

¹Duke University Medical Center, Durham, North Carolina, United States; ²The EMMES Corporation, Rockville, Maryland, United States; ³University of Minnesota, Minneapolis, Minnesota, United States; ⁴University of California, San Francisco, San Francisco, California, United States; ⁵Texas Transplant Institute, San Antonio, Texas, United States; ⁶Children's Hospital of Los Angeles, Los Angeles, California, United States; ⁷Dana Farber Cancer Institute, Boston, Massachusetts, United States; ⁸The Mattel Children’s Hospital, Los Angeles, California, United States; and ⁹Memorial Sloan-Kettering Cancer Center, New York, New York, United States. The trial was sponsored by the ¹⁰National Heart, Lung and Blood Institute, Bethesda, MD, USA.

A complete list of the members of the COBLT Steering Committee appears in the “Appendix.”

Correspondence and Reprints: Joanne Kurtzberg, Duke University Medical Center, Box 3350, Durham, NC 27710, Phone: 919-668-1119; Fax: 919-668-1183; Email: kurtz001@mc.duke.edu.

Running Head: UCBT in pediatric malignancies
Scientific Category: Transplantation

Presented in part at Tandem BMT Meetings, February 10 - 14, 2005, Keystone, CO
ABSTRACT

Outcomes of unrelated donor cord blood transplantation (UCBT) in 191 hematologic malignancy children (median age and weight - 7.7 years; 25.9 kg) enrolled between February 1999 and September 2003 and given identical cytoreduction, graft-versus-host disease (GvHD) prophylaxis and supportive care were studied (median follow-up 27.4 months) in a prospective Phase II multi-center National Heart, Lung, and Blood Institute sponsored Cord Blood Transplantation Study (COBLT). HLA matching at enrollment was 6/6(n=17), 5/6(n=58), 4/6(n=111) or 3/6 (n=5) by low-resolution molecular typing for HLA-A, -B and high-resolution (HR) DRB1. Retrospectively, 179 pairs were HLA typed by HR. The median pre-cryopreservation total nucleated cell (TNC) dose was 5.1×10^7TNC/kg (range 1.5-23.7) with 3.9×10^7TNC/kg (range 0.8-22.8) infused. The median time to engraftment (ANC>500/mm^3 and platelets 50K/uL) were 27 and 174 days. The cumulative incidence (CINC) of neutrophil engraftment by day 42 was 79.9%(95%CI 75.1%-85.2%); acute grades III/IV GvHD by day 100 was 19.5%(95%CI 13.9-25.5); and chronic GvHD at 2 years was 20.8%(95% CI 14.8-27.7). HR matching decreased the probability of severe acute GvHD. The CINC of relapse at 2 years was 19.9%(95%CI 14.8-25.7). The probabilities of 6-month and 2-year survivals were 67.4% and 49.5%. UCBT from partially HLA-mismatched units can cure many children with leukemias refractory to standard therapy. The study was registered on the clinicaltrials.gov website with registration number NCT00000603.

Key Words:  Cord Blood Transplantation;
            Acute Lymphoblastic Leukemia;
            Acute Myelogenous Leukemia;
            Pediatric Leukemias
            Hematopoietic Stem Cell Transplantation
            Unrelated donor
INTRODUCTION

Despite major advances in curing children with leukemias over the last 30 years, approximately 20% of patients relapse and are candidates for transplantation\(^1,2\). Many of these patients will not be able to identify a matched related or unrelated bone marrow donor in a timely fashion\(^3\). Partially HLA-mismatched unrelated donor cord blood is readily available for the majority of these patients. While results of unrelated donor cord blood transplantation (UCBT) in children with hematological malignancies have been published from registry data\(^4-9\), no prospective, multi-center study has been reported to date.

The COBLT study was an NHLBI-sponsored, Phase II, multi-center study designed to establish public cord blood banks following common standards and operating procedures\(^10,11\) and to determine through a multicenter clinical trial if banked unrelated donor umbilical cord blood could serve as an adequate hematopoietic stem cell source for adults\(^12\) and children with malignancies, immune deficiencies, inherited marrow failure, or inborn errors of metabolism\(^13,14\). The largest stratum studied pediatric patients with hematologic malignancies. We now report the outcomes of UCBT in the pediatric patients enrolled on this stratum of the COBLT trial.

