duke patients were treated on a protocol that prescribed a higher dose of MP.

Graft Characteristics

HLA-matching: 6/6 loci in 18 patients, 5/6 loci in 90 patients, 4/6 loci in 123 patients, and 3/6 loci in 15 patients. High resolution DRB1 typing was not available for 11 patients. The median nucleated cell dose (pre-cryopreservation) was $3.7 \times 10^7/\text{kg}$ with a range of $0.7 - 57.9 \times 10^7/\text{kg}$. The

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

median CD34 cell dose (post-thaw) was $3.3 \times 10^5/\text{kg}$ with a range of 0.2 - $105 \times 10^5/\text{kg}$. The median CD3 cell dose (post-thaw) was $7.0 \times 10^6/\text{kg}$ with a range of 0.0 - $101 \times 10^6/\text{kg}$.

Neutrophil Recovery

The probability of neutrophil recovery ($\text{ANC} \geq 5 \times 10^8/\text{L}$) by day 42 was 0.87 (0.83-0.92). In univariate analysis, younger recipient age, lower recipient weight, diagnosis of malignant disease, non-TBI containing preparative regimen, higher UCB unit cell dose, and use of G-CSF correlated with faster neutrophil recovery and superior engraftment. At the University of Minnesota, CD34 cell dose also strongly correlated with neutrophil recovery. (Changes in methodology precluded this analysis at Duke.) Notably, HLA disparity had no demonstrable effect on rate of neutrophil recovery or probability of engraftment ($p=0.62$).

In a multivariate analysis of the first 146 patients, only higher cell dose and diagnosis of malignant disease were identified as significant factors associated with superior neutrophil recovery and engraftment. Recipient age and weight interact with cell dose making it difficult to separate the effects of these variables. A randomized trial would be required to determine if there is any true beneficial effect on the use of G-CSF. Notably, patients undergoing a second transplant using UCB had poorer engraftment; however, reasons for second transplant included graft rejection which may explain this observation.

Platelet Recovery

The cumulative incidence of platelet recovery by 6 months was 0.51 (0.44-0.58). In univariate analysis, younger recipient age, lower recipient weight, diagnosis of malignant disease, standard risk malignancy, non-TBI containing preparative regimen, CMV negative serostatus, and higher UCB unit cell dose were correlated with faster platelet recovery and superior engraftment. Notably, HLA disparity had no demonstrable effect on rate of platelet recovery or probability of engraftment.

On the basis of a prior analysis of the first 146 patients, only higher cell dose and CD34 cell dose were significant factors associated with superior platelet recovery and engraftment in multivariate analysis.

Acute Graft-versus-Host Disease

The overall probabilities of grade II-IV and grade III-IV acute GVHD for the entire group of patients were 0.30 (0.24-0.36) and 0.12 (0.08-0.16) by day 100 post transplant, respectively. In univariate analysis, no factor was associated with risk of acute GVHD, including degree of HLA disparity. Higher CD3 cell dose was associated with less GVHD; however, this is confounded with younger patient age and thus hard to interpret. Notably, no difference in the probability of grade II-IV acute GVHD could be discerned between patients treated with CsA plus high dose MP, versus lower dose MP versus other regimens.

A multivariate analysis of the first 146 patients found that no factor was associated with acute GVHD. Younger recipient age, HLA match and lower CD3 cell dose are known to be associated with lower GVHD in recipients of unrelated donor marrow but cannot be discerned in these analyses.

Chronic Graft-versus-Host Disease

The overall probability of chronic GVHD for the entire group of patients was 0.07 (0.04-0.10) at 1 year after transplant. In univariate analysis, recipient age, recipient weight, use of high dose

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

methylprednisolone and other GVHD prophylaxis, diagnosis of non malignant disease, higher CD3 cell dose, and use of a non-TBI containing regimen were associated with lower risk of chronic GVHD. Also, use of high dose melphalan (MEL) was associated with a higher risk of chronic GVHD.

Results of unrelated donor marrow transplants suggest that younger recipient age is associated with less chronic GVHD and that greater HLA disparity and higher CD3 graft content is associated with more chronic GVHD. However, these findings were not observed in this study of unrelated cord blood transplantation. Multivariate analysis was not previously performed for this endpoint.

