SAFETY REVIEW
DOCKETS AND PUBLIC INFORMATION

Hematopoietic Progenitor Cells-Cord Blood

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Table of Abbreviations

AE	Adverse event
ALD	(X-linked) Adrenoleukodystrophy
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
ATG	Antithymocyte globulin
BLA	Biologics license application
BMF	Bone marrow failure
CFU	Colony forming unit
CI	Confidence interval (95%, unless otherwise specified)
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
COBLT	The Cord Blood Transplantation Study
DMSO	Dimethyl sulfoxide
EAP	Expanded Access Protocol
EBV	Epstein Barr virus
ES	Engraftment syndrome
Gr	Grade
GVHD	Graft versus host disease
HHV	Human herpes virus
HLA	Human leukocyte antigen
HPC-A	HPC-apheresis
HPC-C	Hematopoietic progenitor cells – cord blood
HPC-M	HPC-marrow
HUS/TTP	Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura
LGL	Large granular lymphocytic leukemia
MDS	Myelodysplastic syndrome
MPD	Myeloproliferative disorder
MPS	Mucopolysaccharidosis
NHLBI	National Heart, Lung and Blood Institute
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
OS	Overall survival
PCR	Polymerase chain reaction
PID	Primary immunodeficiency disorders
PIR	Pre-engraftment immune reaction
PLT	Platelet
PTLD	Posttransplant lymphoproliferative disorder
RAEB	Refractory anemia with excess blasts
SHR	Subhazard ratio
THAL	Thalassemia
TNC	Total nucleated cells
TRM	Treatment related mortality
VCA IgG	Viral capsid antigen immunoglobulin G

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

See the BLA clinical review for recommendations on regulatory actions.

1.2 Risk Benefit Assessment

See the BLA clinical review for the risk benefit assessment.

2 Introduction and Regulatory Background

The purpose of this review is to provide an assessment of the safety of minimally manipulated, unrelated donor, hematopoietic progenitor cells-cord blood (HPC-C). This document represents a collaboration between the clinical and statistical reviewers. This review is limited in scope to information in the published literature, the FDA dockets FDA-1997-N-0010 and FDA-2006-D-0157, and data in the public domain. This review will serve to complement the clinical reviews of BLAs for HPC-C submitted in accordance with the FDA publication "Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Specified Indications," and which cross reference the dockets for supporting safety information. See the BLA clinical review for the regulatory background.

3 Ethics and Good Clinical Practices

See Efficacy Review (Non-Oncology) – Dockets and Public Information for a description of the data quality and integrity.

4 Significant Issues Related to Other Review Disciplines

See the BLA clinical review for issues related to other disciplines.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The key materials used in this review include:

- Dataset for The COBLT Study (Available from the National Heart, Lung and Blood Institute (NHLBI) via its data-sharing portal at https://biolincc.nhlbi.nih.gov/home/)
- Docket FDA-1997-N-0010 (Legacy Docket number 97N-0497)
- Docket FDA-2006-D-0157 (Legacy Docket number 06D-0514)
- Relevant literature

5.2 Study Information

5.2.1 The COBLT Study

The COBLT Study (NCT00000603) is comprised of a main protocol and an expanded access protocol. Version 07/00 of the main protocol and version 07/00 of the expanded access protocol were obtained from The COBLT Study web site at https://web.emmes.com/study/cord/. The main protocol is a prospective, single-arm trial of unrelated donor HPC-C transplantation for patients with hematological malignancies, marrow failure, inborn errors of metabolism, and primary immunodeficiency disorders. The preparative regimens and GVHD prophylaxis were predefined. The minimal HLA matching was at least 4/6 with serological typing for Class I or at least 3/6 with high resolution typing at all loci. The minimum required cell dose was 1×10^7 TNC/kg. The expanded access protocol was open to subjects with a disease that warranted HPC-C transplantation but who were not eligible for the main protocol. Treatment on the expanded access protocol was not standardized. Safety and outcomes data were to be submitted by the investigator at specified time points using standardized data collection forms. This dataset represents the only available raw data from a prospectively conducted clinical trial of unrelated donor HPC-C transplantation. Study synopses are provided in Appendices 9.3.1 and 9.3.2.

5.2.2 Dockets

See Efficacy Review (Non-Oncology) – Dockets and Public Information for a description of the information in dockets FDA-1997-N-0010 and FDA-2006-D-0157.

5.2.3 Literature Review

The literature was searched for publications in peer-reviewed journals associated with HPC-C transplantation. The literature search strategy and cited references are provided in Section 9.

5.3 Review Strategy

The safety review emphasized early deaths, infusion reactions, delayed hematopoietic recovery and graft failure, acute GVHD, engraftment syndrome, and transmission of malignancy, infection or genetic disorder from the donor to the recipient.

Information submitted to the docket was reviewed for reports for each of the safety outcomes. The results were supplemented with analyses of the COBLT dataset. Where sufficient detail is available, the safety outcomes were also assessed for each proposed indication. The published literature was searched for additional information addressing the description, diagnosis, risk factors for and methods of mitigation of the critical safety events.

Datasets where available were pooled to allow for a better assessment of correlations between product characteristics (e.g., cell dose) and safety outcomes. The pooled dataset was also used to develop mathematical models for safety outcomes that could be used to assist with safety reviews of BLAs. p-Values <0.05 were considered to be significant. However, p-values

presented in the following sections should be interpreted with caution due to the exploratory nature of the analyses.

6 Review of Efficacy

See Efficacy Review (Non-Oncology) – Dockets and Public Information and Efficacy Review (Oncology) – Dockets and Public Information for the review of data supporting the efficacy of unrelated donor HPC-C transplantation for the treatment of patients with hematologic malignancies, Hurler Syndrome (MPS I), Krabbe Disease (Globoid Leukodystrophy), X-linked adrenoleukodystrophy, primary immunodeficiency diseases, bone marrow failure and beta thalassemia.

7 Review of Safety

7.1 Safety Summary

The safety of HPC-C was based on a review of submission to Docket FDA-1997-N-0010 (Legacy Docket number 97N-0497) and to Docket FDA-2006-D-0157 (Legacy Docket number 06D-0514), the dataset for The COBLT Study, and published literature. The COBLT study is the only prospective clinical trial included in this review. The information reviewed pertained to HPC-C from various manufacturers, but due to the lack of clear identification of manufacturer for individual subject data, no comparisons between manufacturers were made.

Raw datasets in the docket were submitted from the National Marrow Donor Program (NMDP), New York Blood Center (NYBC) and Duke University, and the COBLT dataset was obtained from the NHLBI. Cases that were not overlapping between these sources were pooled for statistical analyses. The pooled docket dataset included 1572 subjects of median age 6 years (range <1-66 yrs) transplanted from 1993 - 2006. The male:female ratio was 1.4:1. Over 70% of the subjects were being treated for a hematological malignancy. The donor was HLA matched with the subject at 6/6 loci for 11% of the pairs, 5/6 for 39%, 4/6 for 46% and <4/6 for 4%. The median cryopreserved TNC dose was 5.3 (range, 0.7-73.8) x 10^7/kg. A TNC dose $\geq$2.5 x 10^7/kg was administered to 1299 (81.6%) of the subjects.

The safety review emphasized early deaths, delayed hematopoietic recovery and graft failure, acute graft-vs-host disease (GVHD), engraftment syndrome, infusion reactions, and transmission of malignancy, infection or genetic disorder from the donor to the recipient.

Deaths: There were 838 deaths reported (53.3% of the cohort); 469 deaths (29.8% of the cohort) occurred by 100 days after transplantation. The most common (>5%) causes of death by day 100 after transplantation for those who received a TNC $\geq$2.5 x 10^7/kg were infection (7.8%) and organ failure (6.5%). Graft failure was the primary cause of death in 3.7% of the patients, and 69% of the deaths due to graft failure occurred by day 100.

When comparing subjects who received a TNC $\geq 2.5 \times 10^7$/kg vs $<2.5 \times 10^7$/kg, patients with the higher TNC dose had fewer deaths overall (49% vs 74%, $p<0.001$) and fewer deaths by day 100 (25% vs 52%, $p<0.001$). There was a continuous downward trend in early mortality with increasing increments of TNC dose by 1×10^7/kg with an apparent inflection point in the curve between 2 and 3×10^7 TNC/kg. Other factors that correlated with day-100 death were age, gender, diagnosis and degree of HLA mismatch.

The proportions of subjects who died by day 100 varied significantly ($p<0.001$) by indication, ranging from 5% to 41.1% for those who received a TNC dose $\geq 2.5 \times 10^7$/kg. There was a significant inverse correlation between TNC dose and early mortality for patients with hematological malignancies and marrow failure, but not for the other indications, although the numbers of subjects in each group may have been too small to detect a significant correlation.

Graft Failure: The primary graft failure rate was 16.4% (95% CI 14.4-18.6%) for subjects receiving a TNC dose $\geq 2.5 \times 10^7$/kg. The graft failure rates fell below 20% only for incremental TNC doses $\geq 4 \times 10^7$/kg and remained at approximately 7-20% until falling further at TNC doses $\geq 17 \times 10^7$/kg. On multivariate analysis, there was a significant association between graft failure and diagnosis ($p=0.006$), degree of HLA mismatch ($p<0.001$), and TNC dose group ($P<0.001$). The literature review also suggested that alloimmunization may increase the risk of graft failure.

The graft failure rate varied with diagnosis and ranged from 9.5% to 31.1%. When assessed by individual diagnosis, there was a significant inverse correlation between TNC dose group and graft failure for the subjects transplanted for hematological malignancies, bone marrow failure and immunodeficiency disorders. The literature review suggested that a higher TNC dose may be required for patients transplanted for thalassemia to prevent graft failure, but there were too few patients with thalassemia in the pooled dataset to allow for a meaningful analysis within this subgroup of patients.

Time to Neutrophil Recovery: The cumulative incidence of neutrophil recovery by day 42 was 77% (75%-79%) and the median time to neutrophil recovery was 25 days for subjects receiving a TNC dose $\geq 2.5 \times 10^7$/kg. The median time to neutrophil recovery varied by diagnosis and ranged from 19 days to 30 days. This variation was due in part to differences in TNC dose. For all subjects, the median time to neutrophil recovery was delayed substantially with TNC doses $<2 \times 10^7$/kg, but even with TNC doses as high as 20×10^7/kg, the time to neutrophil recovery still exceeded 30 days for 10% of the subjects, a much higher rate of delayed recovery than with HPC-M or HPC-A. On multivariate analysis, degree of HLA mismatch and TNC dose were significantly associated with the time to neutrophil recovery.

Acute GVHD: For patients who received a TNC dose $\geq 2.5 \times 10^7$/kg, the incidence of grades 2-4 GVHD was 42.1%, and for grades 3-4 GVHD it was 18.8%. There was no significant difference in the rates of acute GVHD when comparing TNC doses above vs below 2.5×10^7/kg.

Engraftment Syndrome (ES): ES was reported in 14.7% (11.7-18.0%) of the patients in the COBLT study. Median time to onset of the event was 10 days after transplantation (range, 5-35 days). In literature reports, the reported incidence of ES varied from 30% to 78%.

Infusion Reactions: The COBLT dataset was used for the assessment of infusion reactions. This included 523 infusions of HPC-C in 511 patients. The population included 310 males and 201 females of median age 6 years (range 0.05-67 years). Preparative regimens and graft-vs-host disease prophylaxis were not standardized amongst the patients. Infusion reactions were defined as prespecified events usually associated with HPC-C infusions and occurring within 24 hours of transplantation. These were graded by the National Cancer Institute Common Toxicity Criteria (NCI CTC). The most common infusion reactions noted were hypertension, vomiting, nausea and bradycardia. The rate of serious adverse cardiopulmonary events was 0.8%.

Table 1: Incidence of Infusion-Related Adverse Events Occurring in ≥1% of Subjects in The COBLT Study

	All Infusions (N=523)		Infusions with a TNC Dose ≥2.5 x 10^7/kg (N=442)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any reaction	65.4%	26.6%	65.4%	27.6%
Hypertension	46.5%	19.9%	48.0%	21.3%
Vomiting	15.7%	0.2%	14.5%	0.2%
Nausea	14.8%	6.1%	12.7%	5.7%
Sinus bradycardia	10.3%	0.0%	10.4%	0.0%
Fever	5.5%	0.2%	5.2%	0.2%
Sinus tachycardia	5.2%	0.8%	4.5%	0.2%
Allergy	3.1%	0.2%	3.4%	0.2%
Hypoxia	2.9%	2.7%	2.0%	2.0%
Hypotension	2.9%	0.6%	2.5%	0.0%
Hemoglobinuria	1.9%	0.0%	2.1%	0.0%
Dyspnea	1.7%	1.1%	0.9%	0.7%
Infection	1.5%	1.5%	0.9%	0.9%
Chills	1.3%	0.0%	0.9%	0.0%

On multivariate analysis, younger age and higher volumes of infusate were significantly associated with development of a grades 3-4 adverse event and with development of any grade of hypertension.

Review of the literature suggested the adverse infusion reactions may in part be due to Dextran 40. DMSO can also cause significant toxicity. Overdosage with DMSO may cause elevated liver enzymes and severe encephalopathy. The toxic effects can be ameliorated in part by plasma exchange. Severe DMSO toxicity can also be prevented by limiting DMSO administration to less than 1 gm/kg/day.

Donor Cell Leukemia: The risk of donor cell leukemia, myelodysplastic syndrome or a myeloproliferative disorder after HPC-C transplantation is estimated as 9/10,000.