MATERIALS AND METHODS

**Study Overview:** The transplant protocol for pediatric malignancies was approved at the Institutional Review Board of each of the 26 participating institutions. The first and last patients were transplanted in March of 1999 and October of 2003, respectively. All subjects or their legal guardian were required to give written informed consent prior to enrollment in accordance with the Declaration of Helsinki.
**Patients:** Eligible subjects were pediatric patients diagnosed with a hematologic malignancy that relapsed or were at very high risk of relapse on frontline therapy (remission induction failures, Ph+, hypodiploid). Patients with acute lymphoblastic leukemia (ALL) with very high risk features were eligible in first complete remission (CR) along with all patients with ALL in 2nd or subsequent CR (CR1<18 months, or ≥CR3) or relapse. Patients with acute myeloid leukemia (AML) were eligible in any CR or relapse. Patients with chronic myeloid leukemia (CML) were eligible in chronic or accelerated phase. Patients with active central nervous system (CNS) disease, human immunodeficiency virus (HIV) seropositivity, Lansky performance scores less than 50%, age >18 years, primary myelofibrosis, suitable related (5/6 or 6/6 matched) donors were ineligible. Patients with prior allogeneic stem cell transplant within 12 months, or autologous transplant within 6 months, were excluded, as were individuals with uncontrolled infections. Patients had to have adequate organ function and no contraindication to TBI therapy. Patients could not have an available matched related donor or an unrelated matched donor who could be harvested in a timely manner.

**Donor Characteristics:** All patients were transplanted with a single cord blood unit which provided a minimum of $1 \times 10^7$ total nucleated cells (pre-cryopreservation) per kg of recipient weight. The donor units were required to match the patient at a minimum of 4/6 HLA loci using low/intermediate resolution typing at HLA Class I A and B and high resolution typing at DRB1 or at 3/6 loci if there was molecular (high resolution) matching at 1 allele of each locus (HLA-A, HLA-B, HLA-DRB1). Matching was not required at HLA-C or DQB1 but was evaluated at some centers. Units were obtained from COBLT, the New York Blood Center or National Marrow Donor program (NMDP) U. S. cord
blood banks. The HLA matching between the CBU and the patient as determined by low/intermediate molecular typing for class I HLA-A and HLA-B alleles, and high resolution molecular typing for HLA-DRB1 alleles at the time of enrollment was referred to as “original HLA typing”.

**Retrospective HLA Typing:** Retrospective typing was performed at increasing levels of resolution, including allele level typing, until a mismatch was discovered on 179 donor/recipient pairs, at two reference laboratories (Baxter-Lowe’s laboratory at University of California San Francisco and the Naval Medical Research Institute laboratory) for HLA-A and HLA-B. High resolution typing for HLA-DRB1 was available on these 179 pairs from the pre-transplant analysis. New HLA data is referred to as “final HLA typing” and used as a separate variable for outcomes analysis.

**Preparative Regimen, Graft versus Host Disease (GvHD) Prophylaxis and Supportive Care:** The conditioning regimen consisted of 1350 cGy of TBI given in 9 BID fractions (150 cGy) on days –8 through –4. Cyclophosphamide 60 mg/kg was administered on days –3 and –2. Methylprednisolone 1 mg/kg was given prior to each dose of anti-thymocyte globulin (equine) of 15 mg/kg BID on days –3 through –1. GvHD prophylaxis included methylprednisolone 0.5 mg/kg BID on days +1 thru +4, 1 mg/kg BID beginning day +5 and continuing until the ANC reached 500/mm³, and then tapered. Cyclosporine was permitted to begin between days -3 and -1 and was dosed to achieve trough levels measured by polyclonal immunoassay of ≥200 ng/ml when administered by bolus dosing or 400 ng/ml when administered by continuous infusion. Cyclosporine prophylaxis was continued for at least 6 months and then tapered per institutional protocol. Granulocyte colony stimulating factor (G-CSF) was administered
to all patients beginning on day 0 and continued until engraftment. All patients were supported with empiric antibiotic therapies for fever; anti-fungal, anti-viral and anti-pneumocystis carinii pneumonia prophylaxis and IVIG according to institutional practices. Cytomegalovirus (CMV) was monitored by weekly antigen or PCR screening and pre-emptive therapy was initiated with ganciclovir and CMV immune globulin if rising CMV in the blood or signs of clinical disease were observed. Acute and chronic graft versus host disease was scored according to the standard criteria.15;16

**Transplantation Procedure:** CBUs were thawed, washed and processed according to the standard procedures provided by the study. All centers were trained in and used the same thawing procedure to prepare the cord blood unit for infusion. The total number of nucleated cells, clonal hematopoietic progenitor cells, CD3+ and CD34+ cells were counted, ABO and Rh typing were performed, cell viability was assessed and bacterial and fungal cultures obtained both at the time of banking and thawing. There was no special treatment of the cord blood if ABO and/or RH incompatibility was present because overall RBC content was small and isoagglutinins are not present in cord blood. After processing the CBU was brought to the bedside and infused through a central venous line over 10-30 minutes.