Survival

With a median follow up of 1.7 years, the probabilities of survival at 2 years and 4 years after unrelated donor UCB transplantation were 0.45 (0.39-0.52) and 0.41 (0.33-0.48), respectively. In univariate analysis, younger recipient age, lower recipient weight, diagnosis of non-malignant disease, standard risk malignancy, recipient CMV negative serostatus, higher graft nucleated cell dose, absence of acute GVHD, use of UCB for primary transplant and Caucasian race were associated with improved survival. Increased degree of HLA disparity did not significantly alter the probability of survival post transplant. Notably, the effect of recipient age and cell dose was preserved even when evaluating only those patients that engrafted. In the multivariate analysis of the first 146 patients, only recipient age and higher cell dose were identified as significant factors associated with superior survival.

Summary

These results demonstrate that cryopreserved UCB from HLA 0-3 antigen mismatched unrelated donors contains sufficient numbers of transplantable hematopoietic stem and progenitor cells for most small patients. The data presented indicate that the probabilities of grade III-IV acute GVHD and extensive chronic GVHD are low. Moreover, the results of this statistical analysis demonstrated the importance of graft cell dose in determining outcome after unrelated donor UCB transplantation. Within the group of patients with either an HLA-1 or HLA-2 antigen disparate donor, graft cell dose rather than degree of HLA disparity had the most significant impact upon the probabilities of engraftment, non-relapse mortality and survival.

Therefore, these data suggest that cell dose rather than degree of HLA disparity should determine the choice of UCB graft when a patient has more than one HLA-mismatched CBU. The importance of cell dose on transplant outcomes also provides a compelling argument for focusing on the collection of larger UCB grafts and for investigating ex vivo HSC expansion for future clinical trials.

1.1.2.3 Unrelated UCB Transplantation in Adult Recipients-Duke University

Twenty-four adult patients ≥ 18 years of age, the majority of whom had high risk hematologic malignancies, were consecutively transplanted at Duke University from February 1995 through September 1997 with partially HLA-matched UCB. These patients are a subset of those reported in Section 1.1.2.2. The median weight of these patients was 68.8 kg (range 43 to 91.7 kg), and the median age was 30 years (range 18 to 58 years). Six patients underwent UCB transplantation as a second transplant following relapse after a prior transplant.

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

Graft Characteristics

HLA-matching: 6/6 loci in one patient, 5/6 loci in five patients, 4/6 loci in 16 patients, and 3/6 loci in two patients. The median nucleated cell dose (pre-cryopreservation) was $2.1 \times 10^7/\text{kg}$ (range 1.1 to $6.3 \times 10^7/\text{kg}$). CD34+ progenitor cells (post-thaw) were $3.6 \times 10^5/\text{kg}$ (0.7 to $16.7 \times 10^5/\text{kg}$), total colony-forming units (CFU, post-thaw) were $1.0 \times 10^4/\text{kg}$ (0 to $7.3 \times 10^4/\text{kg}$), and CD3+ cells (post-thaw) were $4.2 \times 10^6/\text{kg}$ (2.4 to $8.8 \times 10^6/\text{kg}$).

Hematopoietic Recovery

There was evidence of myeloid engraftment in 19 of 24 patients, with a median of 24 days to attain an ANC of 500/mL (range 13 to 37 days). Two patients experienced primary graft failure. Three patients died before day 34 without evidence of engraftment. There was evidence of platelet recovery in 14 patients, with a median recovery time of 58 days (range 35 to 142 days). Platelet counts of 50 and 100K/mL in surviving patients were attained at median day +110 (range 42 to 188 days) and +134 days (range 88 to 176 days), respectively. Twelve patients attained RBC recovery independent of transfusion support at median day +80 post transplant (range 27 to 160 days). All patients who had hematologic recovery showed >98% donor engraftment by chimerism analyses, and no late graft failures have been observed.

Time to attain neutrophil recovery (ANC $\geq 500/\text{mL}$), but not RBC or platelet recovery, correlated with number of infused nucleated cells ($p=.02$) and CFU ($p=.003$). Although there was a trend toward improved survival in patients whose graft contained $\geq 2 \times 10^7/\text{kg}$ cryopreserved cell dose, this trend did not attain statistical significance ($p=0.08$).