Transmission of Serious Infection: The risk of transmission of serious infection is 1/10,000 based on a case report. However, in vitro testing suggests that 0.6% of units may be positive for HHV-6, and 0.15% of units from CMV-seronegative donors may be positive for CMV by PCR.

Transmission of Rare Genetic Disorders: There are no reported cases of transmission of a rare genetic disorder by HPC-C transplantation. The risk is estimated to be less than 1/10,000.

7.2 Methods

7.2.1 Studies/Clinical Trials Used to Evaluate Safety

The key materials used in the review include:

- Dataset for The COBLT Study
- Docket FDA-1997-N-0010 (Legacy Docket number 97N-0497)
- Docket FDA-2006-D-0157 (Legacy Docket number 06D-0514)
- Relevant literature

7.2.2 Categorization of Adverse Events

There were no standard definitions of endpoints or consistent use of grading for the data in the docket. Endpoint definitions and grading systems for The COBLT Study are provided in Section 5.2 above.

7.2.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Raw datasets in the docket were submitted from the NMDP, NYBC and Duke University, and the COBLT dataset was obtained from the NHLBI.

- The NMDP dataset included 581 US subjects who received a single, nonexpanded HPC-C unit from February 2000 to December 2006 for their first allogeneic transplantation.

- The NYBC dataset included the first 562 subjects transplanted from August 1993 to January 1998 with HPC-C units from the NYBC.

- The Duke dataset included 160 subjects transplanted with unrelated donor HPC-C for an inherited metabolic disorder at Duke University August 1995 to March 2007.

- The COBLT dataset include 364 subjects from the main protocol with outcomes information and 163 subjects from the expanded access protocol with partial information. These subjects were transplanted December 1998 to February 2004.

The dataset from Duke had substantial overlap with those from COBLT, NMDP and NYBC, but it also indicated the bank from which each unit was obtained, so overlapping cases could be excluded by matching the source bank and time period. The final pooled dataset included the data from COBLT, NMDP, NYBC and the non-overlapping entries from the Duke dataset. The subjects had to have at least a total nucleated cell dose, diagnosis and some outcome information to be included in the pooled dataset.

7.3 Adequacy of Safety Assessments

7.3.1 Overall Exposure at Appropriate Doses

The pooled docket dataset includes 1572 subjects; 577 subjects are from NMDP, 550 from NYBC, 356 from COBLT and 89 from Duke. A TNC dose $\geq$2.5 x 10^7/kg was administered to 1299 (81.6%) of the subjects. The demographics for the pooled dataset are shown in Table 2.

Table 2: Demographics of Pooled Dataset

Subject Characteristics		**All Subjects Transplanted (N=1572)**	**Subjects with a TNC Dose $\geq$2.5 x 10^7/kg (N=1299)**
Median Age (Range)		6 (<1-66) yrs	7 (<1-66) yrs
Age Category	<2 yr	394 (25.1%)	393 (30.3%)
	2 – <17 yr	902 (57.4%)	786 (60.5%)
	$\geq$17 yrs	276 (17.6%)	120 (9.2%)
Gender	Male	592 (37.7%)	524 (40.3%)
	Female	430 (27.4%)	389 (30.0%)
	Unknown	550 (35.0%)	386 (29.7%)
Ethnicity	White	646 (41.1%)	573 (44.1%)
	African-American	104 (6.6%)	90 (6.9%)
	Hispanic	143 (9.1%)	129 (9.9%)
	Asian	31 (2.0%)	28 (2.2%)
	Other	16 (1.0%)	14 (1.1%)
	Unknown	632 (40.2%)	465 (35.8%)
Diagnosis	Hematologic malignancies	1103 (70.2%)	862 (66.4%)
	Hurler Syndrome	74 (4.7%)	74 (5.7%)
	Krabbe Disease	41 (2.6%)	40 (3.1%)
	X-linked Adrenoleukodystrophy	25 (1.6%)	20 (1.5%)
	Primary immunodeficiency diseases	96 (6.1%)	93 (7.2%)
	Bone marrow failure	114 (7.3%)	95 (7.3%)
	Beta thalassemia	8 (0.5%)	8 (0.6%)
	Other	111 (7.0%)	107 (8.2%)
Year of Transplantation	1993-2000	633 (40.3%)	459 (35.3%)
	2001-2006	939 (59.7%)	840 (64.7%)
Lowest HLA Match Level	2-3	55 (3.5%)	40 (3.1%)
	4	723 (46.0%)	583 (44.9%)
	5	613 (39.0%)	524 (40.3%)
	6	170 (10.8%)	143 (11.0%)
	Unknown	11 (0.7%)	9 (0.7%)
Median Dose (TNC x 10^7/kg) (Range)	All	5.3 (0.7-73.8)	6.4 (2.5-73.8)
	Adults	2.3 (0.7-6.5)	3.2 (2.5-6.5)
	Children	6.4 (0.8-73.8)	6.9 (2.5-73.8)

The majority of the population was comprised of children with a diagnosis of a hematological malignancy. There were 13 patients with hemoglobinopathy, including 8 identified as beta thalassemia, and there were a total of 236 patients with inherited metabolic disorders. Over 80% of the patients received a TNC dose $\geq 2.5 \times 10^7$/kg.

It was noted that there was a high degree of correlation in the pooled dataset between the established prognostic factors (including age group, gender, race, diagnosis, degree of HLA match and TNC dose group). The p-values for the correlations by Chi square are shown in Table 3.

Table 3: Significance Values For Correlations Between Prognostic Factors

	Age	Gender	Race	Diagnosis	HLA
Gender	0.26	-	-	-	-
Race	***<0.001***	0.21	-	-	-
Diagnosis	***<0.001***	***<0.001***	***<0.001***	-	-
HLA	***<0.001***	0.56	***<0.001***	***0.009***	-
TNC Dose	***<0.001***	0.60	0.52	***<0.001***	***<0.001***

7.3.2 Explorations for Dose Response

The dose of cells to be administered was chosen by the treating physician and not stipulated by the manufacturer with the exception of the COBLT Study where the minimum TNC dose indicated in the protocol was 1×10^7/kg. A summary of the doses by indication and dose group is shown in Table 4. The dose range is sufficiently wide to allow as assessment of safety outcomes by dose.

Table 4: TNC Doses by Diagnosis – Pooled Dataset

Diagnosis	N	Median TNC x 10^7/kg (range)	% of Patients in Each TNC Dose Group (x 10^7/kg)				
			<2.5	2.5-<5	5-<10	10-<20	≥20
Heme Malignancies	1103	4.3 (0.7-35.0)	21.9	35.5	27.5	13.5	1.6
Hurler Syndrome	74	10.1 (3.4-30.0)	0.0	4.1	46.0	41.9	8.1
Krabbe Disease	41	15.2 (2.4-50.4)	2.4	2.4	24.4	46.3	24.4
Adrenoleukodystrophy	25	4.3 (1.7-14.2)	20.0	36.0	24.0	20.0	0.0
Immunodeficiency	96	10.2 (1.7-73.8)	3.1	9.4	34.4	36.5	16.7
Marrow Failure	114	4.4 (0.8-36.8)	16.7	36.8	24.6	19.3	2.6
Thalassemia	8	6.4 (2.5-18.2)	0.0	25.0	50.0	25.0	0.0
Other	111	7.3 (2.1-33.6)	3.6	13.5	47.8	30.6	4.5
All	1572	5.3 (0.7-73.8)	17.4	30.1	30.0	18.9	3.7

7.3.3 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The assessment of safety for HPC-C units provided in this review of information covers information for HPC-C from different manufacturers as available in the docket and in the public domain. However, since most of the information concerned patient outcomes and did not always link outcome to the source of the HPC-C, comparisons between manufacturers were not made in this review.

7.4 Deaths

7.4.1 Review of Docket Submissions

1997-N-0010-DRAFT-0042: NYBC submitted a tabulation of detailed causes of death without further analysis. No conclusions could be drawn.

7.4.2 Analysis of the Pooled Dataset

There were 838 deaths reported (53.3% of the cohort); 469 deaths (29.8% of the cohort) occurred by 100 days after transplantation. When comparing those who received a TNC $\geq 2.5 \times 10^7$/kg vs $<2.5 \times 10^7$/kg, patients with the higher TNC dose had fewer deaths overall (49% vs 74%, $p<0.001$) and fewer deaths by day 100 (25% vs 52%, $p<0.001$).

The most common causes of death were infection, recurrence of the primary disease and organ failure (Table 5). The most common causes of death by day 100 were infection and organ failure. Graft failure was the primary cause of death in almost 4% of the patients, and 74% of the deaths due to graft failure occurred by day 100.

Table 5: Causes of Death After Transplantation – Pooled Dataset

	All Subjects Transplanted (N=1572)		**Subjects with a TNC Dose >2.5 x 10^7/kg (N=1299)**	
	Total	**Day 100**	**Total**	**Day 100**
Number of Deaths	838 (53.3%)	469 (29.8%)	635 (49.2%)	328 (25.3%)
Causes of Death				
Graft Failure	57 (3.6%)	42 (2.7%)	48 (3.7%)	33 (2.5%)
Organ failure	153 (9.7%)	112 (7.1%)	115 (8.9%)	84 (6.5%)
Infection	249 (15.8%)	168 (10.7%)	170 (13.2%)	101 (7.8%)
GVHD	98 (6.2%)	55 (3.5%)	72 (5.6%)	39 (3.0%)
Primary disease	202 (12.9%)	50 (3.2%)	168 (13.0%)	42 (3.2%)
Second malignancy	5 (0.3%)	0 (0.0%)	4 (0.3%)	0 (0.0%)
Other*	31 (2.0%)	23 (1.5%)	19 (1.5%)	13 (1.0%)
Unknown	43 (2.7%)	19 (1.2%)	39 (3.0%)	16 (1.2%)

*Other includes hemorrhage, pulmonary embolism, HUS/TTP, cardiac events and drug reactions.

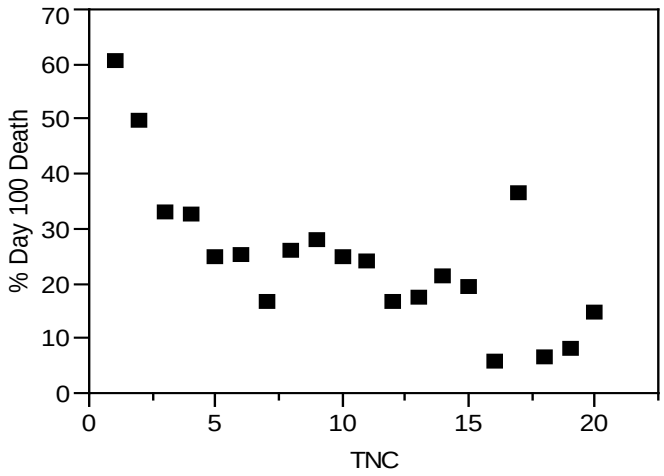
Table 6 below lists the day 100 death rates by indication. The proportions of subjects who died by day 100 varied significantly by indication, ranging from 4.0% to 46.5% for all subjects and from 5% to 41.1% for those who received a TNC dose $\geq 2.5 \times 10^7$/kg.

Table 6: Day 100 Deaths by Indication

Diagnosis	Total N	All Subjects Transplanted		Subjects with a TNC Dose $\geq 2.5 \times 10^7$/kg	
		Deaths (%)		Deaths (%)	
Heme Malignancies	1103	353	(32.0%)	229	(26.6%)
Hurler Syndrome	74	13	(17.6%)	13	(17.6%)
Krabbe Disease	41	4	(9.8%)	4	(10.0%)
Adrenoleukodystrophy	25	1	(4.0%)	1	(5.0%)
Immunodeficiency	96	17	(17.7%)	16	(17.2%)
Marrow Failure	114	53	(46.5%)	39	(41.1%)
Thalassemia	8	2	(25.0%)	2	(25.0%)
Other	111	26	(23.4%)	24	(22.4%)
p (Chi Square)		***<0.001***		***<0.001***	

To determine if there was a clear cut point in TNC dose for death by day 100, the day 100 death rates were graphed by TNC dose rounded to the nearest whole number. Only data through TNC doses of 20 x 10^7/kg were used, since the numbers of patients at higher doses was too low to provide a meaningful analysis. The plot in Figure 1 shows a continuous downward trend in mortality with no clear plateau with increasing TNC dose, with the especially highest rates of early mortality (>40%) at TNC doses of $\leq 2 \times 10^7$/kg.

Figure 1: Day 100 Deaths By TNC Dose (x 10^7/kg)



Whether day 100 mortality varied by dose for specific indications was also assessed. Figure 2 below shows the percentage of subjects who died by day 100 by incremental increases in TNC dose for each indication and for the remaining diagnoses grouped as "Other." By Cuzick's test for trend, there was a significant correlation between TNC dose group and day 100 mortality for the subjects transplanted for hematological malignancies and marrow failure.

Figure 2: Day 100 Deaths By TNC Dose Group And Indication
(TNC Dose Group 1=<2.5, 2=2.5 - <5, 3=5 - <10, 4=10 - <20, 5=≥20)
Abbreviations: Heme Mal, hematological malignancies; Hurler, Hurler Syndrome; Krabbe, Krabbe Disease; ALD, Adrenoleukodystrophy; PID, primary immunodeficiency disorders; BMF, bone marrow failure disorders; THAL, beta thalassemia major; OTHER, other diagnoses.