**Study Endpoints and Statistical Analysis:** The primary endpoint of the study was survival at 180 days post-transplant. The secondary endpoints included engraftment (neutrophil and platelet), acute and chronic GvHD, disease-free survival, long-term survival, relapse and regimen related toxicities. The impact of HLA match, cell dose, race or ethnicity, disease status, age, performance status, risk status and patient CMV seropositivity were assessed. Risk status is defined in Table 1. Neutrophil engraftment
was defined as the first of 3 consecutives days of achieving an absolute neutrophil count of 500/uL with >90% donor cell chimerism. Platelet engraftment was defined as achieving a platelet count of 50k/uL without transfusion support for 7 days. Primary graft failure was defined as failure to reach an ANC of 500/uL by day +42. Secondary graft failure was defined as either severe persistent neutropenia unresponsive to growth factor therapy or loss of donor chimerism after initial engraftment. Relapse was defined as >25% blasts in the blood or bone marrow or >5% blasts in the bone marrow with reappearance of the original cytogenetic abnormality associated with patient's malignancy or >5% blasts in the bone marrow on multiple occasions or any extramedullary relapse. Infection and toxicity were graded as outlined (<https://web.emmes.com/study/cord/protocol.htm>). Infections were graded according to the IBMTR grading system operative at the start of the protocol in 1999.

Survival estimates were calculated using the Kaplan-Meier method. Testing for differences in survival between groups in the univariate analysis used the log-rank test. Cumulative incidence curves were used for engraftment and GvHD endpoints with death as a competing risk. The Cox proportional hazards model with backward elimination was used for multivariate testing of covariates on the major endpoints. No imputation was used for missing data. All analyses were performed by statisticians at the Data Coordinating Center using SAS software, version 8.2 (SAS Institute Inc, Cary, NC).
RESULTS

**Patient Enrollment:** A total of 193 children (age<=18) were enrolled from 22 centers; 2 died prior to transplant. All patients were followed for a minimum of 6 months with a median follow-up of 27.4 months (8.8 – 63.6 months).

**Patient Characteristics:** Baseline characteristics of enrolled patients are shown in Table 2A. The majority of patients either ALL (n=109, 57%; 17 - 1st CR, 65 - 2nd CR, 20 - 3rd CR, 6 - relapse, 1 - primary induction failure) or AML (n=51, 27%; 13 - 1st CR, 21 - 2nd CR, 6 – primary induction failure and 11 - relapse). The remaining patients had myelodysplastic syndrome (8%, 2 with Kostmann’s), lymphoblastic lymphoma (3%), CML (4%), juvenile myelomonocytic leukemia (0.5%), and biphenotypic leukemia (1%). Most patients (77%) were high risk as defined in Table 1. The median age of the patients was 7.7 years (range 0.9-17.9 years), median weight was 25.9 kg (range 7.5-118.4 kg), 40% were non-Caucasian, 61% were male and 51% were seropositive for CMV. The Lansky performance status was >80 for 85% of patients. No patient had a previous autologous transplant while 1 patient had relapsed after a previous allogeneic transplant.

**Patient/Donor Characteristics:** COBLT banks supplied donor units for 61% of transplants. Donor characteristics are shown in Table 2B. The median TNC, CD34+ and CD3 doses in the cryopreserved grafts were $5.1 \times 10^7$ cells/kg (range 1.5-23.7), $1.9 \times 10^5$/kg (range 0.0-25.3) and $7.9 \times 10^6$/kg (range 0.1-35.6), respectively. Sixty-eight percent of the donor/recipient pairs were ABO matched while 88% were Rh matched (Table 2B). Recipients and donors were matched for ethnicity in 61% and matched for gender in 50%.
**Neutrophil Recovery:** The cumulative incidence of neutrophil recovery (ANC ≥ 500/mm³) by day 42 was 79.9% (95% CI 75.1%, 85.2%) as shown in Figure 1A. An additional fourteen patients recovered neutrophils between days 43-90. At 6 and 12 months, 86.9% of patients had sustained neutrophil engraftment. The median time to neutrophil recovery was 27 days (range 11-90). Primary and secondary graft failure occurred in 21 and 2 patients, respectively.