Graft versus Host Disease

19 patients were evaluable for GVHD. The estimate of the actuarial probability of developing grade III-IV acute GVHD up to 100 days post transplant was .26 (6/19 patients) with a 95% confidence interval of .13-.57. Three patients died of complications of acute GVHD. The estimate of the actuarial probability of chronic GVHD was .38 (.14-.68). The five patients who developed chronic GVHD involving the gastrointestinal tract and liver previously had grade I-III acute GVHD.

Immune Reconstitution

Immune function of patients was analyzed at 3 month intervals during the first year post transplant, and at six month intervals during the second year post transplant. Recovery of circulating naive T lymphocytes and evident *in vitro* proliferative responses to plant mitogens and recall antigens were detected generally 100-180 days after transplantation. Natural killer cells emerged as the predominate lymphocyte population at 100 days post transplant.

Survival

As of June 24, 1998, 8 patients survived in unmaintained remission for 9 to 40 months after UCB transplantation, rendering an event-free survival rate of 33 percent. The probability of survival at 3 months was 54% (95% CI: .36-.72) and at 6 months was 50% (.32-.68). There were five deaths after day +100. There were no long-term survivors of patients undergoing UCB transplantation after failing a previous autologous or allogeneic transplant.

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

Summary

The rate of engraftment in this series of adult recipients was similar to that observed in children. The infused cell dose was the most consistent predictive value for time to myeloid engraftment. Although only 1 of the 24 patients in this study had a 6/6 HLA antigen matched graft, the estimate of the probability of severe acute GVHD was only 32%, and 38% for chronic GVHD. Although this is somewhat higher than the results in children receiving unrelated UCB grafts, it compares favorably with that observed in adults undergoing unrelated-donor marrow transplantation. This analysis demonstrates that partially HLA-matched UCB transplants from unrelated donors are feasible for adults. Additional studies in a larger series of patients are warranted.

1.2 COBLT STUDY BACKGROUND

Despite the apparent clinical success of cord blood transplants, many scientific and clinical questions remain to be answered. Areas in need of active investigation include the identification of surrogates predictive of successful engraftment; the degree of acceptable HLA disparity and its impact on GVHD and engraftment; optimization of UCB transplantation in adults and larger children; and optimal collection, storage and CBU characterization methods.

In 1996, NHLBI initiated the prospective, multi-center Cord Blood Transplantation study (COBLT). The COBLT study was designed to address these questions, and to obtain uniform data on cord blood collection, graft characterization and transplantation in order to assist in development of UCB graft product standards. The original goal of the study was to build a bank of 15,000 racially/ethnically diverse UCB units and perform transplants with units from the bank to determine if UCB cells are a suitable alternative for transplantation of patients with malignant and non-malignant blood diseases who do not have a matched unrelated marrow donor.

Accrual of transplant patients to the study was slower than expected because additional time was needed for the bank to build a critical mass of UCB units. Even when the bank reached 3000 units, recruitment lagged because many potential recipients had a better-matched or larger UCB unit in another bank or an unrelated marrow donor, and most transplant physicians prefer marrow to less-well-studied UCB. The study's Data and Safety Monitoring Board (DSMB) determined that the study was too far behind schedule to meet its accrual goals as originally stated. Because new clinical transplant data were available, the DSMB recommended that NHLBI convene an Ad Hoc Advisory Group composed of experts in marrow and cord blood transplantation to review the study design and recommend changes to the protocol and/or study goals. In their January 2000 report, the Advisory Group recommended that the study be redesigned to emphasize HLA mismatching in pediatric patients. They also recommended that the relationship between cell dose and engraftment in adult patients be examined separately. Offers to participate in the study were extended to new centers with an interest in UCB transplantation. In addition, patients who receive transplants with units from other banks now are eligible for enrollment provided the transplant center agrees to follow the COBLT treatment protocol and the stored units meet quality assurance criteria. Patients receiving transplants with units from the UCB banks in Table 1.1 are currently eligible for enrollment in the study.

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

**Table 1.1
Transplants with Units from UCB Banks**

Bank Name	Searchable Units	Number of Transplants
NYBC	9,000	900
NMDP	5,200	151
COBLT	4,300	40

1.3 TRANSPLANT STUDY OVERVIEW

Previous studies suggest that UCB is a useful source of stem cells for hematopoietic reconstitution but this has not been evaluated in a prospective multi-center study with a standard therapy and supportive care plan and with standard reporting of engraftment, GVHD, and other complications. The purpose of the COBLT study is to accurately describe 180-day survival and other events after UCB transplantation.