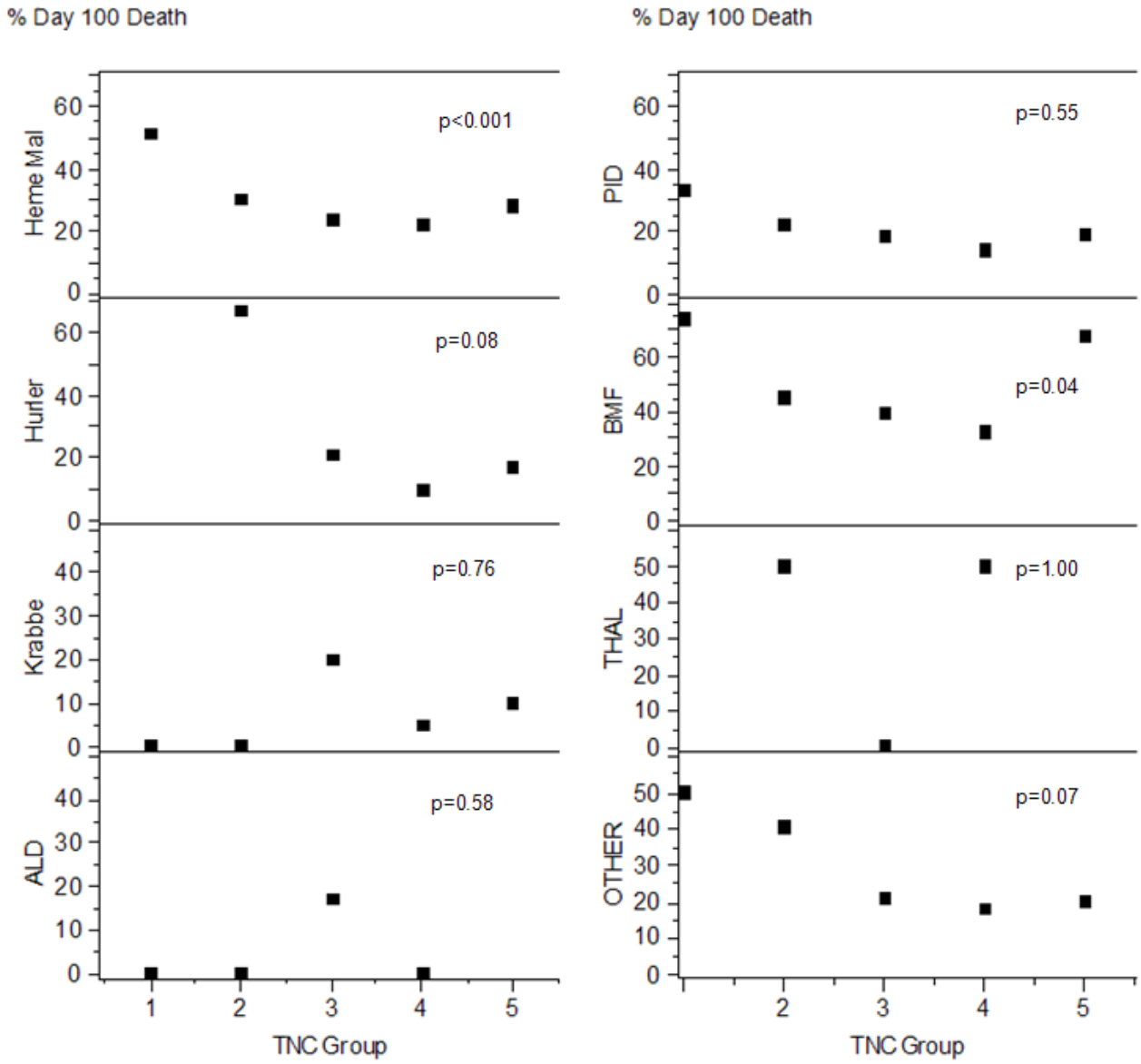


Table 7: Univariate Analysis of Factors Correlated with Day 100 Death

		Day-100 Mortality	p
Age Category	<2 yrs	88 / 394 (22.3%)	***<0.001***
	2 – <17 yrs	247 / 902 (27.4%)	
	≥17 yrs	134 / 276 (48.6%)	
Gender	Male	107 / 592 (18.1%)	***<0.001***
	Female	116 / 430 (27.0%)	
Ethnicity	White	144 / 646 (22.3%)	0.38
	African-American	30 / 104 (28.9%)	
	Hispanic	27 / 143 (18.9%)	
	Asian	6 / 31 (19.4%)	
	Other	5 / 16 (31.3%)	
Diagnosis	Hematologic malignancies	353 / 1103 (32.0%)	***<0.001***
	Hurler Syndrome	13 / 74 (17.6%)	
	Krabbe Disease	4 / 41 (9.8%)	
	X-linked Adrenoleukodystrophy	1 / 25 (4.0%)	
	Primary immunodeficiency diseases	17 / 96 (17.7%)	
	Bone marrow failure	53 / 114 (46.5%)	
	Beta thalassemia	2 / 8 (25.0%)	
	Other	26 / 111 (23.4%)	
Lowest HLA Match Level	2-3	24 / 55 (43.6%)	***<0.001***
	4	243 / 723 (33.6%)	
	5	165 / 613 (26.9%)	
	6	35 / 170 (20.6%)	
	Unknown		
TNC Dose (x 10^7/kg)	<2.5	141 / 273 (51.7%)	***<0.001***
	2.5 - <5	148 / 473 (31.3%)	
	5 - <10	110 / 471 (23.4%)	
	10 - <20	57 / 297 (19.2%)	
	≥20	13 / 58 (22.4%)	

Other factors that correlated with day 100 mortality were also sought. By univariate analysis, age, gender, diagnosis and degree of HLA mismatch, in addition to TNC dose, were found to correlate with the rate of death at day 100 (Table 7).

7.4.3 Summary

In summary, the early mortality was 25%, and 3.7% of subjects died from graft failure. The major causes of early death were infection (7.8%) and organ failure (6.5%). There was a strong correlation between day-100 mortality and TNC dose, with significant differences when comparing above and below 2.5 x 10^7TNC/kg. No more specific TNC cut point was identified by an assessment of mortality with incremental increases in TNC dose. Day-100 mortality also varied by diagnosis, and this variation was not clearly related to TNC dose alone.

7.5 Hematopoietic Recovery

7.5.1 Review of Docket Submissions

1997-N-0010-DRAFT-0016, -0019, 0032: NMDP submitted summary statistics for 353 patients transplanted 2000-2005 for various diseases on their IND. The median TNC dose transplanted was 5.7 x 10^7/kg cryopreserved and 4.1 x 10^7/kg post thaw. Neutrophil recovery was reported for 86% of patients, and platelets recovered to >50,000 for 59% of patients. The median time to neutrophil recovery was 21 (1-88) days, and the median time to platelet recovery was 61 (1-473) days.

An analysis of a raw dataset for 548 patients transplanted 2000-2006 was also submitted. The median TNC dose for adults was 2.3 x 10^7/kg and 6.6 x 10^7/kg for children. For adults, significant factors in a logistic regression model for engraftment at day 42 included a combination of HLA match and cell dose (p=0.022) and male gender (p=0.039). For the model for platelet recovery to >50,000 by day 100, only CMV serostatus was significant (p=0.019). For children, there were no significant factors for neutrophil recovery, and age was the only significant factor for platelet recovery (p=0.045).

1997-N-0010-DRAFT-0034: St. Louis Cord Blood Bank submitted summary statistics for 161 patients. Data was not complete for all patients. The median time to neutrophil recovery was 22 days (2-81), and the median time to platelets >50,000 was 62 days (25-136). Hematopoietic recovery correlated with TNC doses. The summary indicates no significant differences in time to neutrophil or platelet recovery by duration of storage of the unit prior to transplantation when categorized as <12 months, 12-24 months, and >24 months. They recommend a minimum cell dose of 3 x 10^7 TNC/kg.

1997-N-0010-DRAFT-0039: University of Minnesota submitted summary statistics for hematopoietic recovery for 257 patients undergoing HPC-C transplantation 1993-2000 for various malignant and nonmalignant conditions. The median TNC dose in the unit was 3.7 x 10^7/kg (range, 0.7-57.9).

Forty-five (18%) patients failed to engraft by day 45. The probability of neutrophil recovery by day 45 was 87% (83-92%), and the median time to neutrophil recovery was 25 days (range,10-59 days). On univariate analysis, factors significantly associated with neutrophil recovery included patient age (p<0.01), patient weight (p<0.01), disease category (malignant vs benign) (p=0.04), preparative regiment (p<0.01), TNC dose (p<0.01), CD34 dose (p<0.01), and prior transplantation (p=0.04).

The probability of platelet recovery to >50,000 by 6 months was 51% (45-58%). On univariate analysis, factors significantly associated with platelet recovery included patient age (p<0.01), patient weight (>19 kg) (p<0.01), disease category (malignant vs benign) (p<0.01), preparative regimen (p=0.01), CMV serostatus (p=0.01), and TNC dose >6 x 10^7/kg (p<0.01).

Degree of HLA mismatch was not a factor for either endpoint. The report concluded that for a successful outcome, the product should include a TNC dose >1.5 x 10^7/kg at cryopreservation, and HLA mismatches up to 3 of 6 antigens was permissible.

1997-N-0010-DRAFT-0042, -0043: The NYBC submitted summary statistics and a raw dataset for 562 patients undergoing HPC-C transplantation 1993-1998 for various conditions. They report that 70% of patients had neutrophil recovery, and 42% had recovery of platelet to >50,000.

1997-N-0010-DRAFT-0035: The NYBC submitted summary statistics for 1019 patients with various diagnoses transplanted 1993-2000. They report that by multivariate analysis, the factors associated with time to neutrophil recovery are the TNC dose ($p<0.001$), HLA Mismatch ($p=0.005$), diagnosis ($p=0.003$) and geographic location ($p<0.001$). In subsequent analyses, progenitor cell content was a better predictor of time to neutrophil and platelet recovery than TNC dose.

2006-D-0157-0007: CIBMTR submitted summary statistics for neutrophil recovery for 677 patients undergoing HPC-C transplantation 1996-2006 for selected nonmalignant conditions. The cumulative incidence of neutrophil recovery varied by diagnosis and ranged from 54-100%.

2006-D-0157-0044, -0045: Duke submitted summary statistics for 158 children transplanted 1995-2007 for various inherited metabolic disorders.

The probability of neutrophil recovery by day 42 was 83% (77-89%). Factors significantly associated with neutrophil recovery in the multivariate model include age <2 years ($p=0.002$) and CD34 cell dose post thaw ($p=0.01$).

The probability of neutrophil recovery by day 180 was 69% (61-76%). Factors significantly associated with platelet recovery in the multivariate model include age <2 years ($p=0.003$), female gender ($p=0.004$), and colony forming units (CFU) dose post thaw ($p<0.0001$).

2006-D-0157-DRAFT-0064: The NYBC submitted summary statistics for an analysis of 1618 patients transplanted for various diseases 1993-2005. They report that neutrophil recovery varied significantly with disease category, being most rapid with inherited metabolic disorders and least successful with severe aplastic anemia. Neutrophil recovery also varied with CD34 dose.

2006-D-0157-DRAFT-0070, -0077: (b) (4) submitted summary statistics for 118 patients with various disease transplanted 2001-2005. The median TNC dose cryopreserved was 5.6 x 10^7/kg. Neutrophil recovery was achieved by 90% of patients, and the median time to recovery was 22 days. Platelet recovery to 20,000 was achieved by 77% of patients. On univariate analysis, time to neutrophil recovery was significantly longer for patients with a diagnosis of malignancy ($p=0.01$), and platelet recovery was significantly less frequent with a diagnosis of malignancy ($p=0.008$).

(b) (4) also later submitted summary statistics for 283 patients with various diseases undergoing HPC-C transplantation 2001-2006. Neutrophil recovery was achieved by 93% of the patients, and platelet recovery by 77%.

7.5.2 Analysis of the Pooled Dataset

The analysis of hematopoietic recovery for the pooled dataset is summarized in Table 8. The primary graft failure rate was 18.8%. Subjects with graft failure had a median survival of 59 days, day-100 survival of 33% (95% CI, 27-39%), and 1-year survival of 13% (95% CI 9-17%). The graft failure rate was significantly lower in those who received a TNC dose ≥2.5 x 107/kg (16.4% vs. 30.4%, p<0.001).

Table 8: Hematopoietic Recovery – Pooled Dataset

	All Subjects Transplanted	**Subjects with a TNC Dose ≥2.5 x 10^7/kg**
Primary graft failure* (%, 95% CI)	18.8% (16.8-20.8%)	16.4% (14.4-18.6%)
Cumulative Incidence$^+$ of ANC>500 by day 42 (%, 95%CI)	74% (72-76%)	77% (75%-79%)
Proportion with PLT >50,000 by Day 100 (%, 95% CI)	41% (38-43%)	45% (42-48%)
Median time to ANC>500	27 days	25 days
Median time to PLT>50,000	153 days	122 days

* Includes death, 2nd infusion or autologous recovery for patients surviving at least 14 days without ANC recovery
$^+$Using death, 2nd infusion, autologous recovery and relapse as competing risks.
Abbreviations: CI, confidence interval; ANC, absolute neutrophil count; PLT, platelet count.