In univariate analysis, lower recipient weight (p=0.02), higher original HLA match (p=0.03), increasing TNC (p=0.03) and CD34+ dose (p=0.01) positively impacted neutrophil recovery. In a multivariate Cox model, both original HLA match (p=0.04) and TNC dose were independently significant (p=0.04) (Table 3).

**Platelet Recovery:** CINC and 1- Kaplan-Meier estimates of platelet engraftment (≥ 50K/mm³) are displayed in Figure 1B. By day 180, the CINC for platelet engraftment was 50.0% (95% CI 42.1, 56.5) and the Kaplan-Meier estimate of platelet engraftment was 63.0% (95% CI 54.8, 71.2). At 1 year post transplant, 87% of surviving patients had achieved a platelet count >50K/uL. The median duration to platelet engraftment was 174 days (range 21-353). In univariate analysis, lower recipient age (p=0.02) and weight (r p=0.02), Caucasian recipient race (p=0.07), higher TNC (p=0.01) and higher CD34+ cell dose (p=0.03) favorably impacted time to platelet engraftment. In multivariate analysis, only higher TNC (>5.1x10⁷/kg; p=0.03) was significant (Table 3).

**GvHD:** Acute GvHD was graded by center and then reviewed retrospectively by an independent panel\(^1\). The CINC of grades II-IV aGvHD was 41.9% (95% CI, 34.4, 48.7)
with death as a competing risk. Thirty-eight patients (CINC 19.5% (95% CI 13.9, 25.5) had grades III/IV aGvHD (Figure 1C). In univariate analysis, the factors affecting aGvHD were original HLA match and gender. In multivariate analysis, original HLA match of 5/6 or 6/6 versus 4/6 had a hazard ratio of 1.66 (95% CI 1.04, 2.63) (Table 3). High resolution HLA analysis revealed that the probabilities of Grades II-IV (p=0.02) and grades III-IV (p=0.02) aGvHD was significantly higher if the pairs were less than 5/6 matched. In addition, female patients had a significantly higher aGvHD. Other variables considered were post-thaw infused TNC, CD3+, CD34+, recipient/donor gender and recipient/donor ethnicity, but these were not significant.

At 2 years post-transplant the CINC of cGvHD was 20.8% (95% CI 14.8, 27.7) (Figure 1D). The majority of these patients (68%) had limited disease. In a multivariate analysis, younger and female patients had an increased risk of cGvHD (Table 3).

**Infection, Hospitalization and Toxicity:** Maximum toxicity in any organ system by day 42 was 23% grade 0/1, 49% grade 2, 24% grade 3 and 5% grade 4 using the Bearman scale20. Seizures occurred in 34 patients, 20 between days 28-42. At least one severe life-threatening or fatal infection was reported in 166 patients within the first 6 months post-transplant. Bacterial infections were reported in 77% of patients, fungal infections in 33% and viral infections in 61%. Two or more infections were experienced by 77% of patients. Of the 762 infectious episodes, 368 (48%) were attributed to bacteria, 258 (34%) to viruses, and 84 (11%) to fungi.

**Relapse:** The CINC of relapse at 2 years post-transplant was 19.9% (95% CI 14.8-25.7) (Figure 2A). Univariate analyses showed female gender (p<0.01), ABO mismatch
(p=0.02), smaller TNC (p=0.04) and CMV seropositive patient (p<0.01) as significant predictors of relapse. In the multivariate analysis, patients with pre-transplant CMV seropositivity (p<0.01), mismatched donor/recipient ABO (p=0.03), and female recipient gender (p=0.01) were at a significantly increased risk of relapse (Table 3). In patients with ALL or AML, disease status at transplant was also predictive of relapse and patients in first or second CR were significantly better off than those in 3rd CR or relapse (Figures 2B, 3C and 3D).

**Survival:** Survival analysis is based on 191 patients who underwent the transplant procedure. Survival was measured from the date of transplant to date of death and was censored for survivors at the date of the last follow-up. Overall survival was 67.4% (95% CI, 60.7, 74.1) at day 180, 57.3% (95% CI, 50.2, 64.3) at 1 year and 49.5% (95% CI 42.3%-57.0%) at 2 years (Figure 3A). In univariate analysis, age, weight, gender, donor gender, donor/recipient gender combination, ethnicity, donor/recipient ethnicity combination, primary disease, pre-cryo CD34+ dose, pre-cryo CD3+ dose, pre-cryo TNC dose, original HLA match, retrospective HLA match, performance status, risk, CMV and ABO matching were evaluated. Gender, ethnicity (Caucasian), CMV pre-transplant (negative) (Figure 3C), Lansky performance status (>80%), original HLA match (6/6 match), final HLA match (6/6 match), ABO match (matched), and cell dose (>2.5× 10^7/kg) were favorable. In multivariate analysis, CMV (p<0.01), ABO match (donor to recipient) (p=0.02), recipient gender (p<0.01) and TNC (p=0.04) were the only variables that remained significant for survival (Table 3).