Patients will be enrolled under the current transplant community standard for HLA matching which is low resolution typing for HLA-A and HLA-B loci and high resolution typing for HLA-DRB1. Retrospectively, patients and units will be high resolution typed for HLA-A, -B, -DRB1 and classified into one of the eight strata that comprise the study. Tables 1.2 and 1.3 illustrate the eight strata.

**Table 1.2
Patients with Malignant Disease ≤ 18 Years of Age**

5/6 or 6/6	High Resolution HLA Match
4/6	High Resolution HLA Match
3/6	High Resolution HLA Match
<3/6	High Resolution HLA Match

**Table 1.3
Other Strata**

Patients with Inborn Errors of Metabolism/Storage Diseases
Patients with Severe Aplastic Anemia/Fanconi Anemia/Other Marrow Failure Syndromes
Patients with Malignant Disease non-TBI/Alternative Conditioning Regimen
Patients > 18 Years

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

In accordance with the Ad Hoc Advisory Group recommendation, a sample size of up to 300 pediatric patients with malignant disease is sufficient to obtain 75 patients in the 3/6 and 4/6 high resolution strata. This sample size will allow accurate estimates of 180-day survival within each of these strata. In addition, approximately 30 patients are anticipated in each of the strata displayed in Table 1.3.

1.4 CORD BLOOD BANK STUDY OVERVIEW

The National Heart, Lung and Blood Institute (NHLBI) has funded two UCB banks as part of this project to collect approximately 15,000 UCB units. The banked units will have a diverse ethnic/minority representation such that patients in various population groups will have similar chances of finding a suitable unit for transplant.

The UCB banks work closely with obstetricians to obtain informed consent from expectant mothers. Potential participants are told about the study by their doctors, and are provided a written brochure that describes the study, a list of medical history questions, and a sample informed consent document. When possible the consent document is signed before the onset of labor (and reaffirmed following delivery), but especially at the outset, the consent document sometimes was signed at an appropriate time following delivery while the mother remained in the hospital. If consent is not obtained or rescinded, a unit is discarded. The link between the donor's identity and the unit is maintained, but confidentiality is protected carefully. Mothers are contacted approximately 6 months post-delivery to check on the health of the infant. The model informed consent document for cord blood donors is found in Appendix B of the Standard Operating Procedures manual (SOP).

Units are collected in a separate room near the delivery room by dedicated bank staff following delivery and the usual approach to clamping and tying the umbilical cord by the obstetrician. Units must contain at least 60 mL or 600 million nucleated cells of to be considered for processing. A detailed medical history is obtained from the mother, screening for infectious and genetic diseases is performed, and the unit is HLA typed using DNA-based technology. Flow cytometry and an assay for colony forming units are performed on each unit before freezing. Units are quarantined either in a separate freezer or in the vapor phase of liquid nitrogen until results of testing indicate the unit is fit for permanent storage in the liquid phase. A bar code-based labeling system facilitates unit identification, record keeping, and unit inventory. Additional details of the collection, testing, processing, and freezing procedures can be found in the SOP.

Before the start of patient conditioning, units are shipped to transplant center stem cell processing laboratories in liquid nitrogen dry shippers at temperatures less than -120°C. Information including the intended patient, the HLA type of the unit, the pre-freeze cell dose, and the results of all tests performed are provided with the unit. Standard instructions for storage and thawing are provided. Laboratories confirm to the coordinating center that the unit arrived in good condition. Details are provided in the Investigator's Brochure, Chapter 4 of the SOP and Chapters 8 and 9 of the Transplant Center Manual of Procedures (MOP).

When this study began in 1996, only patients receiving CBUs from COBLT banks were to be enrolled. However, in order to increase enrollment, a decision was made subsequently (February 2000) to enroll patients who receive CBUs from other U.S. banks provided the banks can certify that they follow the NetCord-FAHCT, AABB, or NMDP standards.