The cumulative incidence of neutrophil recovery by Day 42 was 74%, and an additional 6% had delayed recovery. The time to neutrophil recovery was significantly faster with a TNC dose ≥2.5 x 10^7/kg than with a lower dose (median 25 vs. 36 days, p<0.001).

Table 9: Hematopoietic Recovery by Indication

	N	**Median time to ANC>500$^+$**	**Primary graft failure (%, 95%CI)$^{+,*}$**
Hematologic malignancies	843	26 days	16.3 (13.8-18.9)%
Hurler Syndrome	74	21 days	9.5 (3.9-18.5)%
Krabbe Disease	39	22 days	10.3 (2.9-24.2)%
X-linked Adrenoleukodystrophy	19	22 days	10.5 (1.3-33.1)%
Primary immunodeficiency diseases	86	19 days	12.8 (6.6-21.7)%
Bone marrow failure	90	30 days	31.1 (21.8-41.7)%
Beta thalassemia	7	31 days	28.6 (3.7-71.0)%
Other	102	25 days	15.7 (9.2-24.2)%

+ Subjects with a TNC Dose >2.5 x 10^7/kg
* Includes death, 2nd transplantation or autologous recovery for patients surviving at least 14 days without neutrophil recovery
Abbreviations: CI, confidence interval; ANC, absolute neutrophil count

Neutrophil recovery was also assessed by the individual indications for those receiving a TNC dose ≥2.5 x 10^7/kg (Table 9 above). The primary graft failure rates ranged from 9.5% to 31.1%, and the median times to ANC>500 ranged from 19 days to 31 days. However, as shown in Table 4 above, there was also a difference in TNC dose median and range for each indication, which confounds direct comparisons of hematopoietic recovery between indications.

To determine if there was a cut point in the TNC dose for neutrophil recovery or primary graft failure, the median time to neutrophil recovery and graft failure rates were graphed by TNC dose rounded to the nearest whole number. Only data through TNC doses of 20 x 10^7/kg were used, since the numbers of patients at the higher doses was too low to perform the analysis. There is a continuous improvement in the hematopoietic outcomes over the range of TNC doses assessed, and no plateau is identified (Figures 3 and 4).

Figure 3: Time to ANC>500 By TNC Dose (x 10^7/kg)

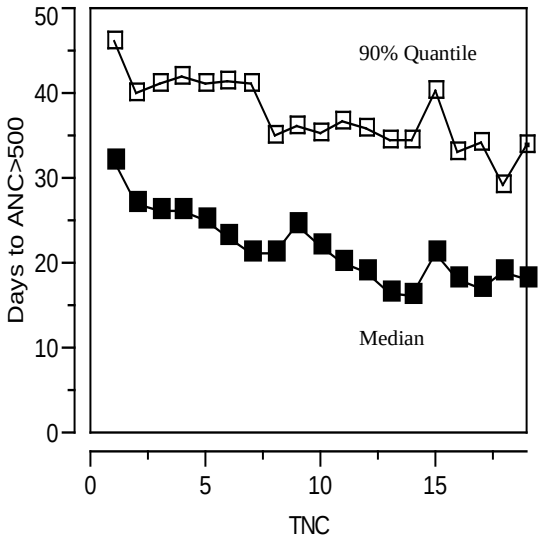
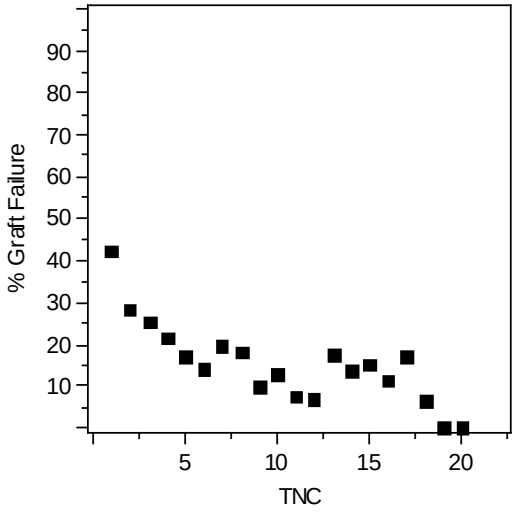


Figure 4: Primary Graft Failure By TNC Dose (x 10^7/kg)

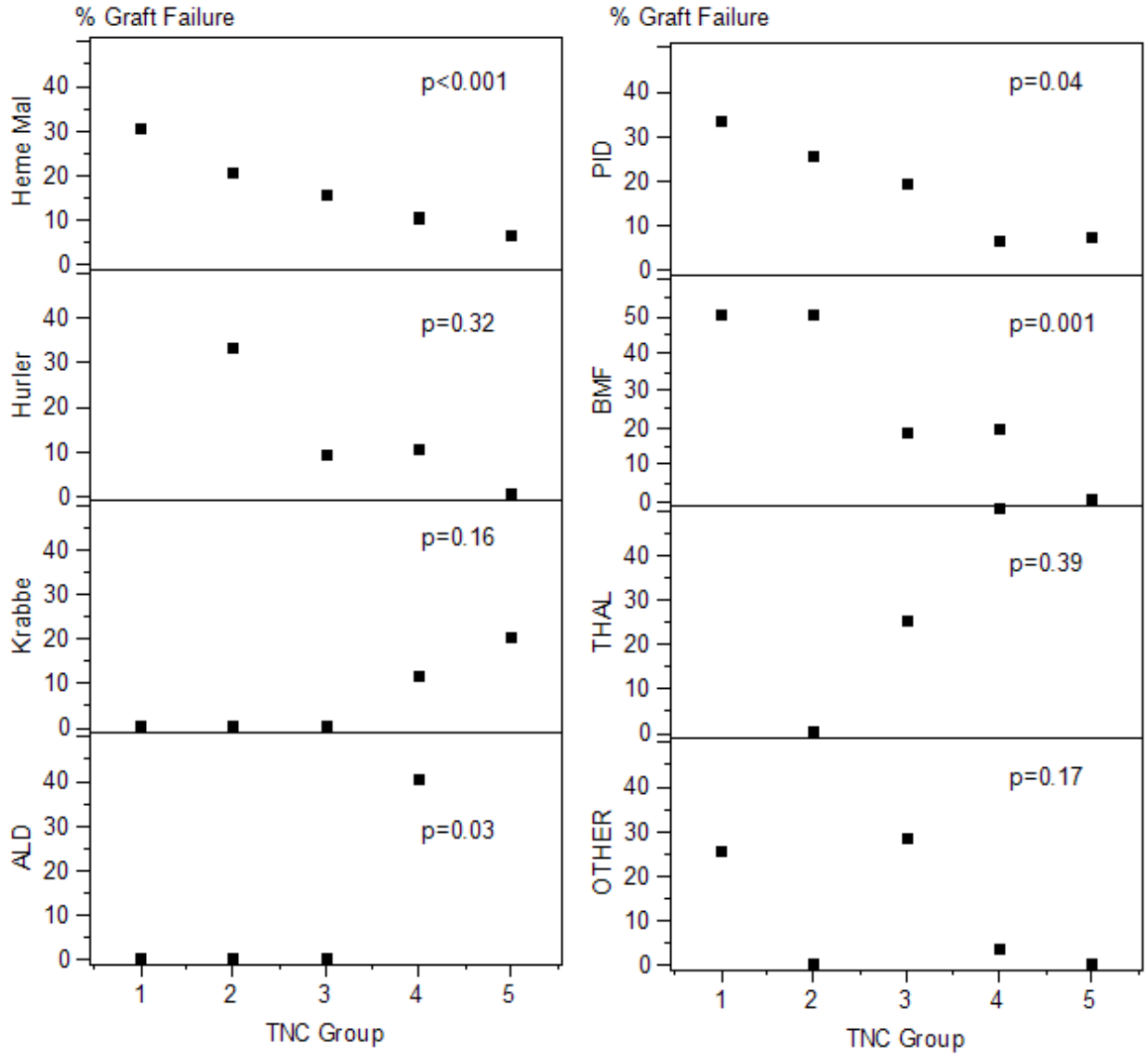


Most patients undergoing HPC-M transplantation achieve neutrophil recovery by 30 days after transplantation. For subjects in the pooled dataset, the median time to neutrophil recovery was less than 30 days for TNC doses >2 x 10^7/kg; however, even with TNC doses as high as 20 x 10^7/kg, the time to neutrophil recovery still exceeded 30 days for 10% of the subjects (Figure 3).

By contrast, graft failure rates fell below 20% only for TNC doses ≥4 x 10^7/kg and remained at approximately 5-20% until falling further at TNC doses ≥17 x 10^7/kg (Figure 4).

***Analyses of Graft Failure*:** Whether hematopoietic outcomes varied by dose for specific indications was also assessed. Figure 5 shows the percentage of subjects with primary graft failure through incremental increases in TNC dose for each indication and for the remaining diagnoses grouped as "Other." By Cuzick's test, there was a significant inverse correlation between TNC dose group and graft failure for the subjects transplanted with hematological malignancies, adrenoleukodystrophy, immunodeficiency disorders, and marrow failure. It should be noted that 96% of the patients with Hurler Syndrome received a TNC dose $\geq$5 x 10^7/kg, and with so few subjects at the lower dose levels, a trend might not be detectable.

Figure 5: Primary Graft Failure By TNC Dose Group And Indication
(TNC Dose Group 1=<2.5, 2=2.5 - <5, 3=5 - <10, 4=10 - <20, 5=>20)
See Figure 4 for abbreviations.



Other factors that correlated with graft failure were also sought. By univariate analysis, graft failure correlated with age group, diagnosis, degree of HLA mismatch and TNC dose group (Table 10).

Table 10: Univariate Analysis of Factors Correlated with Primary Graft Failure

		Primary Graft Failures	p
Age Category	<2 yr	41 / 376 (10.9%)	***<0.001***
	2 – <17 yr	179 / 884 (20.2%)	
	≥17 yrs	65 / 257 (25.3%)	
Gender	Male	96 / 581 (16.5%)	0.23
	Female	58 / 421 (13.8%)	
Ethnicity	White	91 / 632 (14.4%)	0.51
	African-American	21 / 103 (20.4%)	
	Hispanic	19 / 141 (13.5%)	
	Asian	6 / 29 (20.7%)	
	Other	2 / 15 (13.3%)	
Diagnosis	Hematologic malignancies	205 / 1071 (19.1%)	***<0.001***
	Hurler Syndromes	7 / 74 (9.5%)	
	Krabbe Disease	4 / 40 (10.0%)	
	X-linked Adrenoleukodystrophy	2 / 24 (8.3%)	
	Primary immunodeficiency diseases,	12 / 89 (13.5%)	
	Bone marrow failure	36 / 106 (34.0%)	
	Beta thalassemia	2 / 7 (28.6%)	
	Other	17 / 106 (16.0%)	
Lowest HLA Match Level	2-3	18 / 51 (35.3%)	***<0.001***
	4	149 / 701 (21.3%)	
	5	105 / 590 (17.8%)	
	6	13 / 165 (7.9%)	
TNC Dose (x 10^7/kg)	<2.5	78 / 257 (30.4%)	***<0.001***
	2.5 - <5	99 / 451 (22.0%)	
	5 - <10	75 / 464 (16.2%)	
	10 - <20	29 / 291 (10.0%)	
	≥20	4 /54 (7.4%)	

A multivariate logistic regression model was developed by backward stepping starting with the factors significant on univariate analysis. The final model identified diagnosis, degree of HLA mismatch, and TNC dose group as significantly associated with primary graft failure (Table 11).

Table 11: Primary Graft Failure – Multivariate Analysis

Factor	Odds Ratio	p
HLA Match[1]		***<0.001***
2	14.67	
3	4.89	
4	3.15	
5	2.76	
Diagnosis[2]		***0.006***
Hurler Syndrome	0.74	
Krabbe Disease	0.86	
Adrenoleukodystrophy	0.42	
Immunodeficiency	1.14	
Marrow Failure	2.54	
Thalassemia	2.77	
Other	1.20	
TNC x 10^7/kg[3]		***<0.001***
<2.5	1.64	
5-<10	0.72	
10-<20	0.42	
≥20	0.30	

[1]vs 6/6 match
[2]vs Hematological malignancies
[3]vs TNC dose 2.5 to <5 x 10^7/kg

The subjects with hematopoietic malignancies represent the largest subgroup with sufficient homogeneity to serve as an example of how TNC dose and degree of HLA match affect graft failure. Table 12 shows the incidence of primary graft failure for patients with hematologic malignancies by TNC dose and number of HLA antigens matched.

Table 12: Incidence of Graft Failure by HLA Mismatch for Hematologic Malignancies

	TNC Dose (x 10^7/kg)			
HLA Match	**<2.5**	**2.5 - <5**	**5 - <10**	**≥10**
4	31.1% (37/123)	21.4% (43/201)	15.2% (21/138)	9.0% (6/67)
5	35.1% (26/74)	16.1% (19/118)	18.7% (23/123)	9.0% (7/78)
6	4.8% (1/21)	18.4% (7/38)	2.9% (1/34)	11.1% (2/18)

***Analyses of Neutrophil Recovery*:** Other factors that correlated with time to neutrophil recovery were assessed by competing risk regression. On univariate analysis, graft failure correlated with age group, diagnosis, degree of HLA mismatch and TNC dose group (Table 13). A competing-risk regression model was developed by backward-stepping starting with the factors significant on univariate analysis. Death, 2nd transplantation, autologous recovery and relapse were use as competing risks. The final model identified degree of HLA mismatch ($p<0.001$) and TNC dose group ($p<0.001$) as significant. The subhazard ratios for the model are also displayed in Table 13.