**Causes of Death:** Ninety-five of the 193 enrolled patients have died, and 93/191 transplanted patients have died. Sixteen patients died from graft failure, 25 from GvHD
(18 Acute and 7 Chronic), 9 from infections, 37 from relapse, 4 from organ failure, 1 from pulmonary hemorrhage, and 1 from Epstein-Barr virus post-transplant lymphoproliferative disease. Infection was the secondary cause of death in 29 patients. There were 23 graft failures (21 primary and 2 secondary) of which 19 died (12 of graft failure, 4 from aGvHD + graft failure and 3 who relapsed before day 42). The cumulative incidence of regimen related mortality at 100 Days was 17.0% (95% CI, 11.7, 22.8). The probability of non-relapse mortality at 6 months was 25.8% (95% CI 18.6%-31.9%).

**HLA Matching**: By original HLA typing, the majority of recipient/donor pairs were mismatched in both the GvHD and rejection directions at either one (30%) or two (58%) loci (Table 2C). Only 9% of the pairs were 6/6 matched. Analysis of original HLA match by final HLA match in either the GvHD or rejection direction is given in Table 2C. Overall, HLA matching was demoted in 32% of recipient/donor pairs when comparing original to final HLA match. Of 111 patients who were originally a 4/6 match, 8 were determined to be a 2/6 match and 30 to be a 3/6 match. Similarly, of the 58 patients originally considered to be a 5/6 match, 11, 2 and 1 were determined to be 4/6, 3/6 and 2/6, respectively, following high resolution typing. Of 17 patients originally a 6/6 match, 2 were found to be a 5/6 and 1 a 3/6 match by high resolution typing.

**DISCUSSION**

We describe the results of the first prospective, multi center, national trial of UCBT in 193 pediatric patients with hematologic malignancies. The study was undertaken to examine the outcomes of these transplants and determine the usefulness of unrelated
banked cord blood units in expanding the donor pool for children with leukemia in need of transplant but lacking adult BM donors. To answer above question, only the patients that did not have a matched related or unrelated adult donor who was available for transplant in a timely manner were enrolled on the study. The majority of patients (91%) received partially HLA mismatched grafts and 40% represented ethnic minorities. All patients received a common conditioning regimen, GvHD prophylaxis and similar supportive care. The majority of the children had high risk leukemia (77%) and a good performance status score (84.8%). This study on the outcome of UCBT in this well-defined cohort provides very useful information. The overall survival in our patient population at 6 months and 1 year were 67.4 and 57.3%, respectively. These results are compared favorably to those published from registry data\textsuperscript{7,21}. The CINC of neutrophil recovery with donor cells by day +42 was 79.9%. Grades III/IV acute and overall chronic GvHD occurred in 19.5% and 20.2% of patients, respectively. Leukemic relapse occurred in 18.6% of patients with very few relapses after the first post-transplant year. The most common primary causes of death were relapse (40%), GvHD (27%) with or without infection, and graft failure (17%).

Higher total nucleated cell (TNC) dose (>5.1x10\textsuperscript{7}/kg vs. \leq 5.1x10\textsuperscript{7}/kg) significantly improved the engraftment of neutrophils (p=0.03) as well as the platelets (p=0.03). The median cell dose of units selected and infused for transplantation in this pediatric patient cohort (selected pre-cryopreservation count 5.1x10\textsuperscript{7}, infused 3.9x10\textsuperscript{7}) were larger than those previously reported in registry series\textsuperscript{21}. Patients receiving grafts selected to deliver a cell dose of \leq 2.5x10\textsuperscript{7} cells/kg had lower and slower engraftment than patients above this threshold (p=0.04). In addition, patients receiving grafts containing pre-cryopreserved TNC of \leq 2.5x10\textsuperscript{7} cells/kg had significantly lower overall survival (p=0.04).
On the basis of these findings we recommend that UCB grafts selected for pediatric patients receiving myeloablative transplants for hematological malignancies contain greater than $2.5 \times 10^7$ cells/kg based on the pre-cryopreservation total nucleated cell count.