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

1.5 REFERENCES

1. Gluckman E, Broxmeyer HE, Auerbach AD et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical cord blood from an HLA-identical sibling. *New Engl J Med* 1989; 321: 1174-78.
2. Broxmeyer HE, Kurtzberg J, Gluckman E et al. Umbilical cord blood hematopoietic stem and repopulating cells in human clinical transplantation. *Blood Cells* 1991; 17: 313-29.
3. Wagner JE, Broxmeyer HE, Byrd RL et al. Transplantation of umbilical cord blood after myeloablative therapy: Analysis of engraftment. *Blood* 1992; 79: 1874-81.
4. Vilmer E, Sterkers G, Rahimy C et al. HLA-mismatched cord blood transplantation in a patient with advanced leukemia. *Transplantation* 1992; 53:1155-57.
5. Vanlemmens P, Plouvier E, Amsallem D et al. Transplantation of umbilical cord blood in neuroblastoma. *Nouv Rev Fr Hematolol* 1992; 34: 243-46.
6. Kernan NA, Scroeder ML, Ciavarella D et al. Umbilical cord blood infusion in a patient for correction of Wiskott-Aldrich syndrome. *Blood Cells* 1994; 20: 242-4.
7. Kurtzberg J, Graham M, Casey J et al. The use of umbilical cord blood in a mismatched related and unrelated hematopoietic stem cell transplantation. *Blood Cells* 1994; 20: 275-84.
8. Pahwa RN, Fleischer A, Than S et al. Successful hematopoietic reconstitution with transplantation of erythrocyte-depleted allogeneic human umbilical cord blood cells in a child with leukemia. *Proc Nat Acad Sci* 1994; 91: 4485-88.
9. Bogdanic V, Nemet D, Kastelan A et al. Umbilical cord blood transplantation in a patient with Philadelphia-chromosome positive chronic myeloid leukemia. *Transplantation* 1993; 56: 477-79.
10. Vowels MR, Lam-PO-Tang R, Berdoukas V et al. Brief report: Correction of X-linked lymphoproliferative disease by transplantation of cord-blood stem cells. *New Engl J Med* 1993; 329: 1623-25.
11. Kohli-Kumar M, Shahidi NT, Broxmeyer HE et al. Haematopoietic stem/progenitor cell transplant in Fanconi anaemia using HLA-matched sibling umbilical cord blood cells. *Brit J Haematol* 1993; 85: 419-22.
12. Issaragrisil S, Visuthisakchai S, Suvatte V et al. Transplantation of cord blood stem cells into a patient with severe thalassemia. *N Engl J Med* 1995; 332: 367-9.
13. Neudorf SML, Blatt J, Corey S et al. Graft failure after an umbilical cord blood transplant in a 11 *Allogeneic Umbilical Cord Blood Banking and Transplantation*.
14. Miniero R, Busca A, Roncarolo MG et al. HLA haploidentical umbilical cord blood stem cell transplantation in a child with advanced leukemia: Clinical outcome and analysis of hematopoietic recovery. *Bone Marrow Transplant* 1995; 16: 229-40.
15. Wagner JE, Kernan NA, Steinbuch M, Broxmeyer HE, Gluckman E. Allogeneic sibling umbilical-cord-blood transplantation in children with malignant and non-malignant disease. *Lancet* 1995; 346: 214-19.
16. Kurtzberg J, Laughlin M, Graham ML et al. Placental blood as a source of hematopoietic stem cells for transplantation in unrelated recipients. *New Engl J Med* 1996; 335: 157-166.
17. Wagner JE, Rosenthal J, Sweetman R, et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: Analysis of engraftment and acute graft-versus-host disease. *Blood* 1996; 88:795-802.
18. Wagner JE. Allogeneic umbilical cord blood transplantation. In: (Winters JN, ed) *Blood Stem Cell Transplantation*; Kluwer Academic Publishers, Norwell, MA, 1996, pp 187-216.

CORD BLOOD TRANSPLANTATION STUDY PROTOCOL

19. Broxmeyer HE, Douglas GW, Hangoc G et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. *Proc Nat Acad Sci USA* 1989; 86: 3828-32.
20. Sugarman J, Kaalund V, Kodish E et al. Ethical issues in umbilical cord blood banking. *J Am Med Assoc* 1997; 278: 938-43.
21. Stagno S, Pass RF, Cloud G et al. Primary cytomegalovirus infection in pregnancy. *J Am Med Assoc* 1986; 256: 1904-8.
22. Chang RS, Seto DSY. Perinatal infection by Epstein-Barr virus. *Lancet* 1979; 2: 201-5.
23. Rubinstein P, Carrier C, Scaradavou A, et al. Outcomes among 562 recipients of placental-blood (PCB) transplants from unrelated donors. *New Engl J Med* 1998; 339: 1565-1577.