Table 13: Analysis of Factors Correlated with Time to Neutrophil Recovery

	Univariate		Multivariate	
Covariate*	**SHR (95% CI)**	**p**	**SHR (95% CI)**	**p**
Age Category	0.72 (0.66-0.80)	***<0.001***	-	-
Gender	1.03 (0.91-1.18)	0.62	-	-
Race	0.99 (0.94-1.04)	0.75	-	-
Diagnosis	1.08 (1.04-1.13)	***<0.001***	-	-
HLA Mismatch	1.22 (1.13-1.31)	***<0.001***	1.16 (1.08-1.26)	***<0.001***
TNC Dose Group	1.35 (1.28-1.43)	***<0.001***	1.33 (1.25-1.41)	***<0.001***

*See Table 10 above for subgroup definitions.

A model was developed from the pooled dataset to determine the expected upper 95% confidence limit for time to neutrophil recovery using the degree of HLA mismatch and TNC dose as covariates. The analysis cohort was limited to patients with hematological malignancies receiving allografts with at least a 4 of 6 HLA antigen match and a TNC dose $\geq 2.5 \times 10^7$/kg. The parameters of the model are shown in Table 14. Using the model, 4.4% of subjects in the training set and 4.6% of subjects in the testing set had neutrophil recovery times that exceeded the expected upper 95% confidence limit.

Table 14: Parameters for Calculation of Expected Upper 95% Confidence Interval of Time to Neutrophil Recovery*

Term	**Estimate**	**Std Error**	**p**
Intercept	110.79	0.06	***<0.001***
HLA match 6/6	-0.96	0.004	***<0.001***
HLA match 5/6	1.32	0.003	***<0.001***
Log TNC dose	-8.36	0.008	***<0.001***

*For engrafting patients with hematological malignancies receiving allografts with at least a 4 of 6 HLA antigen match and a TNC dose $\geq 2.5 \times 10^7$/kg

7.5.3 Relevant Literature

In a comprehensive review, Petropoulou and Rocha[1] reported that the cumulative incidence of graft failure after unrelated donor HPC-C transplantation varied from 10% to 20%, and the median time to neutrophil recovery was 22 to 27 days. Factors affecting neutrophil recovery were diagnosis, cell dose (TNC, CFU or CD34), HLA matching, presence of noninherited maternal HLA antigens on the cord blood cells, use of fludarabine in the preparative regimen, and use of methotrexate for prevention of GVHD.[1,2]

The correlation between diagnosis and risk of graft failure was especially high in patients with nonmalignant disorders, such as hemoglobinopathies. Such patients are more likely to be alloimmunized from transfusion of nonlymphodepleted blood products, and they have not been exposed to immunosuppressive and myelosuppressive chemotherapy prior to transplantation. Ruggeri et al have found that this risk can in part be overcome by increasing the TNC dose to $>5 \times 10^7$/kg.[3]

How alloimmunization impacts neutrophil recovery is not clear. The risk of graft rejection is higher in haploidentical and unrelated donor transplant recipients who have antibodies directed against the mismatched donor HLA antigens, raising the concern that the same may be true for mismatched HPC-C transplant recipients. Cutler et al[4] and Takanashi et al[5] have, in fact, reported that the presence of anti-donor HLA antibodies in HPC-C transplant recipients correlated with a higher rate of graft failure, prolonged time to engraftment in those who did engraft, and an inferior overall survival. The risk of graft failure was especially high in double cord transplant recipients when antibodies were directed against both units being transplanted (odds ratio 16.3, p=0034). By contrast, Brunstein et al[6] found that time to neutrophil recovery was longer in those with anti-donor antibodies than in those without (24 days vs 19 days), albeit the difference was not significant, and the rates of graft failure were similar (78% vs 86%, respectively). The reason for the disparities between publications is not clear.

7.5.4 The COBLT Study

The COBLT study represents the only prospective clinical trial of minimally-manipulated, unrelated-donor HPC-C transplantation for which data are available for review. The main protocol of The COBLT Study (described in Appendix 9.3.1) is a single-arm trial that enrolled 364 subjects. Hematopoietic recovery data are available for 324 subjects from the main protocol who received TNC doses $\geq 2.5 \times 10^7$/kg. Demographics are shown in Table 15.

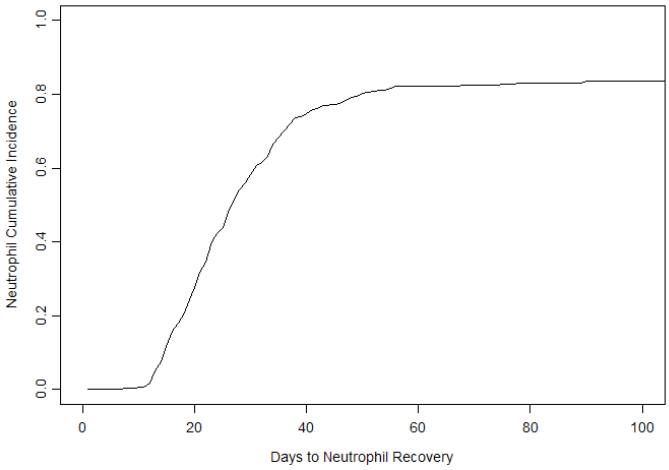
Table 15: Demographics of Subjects with a TNC Dose ≥2.5 x 10^7/kg in The COBLT Study Main Protocol (N=324)

Median Age (Range)		4.6 years (0.07–52.2 years)
Gender	Male	192 (59.3%)
	Female	132 (40.7%)
Ethnicity	White	168 (51.9%)
	African-American	36 (11.1%)
	Hispanic	35 (10.8%)
	Asian	10 (3.1%)
	Other	1 (0.3%)
	Unknown	74 (22.8%)
Diagnoses	Hematologic malignancies	231 (71.3%)
	Inherited Metabolic Disorders	69 (21.3%)
	Primary immunodeficiency diseases	19 (5.9%)
	Bone marrow failure	5 (1.5%)
HLA Match Level	Unknown	1 (0.3%)
	2-3	6 (1.8%)
	4	171 (52.8%)
	5	120 (37.0%)
	6	26 (8.0%)
Median TNC Dose (Range)		6.7 x 10^7/kg ($2.6 – 38.8 \times 10^7$/kg)

The primary endpoint of the study was day-180 survival. The target day-180 survival is 60%. A sample size of 300 with a true survival proportion of 60% provides at least 94% power to exclude a survival probability of 50% or less. The Kaplan-Meier estimate (95% CI) of day-180 survival was 66.9% (62.0% - 72.2%).

Secondary endpoints included neutrophil, platelet and red cell recovery. The cumulative incidence of neutrophil recovery to >500/uL at day 42 was 76% (95% CI 71%-81%) (Figure 6).

Figure 6: Neutrophil Recovery - The COBLT Study



Results of the analyses of hematopoietic recovery are show in Table 16.

Table 16: Hematopoietic Recovery – The COBLT Study Main Protocol

Neutrophil Recovery at Day 42	76% (71%-81%)*
Platelet Recovery at Day 100 (20,000/uL level)	57% (51%-63%)
Platelet Recovery at Day 100 (50,000/uL level)	46% (39%-51%)
Erythrocyte Recovery at Day 100	65% (58%-71%)
Median time to Neutrophil Recovery	27 days
Median time to Platelet Recovery (20,000/uL level)	90 days
Median time to Platelet Recovery (50,000/uL level)	113 days
Median time to Erythrocyte Recovery	64 days

*Cumulative incidence (95% confidence interval)

7.5.5 Summary

In summary, the primary graft failure rate was 16.4% (14.4-18.6%) for subjects receiving a TNC dose $\geq$2.5 x 10^7/kg. The graft failure rates fell below 20% only for incremental TNC doses $\geq$4 x 10^7/kg and remained at approximately 5-20% until falling further at TNC doses $\geq$17 x 10^7/kg. On multivariate analysis, there was a significant association between graft failure and diagnosis (p=0.006), degree of HLA mismatch (p<0.001), and TNC dose group (P<0.001). Graft failure was more common in patients with bone marrow failure (34%) and beta thalassemia (28.6%) and

less common in the inherited metabolic disorders (8.3-10%) as compared with the hematologic malignancies (19%). Graft failure was less common in patients with 6/6 HLA match (7.9%) and with increasing TNC doses to $\geq 5 \times 10^7$/kg. The literature review also suggests that alloimmunization may increase the risk of graft failure.

The graft failure rate varied with diagnosis and ranged from 9.5% to 31.1%. When assessed by individual diagnosis, there was a significant inverse correlation between TNC dose group and graft failure for the subjects transplanted with hematological malignancies, bone marrow failure and "other" diagnoses. For Hurler syndrome and bone marrow failure, a substantial decrease in graft failure especially occurs with a TNC dose $\geq 5 \times 10^7$/kg. The literature review suggests that the higher TNC dose may also be required for patients transplanted for thalassemia.

The cumulative incidence of neutrophil recovery by day 42 was 77% (75%-79%), and the median time to neutrophil recovery was 25 days for subjects receiving a TNC dose $\geq 2.5 \times 10^7$/kg. The median time to neutrophil recovery varied by diagnosis and ranged from 19 days to 31 days. This variation was due in part to difference in TNC dose. For all subjects, the median time to neutrophil recovery was delayed substantially with TNC doses $< 2 \times 10^7$/kg. but even with TNC doses as high as 20×10^7/kg, the time to neutrophil recovery still exceeded 30 days for 10% of the subjects, a much higher rate of delayed recovery than with HPC-M or HPC-A. On multivariate analysis, degree of HLA mismatch and TNC dose were significantly associated with the time to neutrophil recovery.

Subjects in The COBLT Study receiving a TNC dose $\geq 2.5 \times 10^7$/kg had hematopoietic recovery rates similar to those for the pooled dataset overall, and the day-180 survival for these subjects met the target for the protocol.

7.6 Acute GVHD

7.6.1 Review of Dockets

1997-N-0010-DRAFT-0016, -0019, 0032: NMDP submitted summary statistics for 353 patients transplanted 2000-2005 for various diseases. Grades 2-4 GVHD occurred in 38% of patients and grades 3-4 in 22%.

An analysis of the raw dataset for 548 patients transplanted 2000-2006 was also submitted. For adults, significant factors in a proportional hazards model for grades 2-4 GVHD included gender ($p=0.003$) and preparative regimen intensity ($p=0.002$). The model for grades 3-4 GVHD included only year of transplantation ($p=0.039$). For children, there were no significant factors for grades 2-4 GVHD, and only age was significant for grades 3-4 GVHD ($p<0.001$)

1997-N-0010-DRAFT-0034: St. Louis Cord Blood Bank submitted summary statistics for 161 patients. Data was not complete for all patients. Grades 2-4 GVHD occurred in 45% of 75 evaluable patients and grades 3-4 in 23%.

1997-N-0010-DRAFT-0039: University of Minnesota submitted summary statistics for hematopoietic recovery for 257 patients undergoing HPC-C transplantation 1993-2000 for various malignant and nonmalignant conditions. The median TNC dose in the unit was 3.7 x 10^7/kg (range, 0.7-57.9). The probability of grades 2-4 GVHD was 30% (24-36%), and 12% (8-16%) for grades 3-4 GVHD. On univariate analysis, there were no factors significantly associated with grades 2-4 GVHD.

1997-N-0010-DRAFT-0042, -0043: The NYBC submitted summary statistics and a raw dataset for 562 patients undergoing HPC-C transplantation 1993-1998 for various conditions. They report that 24% of evaluable patients had grades 2-4 GVHD and 18% had grades 3-4 GVHD.

2006-D-0157-0044: Duke submitted summary statistics for 160 children transplanted for various inherited metabolic disorders. The probability of grades 2-4 GVHD was 39% (31-46%), and 10% (6-15%) for grades 3-4 GVHD.

2006-D-0157-DRAFT-0070: (b) (4) submitted summary statistics for 118 patients with various diseases transplanted 2001-2005. The rate of grades 3-4 GVHD was 15%.

7.6.2 Analysis of the Pooled Dataset

In the pooled dataset, 88% of the patients had an assessment for acute GVHD reported (see Table 17 for numbers of patients in the analysis). The time to onset of each grade of acute GVHD was not available, so only a crude incidence of acute GVHD by maximum grade can be calculated. For all patients with data, 42.2% had grades 2-4 GVHD, and 19.5% had grades 3-4 GVHD (Table 17). When comparing patients who received a TNC dose $\geq$2.5 x 10^7/kg to those who received a lower TNC dose, the incidences of grades 2-4 GVHD (42.1% vs. 42.7%, p=0.88) and grades 3-4 GVHD (18.8% vs. 23.6%, p=0.12) were similar.

Table 17: Acute GVHD – Pooled Dataset

	All Subjects Transplanted (N=1381)	**Subjects with a TNC Dose ≥2.5 x 10^7/kg (N=1182)**
Number (%) with maximum grade 0	451 (32.7%)	369 (31.2%)
1	347 (25.1%)	315 (26.7%)
2	314 (22.7%)	276 (23.4%)
3	176 (12.7%)	149 (12.6%)
4	93 (6.7%)	73 (6.2%)

The incidence of grades 2-4 and grades 3-4 acute GVHD by diagnosis are displayed in Table 18. Comparisons between diagnoses are limited by the small number of cases with a GVHD assessment reported for some of the indications, such as adrenoleukodystrophy and beta thalassemia.