We examined the significance of retrospective high resolution HLA matching between donor and recipient. Original matching was based on low/intermediate resolution HLA Class I A and B typing and high resolution DRB1 typing. When typed at high resolution for all 6 alleles, approximately 1/3 of the pairs were found to be more disparate. On multivariate analysis, higher original HLA match ($\geq 5/6$ vs. $\leq 4/6$) improved the engraftment of neutrophils ($p=0.04$) but had no impact on the engraftment of platelets. Again on multivariate analysis, the level of HLA matching at original typing had no impact on the occurrence of moderate-severe (grade II-IV) or severe (III-IV) acute GvHD. However, high resolution retrospective typing revealed that the probability of developing severe (grade III-IV) was significantly higher ($p=0.02$) if the donor/recipient pair were matched for less than 5/6 alleles. In this patient cohort, the impact of original HLA match and final HLA match on graft failure and relapse did not reach statistical significance, possibly due to the small number of events. The impact of original and retrospective HLA matching on overall survival was also examined (Figures 3E and 3F). When original typing was considered, there was no difference in survival for patients receiving 5/6 or 4/6 matched grafts. There was, however, a trend for a survival advantage for the small number of patients ($n=17$) receiving 6/6 matched grafts ($p=0.07$). Conversely, the small number of patients transplanted with 3/6 matched grafts ($n=5$) trended towards poorer survivals ($p=0.08$). By retrospective, high resolution, HLA matching, there appeared to be a trend towards a survival advantage.
for patients receiving 6/6 matched grafts (n=16, p=0.12) although there was no statistically significant difference in overall survival between patients receiving 4/6 or 5/6 matched grafts. However the small numbers of patients in this study may have decreased the statistical power of this analysis. On the basis of current data we recommend selecting UCB units that are at least 4/6 by low/intermediate resolution typing at HLA Class I (-A and -B) and high resolution typing at DRB1.

On multivariate analysis, the incidence of acute GvHD was favorably influenced by matching for HLA and male gender. The incidence of chronic GvHD was significantly higher in female patients and younger age of the patient. Male gender, ABO matching and negative pre-transplant recipient CMV serostatus were all protective against relapse. Overall survival was favorably impacted by pre-transplant CMV seronegativity of the recipient, recipient male gender, donor/recipient ABO matching (matched), HLA match (5/6 of 6), and TNC (higher TNC). Patients with ALL in CR1/CR2 fared significantly better than those in subsequent CR/Relapse. In a recently reported correlative sub-study, patients capable of mounting T-cell proliferative responses to Herpes viruses had a lower probability of relapse and higher overall survival. It is important to note that the overall survival in the minority patients was similar to that seen in Caucasian patients (p=0.13).

It is interesting that many outcome measures showed advantage for a male recipient. On multivariate analysis, boys had lower incidence of Grade II-IV acute GvHD (HR-1.78; p=0.01), lower relapse rates (HR-2.34; p=0.01), and better survival (HR-1.74; p<0.01). These observations about gender differences may be clinically important. It is possible that the gender differences in the biology of leukemia may be contributing to
these observations. However, we have seen higher survival in boys with inherited metabolic disorders undergoing UCBT\textsuperscript{23}. One might speculate that disparities of the H-Y minor histocompatibility antigens may be contributing to these findings. This hypothesis should be tested in a much larger series of patients to be accepted as valid.

Engraftment did not occur in 12% of the patients enrolled on this study in spite of the fact that the median cell dose was adequate. Other factors delaying or preventing engraftment included viral infections, persistent leukemic relapse and inadequate host immunosuppression. Novel approaches to increasing engraftment include the use of two cord bloods for a single transplant\textsuperscript{24} which appears in pilot studies to increase the incidence of engraftment to 95% in adults. Augmentation of immunosuppression with pre-transplant fludarabine may also facilitate engraftment of these lower cell dose grafts.

In another strata of the COBLT study, children (n=32) with infant leukemia who received non-limiting cell doses of TNC/kg, CD3+ cells/kg and CD34+ cells/kg, we noted similar estimates of neutrophil recovery and grade III-IV acute GvHD at day 100 and chronic GvHD.\textsuperscript{(14)} Notably in that cohort, higher-level HLA match showed improved survival with the difference being statistically significant when considering the final high resolution HLA -A, -B and -DRB1 match. Conversely, the cohort of children with metabolic diseases (n=69), also receiving comparable cells doses to those with infant leukemia; HLA did not influence engraftment, GvHD or survival\textsuperscript{25}. In the present study HLA matching by low or high resolution criteria did not show conclusive impact on survival. These observations in different COBLT strata may reflect limited power of the data due to small sample sizes. High resolution HLA matching did decrease the risk of
GvHD and it is possible that the overall survival may remain unchanged due to the competing contributions of GvHD and graft-versus (GvL) effects. Further analysis in larger series will hopefully provide more conclusive observations about the impact of HLA matching and cell doses on the outcomes of UCBT.

More than 50% of the patients requiring hematopoietic stem cell transplantation are unable to find a suitable adult stem cell donor in a timely fashion, making donor availability a major obstacle to effective anti-leukemic therapy. Banked umbilical cord blood is prospectively HLA typed, screened for infections and other risk factors and is readily available for use in patients who cannot identify a matched related or unrelated donor. The results using banked unrelated donor umbilical cord blood to treat children with hematological malignancies presented in this study are similar to those reported using related and unrelated donor bone marrow in children with leukemia. Furthermore, as shown with bone marrow donors, transplantation in earlier stages of disease results in higher overall survival and leukemic cure. Thus, children who have high risk leukemia or have relapsed after standard therapy who do not have matched related or unrelated adult donors should be immediately referred and evaluated for unrelated donor cord blood transplantation before their disease status worsens decreasing their chances for successful outcomes with transplantation therapy.
ACKNOWLEDGEMENTS

We greatly appreciate the dedication and outstanding care delivered to these patients by their nurses, nurse practitioners, nurse coordinators, social workers, physical, speech and occupational therapists, and other allied health care professionals. We are indebted to Ms. Angela Norman for assistance in the manuscript preparation.

Supported by a contract from the National Heart, Lung and Blood Institute (N01-HB-67138 [JK], N01-HB-67132 [SLC], N01-HB 67139 [JEW], and N01-HB 67135 [NK]).

AUTHORSHIP CONTRIBUTION:

JK, SC, JEW, SF, EG, and NK were PI's on the COBLT study and responsible for conceptualization of the study, collection of clinical data, primary analysis and interpretation of the data as well as writing and editing the manuscript. JK was the PI responsible for the initial analysis and interpretation of data as well as writing and editing the manuscript. VKP was involved with analysis and interpretation of the data and writing and editing of the manuscript. LAB-L was a member of the steering committee and was involved in the conceptualizing and planning of the HLA part of the study; her laboratory provided prospective and retrospective HLA typing and was involved in auditing the HLA data; DW was involved with analysis and interpretation of the data. EW was involved with oversight of and collection of clinical data and preparation and review of the manuscript. NAK was the chair of the COBLT Steering committee and was involved in conceptualizing the study, analysis and interpretation of the data as well as editing the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.
Reference List


Table 1: Definition of Risk Status

<table>
<thead>
<tr>
<th>Diagnosis and disease status</th>
<th>Risk for poor outcome secondary to TRM or relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL-CR1</td>
<td>LOW</td>
</tr>
<tr>
<td>Remission induction failure</td>
<td>LOW</td>
</tr>
<tr>
<td>Philadelphia Chromosome +</td>
<td>LOW</td>
</tr>
<tr>
<td>ALL-CR2</td>
<td>LOW</td>
</tr>
<tr>
<td>Length of CR 1 ≤ 18 mos</td>
<td>HIGH</td>
</tr>
<tr>
<td>ALL ≥ CR3 or Relapse</td>
<td>HIGH</td>
</tr>
<tr>
<td>AML-CR1</td>
<td>LOW</td>
</tr>
<tr>
<td>Remission Induction Failure</td>
<td>LOW</td>
</tr>
<tr>
<td>Monosomy 7, tri 8</td>
<td>HIGH</td>
</tr>
<tr>
<td>5q-</td>
<td>LOW</td>
</tr>
<tr>
<td>Prior MDS</td>
<td>HIGH</td>
</tr>
<tr>
<td>Taml</td>
<td>HIGH</td>
</tr>
<tr>
<td>AML-2CR- any length of 1st CR</td>
<td>LOW</td>
</tr>
<tr>
<td>Remission Induction Failure</td>
<td>LOW</td>
</tr>
<tr>
<td>Monosomy 7, tri 8</td>
<td>HIGH</td>
</tr>
<tr>
<td>5q-</td>
<td>LOW</td>
</tr>
<tr>
<td>Prior MDS</td>
<td>HIGH</td>
</tr>
<tr>
<td>tAML</td>
<td>HIGH</td>
</tr>
<tr>
<td>AML ≥ 3CR or Relapse</td>
<td>HIGH</td>
</tr>
<tr>
<td>JMML</td>
<td>HIGH</td>
</tr>
<tr>
<td>CML-2nd CP, AP, BL</td>
<td>HIGH</td>
</tr>
<tr>
<td>*Infant Leukemia</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