Table 18: Acute GVHD by Diagnosis

	All Subjects Transplanted			Subjects with a TNC Dose ≥2.5 x 107/kg		
	N	% Gr 2-4	% Gr 3-4	N	% Gr 2-4	% Gr 3-4
Hematologic malignancies	975	42.6%	21.5%	795	42.5%	21.0%
Hurler Syndromes	71	47.9%	15.5%	71	47.9%	15.5%
Krabbe Disease	40	45.0%	10.0%	39	43.6%	10.3%
X-linked Adrenoleukodystrophy	23	47.8%	26.1%	19	52.6%	26.3%
Immunodeficiency diseases	93	30.1%	12.9%	91	30.8%	13.2%
Bone marrow failure	78	51.3%	25.6%	70	52.9%	24.3%
Beta thalassemia	6	33.3%	0.0%	6	33.3%	0.0%

7.6.3 Relevant Literature

The reported rates of grades 2-4 acute GVHD range from 14 to 52% after unrelated donor HPC-C transplantation. Several risk factors for acute GVHD have been reported, including CMV serostatus, pretransplant infection, age, CD34 cell dose and HLA mismatch.[7-9] How HLA mismatching impacts the risk of GVHD varies in the literature (reviewed in reference 7) from no impact to increased rates with mismatch at combinations of loci or with increasing degree of mismatch. MacMillan et al[8] also found that the risk of grades 2-4 acute GVHD was higher after double vs single unit transplantation (58% vs 39%, $p<0.01$), although the risks of grades 3-4 acute GVHD were similar (19% vs 18%). In this report, the double unit transplant recipients had significantly higher TNC, CD34 and CD3 doses in comparison to the single unit transplant recipients. The majority of the acute GVHD in the HPC-C transplant recipients appeared to involve skin alone and was responsive to steroid therapy. Such mild GVHD had little impact on treatment-related mortality or event-free survival.[8,9]

7.7 Engraftment Syndrome

7.7.1 Review of Dockets

There were no submissions to the docket that addressed the risk of engraftment syndrome in HPC-C transplant recipients.

7.7.2 Analysis of the COBLT Dataset

Patients in the COBLT Study were assessed for the occurrence of periengraftment onset fever and rash requiring treatment with corticosteroids. This toxicity was recorded as “cytokine storm” or hyperacute GVHD, and it was reported for 76 (14.7%, 95% CI, 11.7-18.0%) of the patients. Median time to onset of the event was 10 days after transplantation (range, 5-35 days).

7.7.3 Relevant Literature

Engraftment syndrome (ES) is a poorly characterized clinical entity that occurs in the pre- or peri-engraftment period in both autologous and allogeneic HPC transplant recipients. Spitzer[10] has recommended standardizing the diagnostic criteria to include noninfectious fever, rash and noncardiogenic pulmonary edema, although early intervention with steroids frequently prevents the pulmonary complications. If left untreated, patients may also go on to develop hyperbilirubinemia, weight gain, renal insufficiency and encephalopathy. The etiology is unclear, but the clinical manifestations appear to result from stimulation of immune cells and release of inflammatory cytokines. Some have distinguished ES from pre-engraftment immune reaction (PIR) largely on the basis of time of onset,[11] but this differentiation is not widely adopted. In fact, because of the overlap in clinical features of ES and GVHD, some centers do not recognize ES as a distinct entity or may call it hyperacute GVHD instead.

ES or ES-like events have been reported in 30-78% of unrelated donor HPC-C transplant recipients.[11-15] Median reported onset is approximately 7-9 days after transplantation, as much as several weeks prior to neutrophil recovery. ES after unrelated donor HPC-C transplantation resolves rapidly with a short course of high-dose steroids, and development of ES seems to have no impact on treatment-related mortality (TRM) or overall survival (OS). The incidence of ES appears to be reduced by use of short-term methotrexate or corticosteroids in the GVHD prophylaxis regimen.

7.7.4 Summary

Engraftment syndrome (ES) is a poorly characterized clinical entity that occurs in the pre- or peri-engraftment period in both autologous and allogeneic HPC transplant recipients and may include fever, rash and noncardiogenic pulmonary edema. The incidence of ES appears to be reduced by use of short-term methotrexate or corticosteroids in the GVHD prophylaxis regimen. ES or ES-like events have been reported in 30-78% of unrelated donor HPC-C transplant recipients in the literature. In The COBLT Study, ES-like events occurred in 15% of patients, and median time to onset was 10 days after transplantation (range, 5-35 days). ES after unrelated donor HPC-C transplantation generally resolves rapidly with a short course of high-dose corticosteroids, and its occurrence seems to have no impact on TRM or OS when treated.

7.8 Infusion Reactions

7.8.1 Review of Dockets

2006-D-0157-DRAFT-0070: (b) (4) submitted summary statistics for 118 patients with various diseases transplanted 2001-2005. The infusion reactions reported included hypertension (8.5%), hemoglobinuria (8.5%), hives (1.7%), nausea and vomiting (1.7%), dyspnea (1.7%), and seizure and encephalopathy (0.9%). The HPC-C was infused without washing for 50 patients and after washing for 67 patients. The safety profile was similar between the two groups except for hemoglobinuria which occurred in 18% with no wash vs 1.5% when the HPC-C unit was washed prior to infusion.

7.8.2 Analyses of The COBLT Study Dataset

The COBLT Study provides the only dataset that includes prospective monitoring for infusion reactions. The dataset includes information for 511 patients who received 523 HPC-C units. Data on TNC dose and administration information were available for 499 infusions, and 442 of these had a TNC dose $\geq 2.5 \times 10^7$/kg. To prepare for infusion, HPC-C units were washed and resuspended in 30-150 mL 8% Dextran 40 with 4% albumin. Infusions were to be completed within 30 minutes.

Table 19 summarizes the administration information that was available for 499 single unit infusions.

Table 19: HPC-C Administration Parameters from The COBLT Study

	N	Median (range)
Infusion Duration	494	35 (1-130) min
Total Volume	499	93 (20-343) mL
Vol/Kg	499	4.3 (0.3-21) mL/kg
Infusion rate	494	7.5 (0.6-105.1) mL/kg/hr
TNC Dose	499	6.2 (0.8-65.0) x 10^7/kg

Premedications were administered for 98.5% of the infusions. Subjects were monitored for predefined infusion reactions identified as occurring within 24 hours of transplantation. Events were graded according to the NCI CTC scale. The incidences of infusion reactions for all 523 infusions are listed in Table 20.

Table 20: Infusion Reactions – The COBLT Study

	All Infusions (n=523)		Subjects with a TNC Dose $\geq 2.5 \times 10^7$/kg (n=442)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Any reaction	65.4%*	26.6%	65.4%	27.6%
Hypertension	46.5%	19.9%	48.0%	21.3%
Vomiting	15.7%	0.2%	14.5%	0.2%
Nausea	14.8%	6.1%	12.7%	5.7%
Sinus bradycardia	10.3%	0.0%	10.4%	0.0%
Fever	5.5%	0.2%	5.2%	0.2%
Sinus tachycardia	5.2%	0.8%	4.5%	0.2%
Allergy	3.1%	0.2%	3.4%	0.2%
Hypoxia	2.9%	2.7%	2.0%	2.0%
Hypotension	2.9%	0.6%	2.5%	0.0%
Hemoglobinuria	1.9%	0.0%	2.1%	0.0%
Dyspnea	1.7%	1.1%	0.9%	0.7%
Infection	1.5%	1.5%	0.9%	0.9%
Chills	1.3%	0.0%	0.9%	0.0%

*Percentage of infusions

The majority of infusions (65%) were associated with a reported reaction, and over a quarter were assessed as grades 3-4 in severity. Emergency medications for reactions were administered for 3.8% of the infusions. The most common reactions (>10%) were hypertension, nausea, vomiting, and sinus bradycardia. The most common grades 3-4 reactions (≥2%) were hypertension, nausea and hypoxia. Four events (0.8%) were reported as serious adverse reactions involving cardiopulmonary signs or symptoms, two of which cited hypertension as an infusion reaction. Narratives are not available for the serious adverse events.

Demographic, product and administration characteristics were assessed by the effect likelihood ratio test for correlations with infusion reactions using the subset of 499 single unit infusions with administration information. These factors included duration of infusion, total volume infused, volume/kg, volume/kg/hour, age, diagnosis, degree of HLA mismatch, race, gender and TNC dose. The outcomes included any adverse event, any grade 3-4 event, and any hypertension. Multivariate analyses were performed using a backward stepping approach.

The development of any adverse event correlated with the infusion duration (p=0.01) and total volume (p=0.02). The highest rates of adverse events were for infusions exceeding 150 mL (75%) and when the infusion required more than 60 minutes to complete (79%). On multivariate analysis, there was no model found with more than one significant parameter.

Table 21: Infusion Reactions – Multivariate Analyses

	Any Grade 3-4 AE		**Any Hypertension**	
	Odds Ratio	**p**	**Odds Ratio**	**p**
Total Volume (per mL change)	1.005	***0.04***	1.008	***<0.001***
Age Group[1] Teen	2.52	***0.002***	2.97	***0.02***
Child	3.73		2.48	
Infant	3.82		2.58	
Neonate	0.00		2.62	

[1] vs Adults

Having any grade 3-4 event correlated with age group (p=0.005), with the highest rates in infants (29%), children (30%) and teens (24%), and the lowest rates in neonates (0%) and adults (11%). On multivariate analysis, both total volume and age group were significantly associated with grade 3-4 adverse events (Table 21).

Developing hypertension as an adverse event correlated with infusion duration, total volume infused, degree of HLA mismatch and diagnosis. The highest rates of hypertension occurred when the infusion duration exceeded 1 hour (58%), for infusions exceeding 150 mL (66%), and in patients with marrow failure (69%) or inherited metabolic disorders (60%). On multivariate analysis, total volume infused and age group were significantly associated with development of hypertension (Table 21).

7.8.3 Relevant Literature

Adverse experiences related to infusion of HPC-C include allergic reactions, immune-mediated events and toxic effects. The specific events reported include fevers, rigors, dysgeusia, headache, dizziness, paresthesias, arrhythmia, chest pain, hypertension, bradycardia, coronary spasm, dyspnea, hypoxia, pulmonary edema, renal failure, abdominal pain, nausea, vomiting, hemolysis and anaphylaxis.[16-24] The reported incidence of HPC-C infusion reactions varies from 4% to 65%. Most of the events were stated to be mild, but as many as 4.6% of the recipients had life-threatening reactions.[22]

Toxicity may in part be due to the cells themselves, plasma proteins, or to agents added to the infusate during processing or preparation for infusion. How HPC-C units are prepared for infusion varies. The most common methods include a) thaw at the bedside and infuse immediately, b) dilute with Dextran 40 and albumin prior to infusion, and c) dilute and replace supernatant prior to infusion. Consequently, the infusion may include not only the cord blood cells, but also cell debris, free hemoglobin, plasma proteins, albumin, Dextran 40 and dimethylsulfoxide (DMSO), each of which may contribute to the toxicity of the HPC-C unit. Dextran 40 and DMSO are of particular concern.

Dextran 40 (reviewed in reference 25) is a mixture of mainly α-1,6-glucan type polysaccharides with average molecular weight 40,000 d. Its known uses include volume expansion for treatment of shock, for priming extracorporeal pumps, and for prevention of venous thromboses and pulmonary emboli. Dextran 40 is supplied as a 10% solution for IV use, and the usual dosage is 5-10 mL/kg (< 1 gm/kg) over 12 to 24 hours. For adults, the starting infusion rate is usually no greater than 100 mL/hr. The lowest molecular weight fraction is cleared by the kidneys within hours of administration, but the higher molecular weight fraction may take days to be excreted and/or metabolized, so monitoring fluid balance to avoid fluid overload is critical.[25] In addition, renal impairment may delay excretion. Known side effects of Dextran 40 include acute renal failure, pulmonary edema, congestive heart failure, bleeding disorders and anaphylactoid reactions. It is estimated that anaphylactoid reactions to Dextran 40 occur in approximately 1-5 cases per 10,000 patients treated with Dextran 40 when premedication with Dextran 1 is not used.[26]

DMSO has no approval for intravenous use in the US. Following administration, DMSO is widely distributed in the body, including across the blood brain barrier. Animal studies showed that DMSO and its metabolites are partially excreted through the kidneys, but the metabolite dimethyl sulfide is also excreted through exhalation.[27,28] Dose-toxicity data are limited. In a small phase I study of intravenous DMSO for treatment of intracranial hypertension, single daily doses of 1 gm/kg as a bolus infusion resulted in severe hypernatremia and fluid overload.[29] The latter may be due to hyperosmolar plasma expansion.[30] Other known side effects of intravenous DMSO include dysgeusia, nausea, vomiting, elevated liver enzymes, hemolysis and renal failure.[29,31-36] Encephalopathy occurs with very high doses (see Section 12.0 Overdosage). Anaphylaxis may occur, and it is not dose-dependent.

Removal of DMSO by washing the HPC-C cells prior to infusion may reduce some of the side effects, especially hypertension, but resuspension of the cells in a Dextran 40-containing medium after washing does not eliminate the potential toxicities due to that agent.[16,19,23,24]

7.8.5 Summary

Reactions related to infusion of HPC-C include allergic reactions, other immune-mediated events and toxic effects. Cell debris, free hemoglobin, plasma proteins, albumin, Dextran 40 and dimethylsulfoxide (DMSO) may contribute to the development of infusion reactions. The COBLT study provided the only dataset that included prospective monitoring for infusion reactions. Reactions were reported in a majority of infusions (65%) in the COBLT study, and over a quarter were assessed as grades 3-4 in severity. The reported incidence of HPC-C infusion reactions in the literature varies from 4% to 65%. Most of the events were stated to be mild, but as many as 4.6% of the recipients had a life-threatening reaction. Removal of DMSO by washing the HPC-C cells prior to infusion may reduce some of the side effects, especially hypertension, but resuspension of the cells in a Dextran 40 containing medium after washing does not eliminate the potential for toxicities.

7.9 Malignancies of Donor Origin

7.9.1 Review of Dockets

There were no submissions to the docket that reported development of malignancies from HPC-C.

7.9.2 Analysis of the Pooled Dataset

The pooled dataset provides no information on development of malignancies from HPC-C.

7.9.3 Relevant Literature

HPC donor-derived malignancies are generally limited to leukemias and the opportunistic lymphoproliferative disorders (PTLD) resulting from EBV infection.

Donor cell leukemia is a rare event in HPC transplant recipients, estimated to occur in 124/100,000, although rates as high as 5% have been reported in single institution studies.[37] In a review of 64 published cases of donor cell leukemia, median time from transplantation to diagnosis of leukemia was 31 months (range 2-312 months), the complete remission rate for treated patients varied by disease (53-76%), and the median survival was 5.5 months from diagnosis of donor cell leukemia.[37]

Nine cases of donor cell leukemia, myelodysplasia or myeloproliferative disorders in HPC-C transplant recipients have been published (Table 22) for an estimated incidence of 9/10,000,[†] an

[†] The denominator is based on the estimated cumulative number of HPC-C transplantations performed worldwide as of 2010 (Gracia J. Transfus Apher Sci 2010;42:257-263).

incidence slightly less than that estimated for all transplant recipients above. A single institution has reported an incidence as high as 3% in HPC-C transplant recipients.[43] Amongst the reported cases in Table 22, one was diagnosed as a lymphoid leukemia, and the remainder were myeloid in nature. Outcome data are incomplete. Follow-up information for the donor was available for 3 of the cases; these donors were reported to be alive and well, two at 1.5 and 7 years after donation.

Table 22: Donor Cell Leukemia, MDS and MPD in HPC-C Transplant Recipients

Reference	Original Diagnosis	Donor Cell Leukemia	Time to Diagnosis of Donor Cell Leukemia	Outcome
38	Histiocytosis	AML	40 mos	Died (10 mos)
39	Lymphoma	AML		
40	AML	T cell LGL		
41	ALL	MPD	5 mos	
42	AML	AML	14.5 mos	Died (11 mos)
42	CLL	MDS	6 mos	Alive (28 mos)
42	ALL	MDS	5 mos	Alive (9 mos)
43	AML	MPD	26 mos	Died
43	Lymphoma	MDS-RAEB	21 mos	Died

Abbreviations: MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; AML, acute myeloid leukemia; LGL, large granular lymphocytic leukemia; CLL, chronic lymphocytic leukemia; RAEB, refractory anemia with excess blasts

EBV-related PTLD is represented by a spectrum of disorders, usually of donor origin, ranging from a polyclonal lymphoproliferation to a highly aggressive monoclonal lymphoma. In a review of over 18,000 HPC transplant recipients, the cumulative incidence of PTLD was 1% at 10 years.[44] Risk factors for early onset (<1 year after transplantation) included unrelated donor, mismatched donor, T-cell depletion of the allograft, use of ATG or anti-CD3 antibody for prevention or treatment of GVHD, grades 2-4 GVHD and radiation in the preparative regimen. PTLD occurred in 8% of patients with 2 risk factors and 22% with 3 risk factors. Chronic GVHD was the only risk factor for late-onset PTLD. Rituximab is the first line treatment of EBV-PTLD, with 55-100% responding.[45,46]

The reported incidence of EBV-related PTLD after unrelated donor HPC-C transplantation varies from 2% to 16%.[43,47,48] The incidence is highest (>20%) in those who received a nonmyeloablative or reduced intensity preparative regimen with ATG.[48] The inciting EBV infection is a reactivation of prior infection in the recipient and is not transmitted from the HPC-C donor to recipient, as in cases were donor cells were available, no evidence of infection by EBV was found,[45,49] although this is not always the case.[50] The reported response to rituximab is 33-55%. Many patients die within weeks of diagnosis from a fulminant lymphoma, and in the case series, 0-50% of the patients were alive at the time of report. Although no comparative study has been performed, it appears that EBV-related PTLD has a worse prognosis in the unrelated donor HPC-C recipients than in patients transplanted with other HPC types.

7.9.4 Summary

Donor-derived malignancies after HPC transplantation are generally limited to donor cell leukemias and the opportunistic lymphoproliferative disorders (PTLD) resulting from EBV infection. Donor cell leukemia, myelodysplastic syndrome and myeloproliferative disorders are extremely rare events in HPC-C transplant recipients, estimated to occur in 9/10,000. EBV-related PTLD is represented by a spectrum of disorders, usually of donor origin, ranging from a polyclonal lymphoproliferation to a highly aggressive monoclonal lymphoma. The reported incidence of EBV-related PTLD after HPC-C transplantation varies from 2% to 16%.

7.10 Transmission of Serious Infection

7.10.1 Review of Dockets

There were no submissions to the docket that reported transmission of serious infections from the HPC-C donor to recipient.

7.10.2 Analysis of the Pooled Dataset

The pooled dataset provides no information on transmission of serious infections from the HPC-C donor to recipient.

7.10.3 Relevant Literature

Weinberg et al[51] assayed 362 HPC-C samples for CMV, HHV-6, HHV-7, HHV-8 and EBV by polymerase chain reaction (PCR). HHV-6 was detected in 2 (0.6%) samples, and testing for the other viruses was negative. The authors tested a further 312 samples from donors having CMV IgM-negative mothers, finding 1 positive sample by PCR, for an overall CMV detection rate of 0.15%. The results indicate that HPC-C may harbor CMV and HHV-6 that may be transmitted to the HPC-C transplant recipient.

Haut et al[50] reported on a patient who died from EBV PTLD 6 months after HPC-C transplantation. Tumor biopsies at autopsy expressed donor-specific HLA typing, confirming its donor origin. A DNA sample from the HPC-C unit that had been stored was positive for EBV (1 copy/100,000 cells). The recipient was seronegative for EBV at diagnosis of leukemia and was found to have low levels of VCA-IgG prior to transplantation, but VCA-IgM was negative. The authors concluded that the VCA-IgG in the recipient resulted from passive transfer through transfusions during prior treatment, and that the EBV infection causing the PTLD was transmitted by the HPC-C; however, no further testing was performed to ensure that the EBV in the recipient was the same strain as the EBV in the donor. No other case of transmission of infection from a HPC-C donor to the recipient was found.

7.10.4 Summary

The estimated incidence of transmission of a serious infection is 1/10,000, generally with CMV, HHV, and EBV.

7.11 Transmission of Rare Genetic Disorders

7.11.1 Review of Dockets

There were no submissions to the docket that reported transmission of rare genetic disorders from the HPC-C donor to recipient.

7.11.2 Analysis of the Pooled Dataset

The pooled dataset provides no information on transmission of rare genetic disorder from the HPC-C donor to recipient.

7.11.3 Relevant Literature

Review of the published literature revealed no reports of transmission of rare genetic disorders from the HPC-C donor to recipient.

7.11.4 Summary

On the basis of the information that is available, the estimated risk of transmission of a rare genetic disorder is less than 1/10,000.

7.12 Overdosage

7.12.1 Review of Dockets

2006-D-0157-DRAFT-0070: (b) (4) submitted summary statistics for 117 patients with various diseases transplanted 2001-2005. There was one case of seizure and encephalopathy reported. The sponsor did not provide additional information about the DMSO load in this patient but cautioned that the DMSO dose should not exceed 1 gm/kg.

7.12.2 Analysis of the Pooled Dataset

The pooled dataset provides no information on overdosage.

7.12.3 Relevant Literature

The three major components of HPC-C that may contribute to clinical overdosage include the cell content, Dextran 40 and DMSO. The literature provides no reports on overdosage due to an excessive number of nucleated cells infused for either HPC-C or other HPC types; the upper

limit of the tolerable cell dose range has not been established. Additionally, there are no reports of overdosage from Dextran 40.

The initial report of a toxic overdose of DMSO included two patients who had received approximately 1.5 gm/kg/day intravenously for 2 days (total dose 3 gm/kg) as treatment of arthritis.[31] The first patient developed vomiting, liver failure, renal insufficiency and loss of consciousness. Peritoneal dialysis had no clinical effect. The patient regained consciousness in 48 hours, and all signs and symptoms of toxicity resolved within 7 days with supportive care. The second patient developed vomiting, jaundice and renal insufficiency, reversing within one week with supportive care as well.

Dhodapkar et al[52] reported a toxic overdose in two patients with myeloma undergoing autologous HPC-A transplantation. The first patient received approximately 225 mL DMSO (approximately 3.2 gm/kg) over 10 hours with infusion of the HPC-A. He became somnolent and developed oliguria. Six days later, a plasma DMSO level was measured as 388 ug/mL. The patient underwent plasma exchange with reduction in the DMSO level to 78 ug/mL and improved clinically thereafter. A second patient received 120 ml DMSO (approximately 1.7 gm/kg) and was somnolent within 6 hours of infusion. His neurological status improved gradually over the next 5-6 days.

There were no reports in the literature of a DMSO overdose related to HPC-C transplantation.

7.12.4 Summary

Three major components of HPC-C that may contribute to clinical overdosage include the cell content, Dextran 40 and DMSO. Toxic overdose of DMSO has been reported in a patient undergoing autologous transplantation; there were no reports in the literature of a DMSO overdose related to HPC-C transplantation.

8 Postmarket Experience

There is no additional postmarket safety information for review.

9 Appendices

9.1 Literature Review/References

9.1.1 Literature Search Strategies

Early Mortality
The following PubMed searches were used:
N=133 for cord blood transplant AND early mortality
N=77 for cord blood transplant AND cause of death

Infusion Reactions
The following PubMed searches were used:
N=26 for cord blood transplant AND infusion reaction
N=33 for cord blood transplant AND allergic reaction
N=32 for cord blood transplant AND hypersensitivity

Adverse Events
The following PubMed searches were used:
N=35 for cord blood transplant AND adverse events
N=13 for hematopoietic AND transplant AND reaction AND DMSO
N=77 for stem cell transplant AND adverse AND DMSO
N=4 for cord blood transplant AND reaction AND DMSO
N=46 for dmso AND toxicity AND (Humans[Mesh] AND Review[ptyp])
N=15 for stem cell transplant AND reaction AND dextran
N=4 for cord blood transplant AND reaction AND dextran
N=38 for dextran AND toxicity AND (Humans[Mesh] AND Review[ptyp])

Hematopoietic Recovery
The following PubMed searches were used:
N=32 for cord blood transplant AND graft failure AND risk factor
N=83 for cord blood transplant AND engraftment AND risk factor
N=43 for cord blood transplant AND platelet AND risk factor
N=68 for cord blood transplant AND graft failure AND cell dose

Acute Graft vs Host Disease
The following PubMed searches were used:
N=81 for cord blood transplant AND GVHD AND risk factors
N=134 for cord blood transplant AND GVHD AND cell dose

Engraftment Syndrome
The following PubMed searches were used:
N=581 for ((Engraftment syndrome) OR (pre engraftment syndrome))
N=340 for ((Engraftment syndrome) OR (pre engraftment syndrome)) AND stem cell transplant

N=76 for ((Engraftment syndrome) OR (pre engraftment syndrome)) AND cord blood transplant

Malignancy of Donor Origin
The following PubMed searches were used:
N=211 for donor origin AND malignancy AND stem cell transplant
N=26 for donor origin AND malignancy AND cord blood transplant

Transmission of Serious Infection
The following PubMed searches were used:
N=48 for transmission of infection AND cord blood transplant
N=50 for donor AND transmission of infection AND stem cell transplant
N=20 for infection transmitted by transplant AND stem cell
N=13 for infection transmitted by transplant AND cord blood

Transmission of Rare Genetic Disorders
The following PubMed searches were used:
N=0 for cord blood transplant AND transmit AND genetic
N=0 for cord blood donor AND transmit AND genetic

Overdosage
The following PubMed searches were used:
N=53 for dmso AND intravenous AND toxicity
N=48 for dmso AND intravenous AND adverse
N=10 for dmso AND intravenous AND (Humans[Mesh] AND Clinical Trial[ptyp])
N=18 for dmso AND intravenous AND (Humans[Mesh] AND Case Reports[ptyp])

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9.2 Labeling Recommendations

The major recommendations for labeling resulting from this safety review are:

- Include a black box warning for fatal infusion reactions

- Include in the instructions for dosage a minimum TNC dose of 2.5 x 10^7 /kg at cryopreservation for units with at least 4 of 6 antigens matching for HLA-A,-B and -DR, and that the DMSO dose should not be greater than 1 mL/kg/day.

- Include in the instructions for administration the recommendations for prehydration, premedication, peri-infusion monitoring, and discontinuation of the infusion if an allergic reaction occurs or if the volume load is not tolerated.

- Include a contraindication for those who are allergic to DMSO or other components in the preparation for infusion.

- Include warning and precautions that address allergic reactions and anaphylaxis, infusion reactions, graft versus host disease, engraftment syndrome, graft failure, malignancies of donor origin, transmission of serious infection, and transmission of rare genetic disease.

- Identify the most common adverse reactions (>5%) as hypertension, nausea, vomiting, bradycardia, tachycardia, fever. Highlight the increased risk of grades 3-4 infusions reactions and hypertension in pediatric patients and with large volumes of infusate.

- Include a description of the clinical manifestations of DMSO overdosage and management of DMSO overdosage.

9.3 Appendices

9.3.1 The Cord Blood Transplantation Study Protocol (The COBLT Study)

Protocol Design

This is a prospective, open-label, single-arm, multicenter Phase 2A trial. The study sites include transplant centers, cord blood banks and a coordinating center. Each bank used the same protocol for recruiting donors, collecting, processing, testing, storage, retrieval from storage, reprocessing from the frozen state, and shipping. Each participating transplant center used the same patient selection criteria, preparative regimen for patients in the same class, initial graft-versus-host disease (GVHD) prophylaxis, indications for the use of cytokines, definitions for events and complications, and methods for evaluating immune reconstitution. Data were also collected on banked cord blood units to establish indicators of quality that correlated with patient outcome.

Objectives

1. The primary endpoint for the study of umbilical cord stem and progenitor cell transplantation is 180 day survival.

2. The secondary endpoints are:

- Disease-free survival (DFS)
- Long-term patient survival
- Incidence of neutrophil engraftment
- Incidence of both primary and secondary graft failure
- Incidence of platelet engraftment
- Incidence of RBC engraftment
- Incidence and severity of acute and chronic GVHD
- Incidence of complications, including infection, VOD, and interstitial pneumonitis
- Incidence of relapse
- Incidence of other malignancies, lymphoproliferative disorders, and post-transplant MDS
- Immune reconstitution

Key Eligibility Criteria

1. Eligible disease
    - Hematological malignancy – AML, ALL, CML, MDS, lymphoma without active CNS disease and without myelofibrosis >grade 2
    - Benign disorders – Marrow failure, inborn error of metabolism, primary immunodeficiency disorders

2. The cord blood unit for transplantation is at least 3/6 matched with recipient and has a minimum of $1x10^7$ TNC/kg cryopreserved
3. Meets defined minimum organ function

4. KPS ≥70% or Lansky ≥50%
5. Age <55 years
6. No uncontrolled infections and seronegative for HIV
7. Prior allogeneic transplantation >12 months from enrollment and prior autologous transplantation >6 months from enrollment.
8. Not pregnant or breast feeding
9. Able to provide consent

Treatment Plan

Upon registration, subjects were enrolled by disease category. Following retrospective high-resolution HLA typing, subjects were stratified as follows:

1. Malignant disease, 5/6 or 6/6 high resolution HLA match, ≤18 years of age
2. Malignant disease, 4/6 high resolution HLA match, ≤18 years of age
3. Malignant disease, 3/6 high resolution HLA match, ≤18 years of age
4. Malignant disease, 2/6 or 1/6 high resolution HLA match, ≤18 years of age
5. Severe aplastic anemia, Fanconi anemia and other marrow failure syndromes
6A. Inborn errors of metabolism/storage diseases
6B. Combined immune deficiencies
6C. Other non-malignant diseases not described above
7. Malignant disease alternative conditioning regimen (busulfan and melphalan)
8. Adult patients (> 18 years of age)

Multiple disease-specific myeloablative busulfan-based or TBI-based preparative regimens were specific in the protocol. GVHD prophylaxis consisted of cyclosporine and corticosteroids. Filgrastim was administered from Day 0 to ANC >2000. High-dose corticosteroids were to be administered for fever and erythroderma between days 5 and 9 (engraftment syndrome). Standard supportive care measures and infection prophylaxis were used.

Safety Monitoring

Study visits were scheduled weekly after transplantation for 14 weeks, and thereafter at day-100, day-120, day-150, 6 months, 9 months, 12 months, 19 months, 24 months, and 36 months.

The required examinations included:

1. Daily CBC, differential through neutrophil recovery; Post-engraftment: CBC and platelet count 3 times a week until discharge; Postdischarge: CBC and platelet count weekly until PRBC and platelet transfusion independent, and at Days 100, 180,270, and 360.
2. Reticulocyte count at 4 weeks post-transplant, then weekly until reticulocyte count > 30,000/mm^3 for two consecutive weekly measurements
3. Bone marrow aspirate on Day 42 for patients who do not have an ANC >500/mm^3 by Day 42
4. CMV surveillance should be performed according to institutional policy
5. For patients with CML, cytogenetic tests should be performed on bone marrow specimens

at 3, 6, and 12 months
6. For patients with lymphoma, radiologic studies which were positive prior to transplantation should be repeated at 3, 6, and 12 months
7. IgG, IgA, and IgM immunoglobulin levels at 6, 12, 18, and 24 months
8. Chimerism studies between Days 28 and 42, Day 100 and 1 year
9. Immune reconstitution at 1, 2, 3, 6, 9 (optional), 12, 18 (optional), 24, 36, and 48 months
10. Kamofsky/Lansky history and physical examination, CBC, renal and liver function tests, cardiac function tests (echocardiogram or MUGA scan), pulmonary function tests, thyroid function tests yearly for 4 years then as clinically indicated, height, weight, head circumference, if age appropriate
11. GVHD grading update weekly through day-100
12. Core toxicities

Endpoint Definitions

1. Primary Graft Failure is failure to achieve ANC > 500/mm^3 for three consecutive measurements on different days by Day 42. The first of the three measurements may occur on Day 42. The ANC recovery must be of donor origin documented by either bone marrow or peripheral blood chimerism assays indicating at least 90% of cells of donor origin. Infusion of stem cells prior to Day 42 will be considered primary graft failure.

2. Secondary Graft Failure: Documented engraftment as defined above followed by ANC < 500/mm^3 absence of donor cells in the marrow or blood as demonstrated by a chimerism assay without subsequent improvement occurring either spontaneously or after growth factor treatment.

3. Neutrophil engraftment is defined as achieving ANC >500/mm^3 for three consecutive measurements on different days by Day 42. The first of the three measurements may occur on Day 42. The ANC recovery must be of donor origin documented by either bone marrow or peripheral blood chimerism assays indicating at least 90% of cells of donor origin. A patient receiving a stem cell infusion prior to Day 42 will be considered a graft failure.

4. Platelet engraftment will be defined as the first day of a minimum of three consecutive measurements on different days such that the patient has achieved a platelet count > 50,000/mm^3 and is platelet transfusion independent for a minimum of seven days.

5. Time to red cell engraftment is defined as the first day of two consecutive measurements on different days such that the patient has achieved an absolute reticulocyte count > 30,000/mm^3.

6. Acute GVHD usually develops within the first three months after transplantation and appears as a characteristic dermatitis often accompanied by cholestasis and enteritis. The staging of acute GVHD will follow NMDP guidelines but will include weekly capture of symptoms and characterization of alternative causes.

7. Initial symptoms of chronic GVHD frequently include nausea and anorexia with ocular and oral sicca. Rash characteristically appears with pigmentary changes progressing to sclerosis and contractures. Other organs may be involved. Symptoms may mimic those seen in patients with scleroderma and other autoimmune disorders. Chronic GVHD typically does not occur until three or more months after transplantation. Details regarding the definition and diagnosis are listed in Appendix C

8. Veno-occlusive disease is defined by the occurrence of two of the following within 30 days of transplantation with no other explanation for these signs and symptoms present at time of diagnosis: hyperbilirubinemia (total serum bilirubin >2 mg/dL), hepatomegaly or right upper quadrant pain of liver origin, and sudden weight gain (> 5% of baseline body weight) because of fluid accumulation. Reversal of hepatic blood flow can frequently be demonstrated on doppler ultrasonography.

9. Interstitial pneumonitis is defined by diffuse interstitial infiltrates on chest x-ray not caused by fluid overload. It may be caused by a virus, bacteria, fungus, or may be of unknown etiology.

10. Infections will be graded according to the following severity scale:

- Mild, no active treatment (e.g., viral syndromes)
- Moderate, requires outpatient PO antibiotic
- Severe, requires N antibiotic or antifungal or hospitalization
- Life-threatening (e.g., septic shock)
- Caused or contributed to death

For infection as a secondary endpoint, only grades 3-5 infections will be considered.

11. The term relapse is used to describe the recurrence of disease after transplantation. For the purposes of this study, relapse will be defined separately for each disease eligible for transplantation. The time to relapse is the time to the first observation of hematologic or cytogenetic changes which result in characterization as relapse. Treatment given for relapse reversal will be considered indicative of relapse even in the absence of laboratory characteristics.

12. Infusion-related toxicities were graded using the NCI CTC system. Regimen-related toxicity was graded according to Bearmans's criteria

Analytic Plan

Accrual was planned to continue until up to 360 pediatric subjects enrolled. This would allow for an estimated 300 pediatric subjects with malignant diseases and at least 75 patients in the 3/6 and 4/6 strata.

The target day-180 survival is 60%. A sample size of 75 with a true survival proportion of 60% will provide 94% power to exclude a survival probability of 40%.

Primary endpoint - The primary analysis will consist of estimating the Day 180 survival probability based on the Kaplan-Meier product limit estimator for Strata 1 to 4 combined and

each strata separately. The Day 180 survival probabilities and confidence intervals will be calculated for each of these cells. All transplanted patients will be used in the analysis.

Secondary endpoints - Similar calculations will be performed for the secondary endpoints, e.g. neutrophil engraftment, red cell engraftment, platelet engraftment, overall survival, disease-free survival, acute GVHD, etc. The primary analysis of neutrophil graft failure will be conducted conditional on patients surviving at least 14 days.

Secondary analyses - Overall relapse rates will be estimated by Kaplan-Meier product limit curves using log-rank tests to compare strata. Adjustments will be made as necessary for covariates including age of recipient, disease risk status, interval between diagnosis and transplant, disease type, gender of donor, post-transplant chimerism, pre-transplant Kamofsky score, or other measure of performance status by use of proportional hazard or other multivariate models as appropriate. A secondary analysis of neutrophil graft failure will be conducted conditional on patients surviving at least 28 days. A secondary analysis will be performed on patients who fail to engraft. Incidence rates of both acute and chronic GVHD will be estimated using Kaplan-Meier product limit curves. Multivariate models will be employed to adjust for covariates. The interaction of cell dose and degree of HLA mismatch on transplant outcomes will be examined using appropriate statistical models. The secondary endpoint of infectious complications will be analyzed with respect to the number, the severity, and the subsequent complications of infectious episodes while controlling for important prognostic factors as previously described. Rates of other complications such as veno-occlusive disease and interstitial pneumonitis will be examined. Type and severity of adverse events will also be analyzed, including incidence of other malignancies, lymphoproliferative disorders, and post-transplant myelodysplasia.

9.3.2 The Cord Blood Transplantation Study Expanded Access Protocol (EAP)

Protocol Design

This is a prospective, open-label, single-arm, multicenter expanded access protocol for use of the cord blood units banked for The COBLT Study. Eligible subjects have a disease that warrant cord blood transplantation but are not eligible for the main protocol. Treatment is not standardized; all subjects are co-enrolled on an IRB-approved treatment plan or treatment protocol that vary by patient and/or institution. Patients are followed for 3 years. Safety and outcomes data are provided at specified time points on standardized data collection forms.

Objectives

Specific objectives were not stated in the expanded access protocol

Key Eligibility Criteria

1. Serious or life-threatening illness where cord blood transplantation is the only satisfactory treatment available.

2. Not eligible for The COBLT Study main protocol
3. The cord blood unit for transplantation is at least 3/6 matched with recipient
4. Able to provide consent
5. Co-enrolled on an IRB-approved treatment plan or treatment protocol

Treatment Plan

The preparative regimen, GVHD prophylaxis and supportive care measures were stipulated in the individual IRB-approved treatment plans or protocol and were not standardized in the expanded access protocol.

Safety Monitoring

Safety monitoring proceeded according to the individual IRB-approved treatment plans or protocol. Standardized registry safety and outcomes data forms were to be completed pretransplantation, at days 28 and 42, and after transplantation at day 100 and 6, 12, 24 and 36 months.

Safety Analytic Plan

The anticipated sample size is 60 subjects.

Primary endpoint - The primary analysis will consist of estimating the Day 180 survival probability based on the Kaplan-Meier product limit estimator. The analysis will include the confidence interval for this probability.

Secondary endpoints - Similar calculations will be made for the secondary endpoints , e.g. neutrophil engraftment, red cell engraftment, platelet engraftment, survival, and acute GVHD

Secondary analyses - A secondary analysis of neutrophil graft failure will be conducted conditional on patients surviving at least 28 days. A secondary analysis will be performed on patients who fail to engraft. Incidence rates of both acute and chronic GVHD will be estimated using Kaplan-Meier product limit curves. Multivariate models will be employed to adjust for covariates. The interaction of cell dose and degree of HLA mismatch on transplant outcomes will be examined using appropriate statistical models. The secondary endpoint of infectious complications will be analyzed with respect to the number, the severity, and the subsequent complications of infectious episodes while controlling for important prognostic factors as previously described. Rates of other complications such as veno-occlusive disease and interstitial pneumonitis will be examined. Type and severity of adverse events will also be analyzed, including incidence of other malignancies, lymphoproliferative disorders, and posttransplant myelodysplasia.