*Definition of Infant Leukemia—Diagnosis prior to 6 months or diagnosis prior to 1 year and MLL+ [or other cytogenetic abnormalities consistent with MLL+ such as t(4;11), 11q23+ or t(9;11)].
Table 2. Baseline Characteristics

2A. Patient Characteristics (N=191)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age (years): Median (Range)</td>
<td>7.7</td>
<td>(0.9, 17.9)</td>
</tr>
<tr>
<td>Patient Weight (kg): Median (Range)</td>
<td>25.9</td>
<td>(7.5, 118.4)</td>
</tr>
<tr>
<td>Patient Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>116</td>
<td>(60.7)</td>
</tr>
<tr>
<td>Female</td>
<td>75</td>
<td>(39.3)</td>
</tr>
<tr>
<td>Patient Blood Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>72</td>
<td>(37.7)</td>
</tr>
<tr>
<td>B</td>
<td>22</td>
<td>(11.5)</td>
</tr>
<tr>
<td>AB</td>
<td>4</td>
<td>(2.1)</td>
</tr>
<tr>
<td>O</td>
<td>93</td>
<td>(48.7)</td>
</tr>
<tr>
<td>Patient Ethnicity/Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>115</td>
<td>(60.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>36</td>
<td>(18.9)</td>
</tr>
<tr>
<td>Black</td>
<td>24</td>
<td>(12.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>8</td>
<td>(4.2)</td>
</tr>
<tr>
<td>Mixed</td>
<td>6</td>
<td>(3.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Patient Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>109</td>
<td>(57.1)</td>
</tr>
<tr>
<td>Primary Induction Failure</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CR-1</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>CR-2</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>CR&gt;2</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>51</td>
<td>(26.7)</td>
</tr>
<tr>
<td>Primary Induction Failure</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>CR-1</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>CR-2</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td>13</td>
<td>(6.8)</td>
</tr>
<tr>
<td>CML</td>
<td>7</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Lymphoblastic Non-Hodgkins Lymphomas</td>
<td>6</td>
<td>(3.1)</td>
</tr>
<tr>
<td>Bi-phenotypic</td>
<td>2</td>
<td>(1.1)</td>
</tr>
<tr>
<td>MDS with Kostmann’s Congenital Agranulocytosis</td>
<td>2</td>
<td>(1.1)</td>
</tr>
<tr>
<td>JMML</td>
<td>1</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Risk Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>44</td>
<td>(23.0)</td>
</tr>
<tr>
<td>Poor</td>
<td>147</td>
<td>(77.0)</td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>162</td>
<td>(84.8)</td>
</tr>
<tr>
<td>&lt;=80</td>
<td>29</td>
<td>(15.2)</td>
</tr>
<tr>
<td>CMV Serostatus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>98</td>
<td>(51.3)</td>
</tr>
<tr>
<td>Negative</td>
<td>92</td>
<td>(48.2)</td>
</tr>
<tr>
<td>Not Tested</td>
<td>1</td>
<td>(0.5)</td>
</tr>
</tbody>
</table>
### 2B. Patient/Donor Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Pre-Cryopreserved Nucleated Cell Dose (× 10⁷/kg)</td>
<td>5.1 (1.5 – 23.7)</td>
</tr>
<tr>
<td>Pre-Cryopreserved CD34+ Cell Dose (× 10⁵/kg) (n=160)</td>
<td>1.9 (0.0 – 25.3)</td>
</tr>
<tr>
<td>Pre-Cryopreserved CD3+ Cell Dose (× 10⁶/kg) (n=119)</td>
<td>7.9 (0.1 – 35.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source of Unit</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COBLT</td>
<td>116</td>
<td>(60.7)</td>
</tr>
<tr>
<td>non-COBLT</td>
<td>75</td>
<td>(39.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donor Race</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>118</td>
<td>(61.8)</td>
</tr>
<tr>
<td>Black</td>
<td>21</td>
<td>(11.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>19</td>
<td>(10.0)</td>
</tr>
<tr>
<td>Mixed</td>
<td>10</td>
<td>(5.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>8</td>
<td>(4.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
<td>(7.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donor Gender</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>102</td>
<td>(53.4)</td>
</tr>
<tr>
<td>Female</td>
<td>85</td>
<td>(44.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>(2.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donor ABO Blood Type (A/B/AB/O)</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>67</td>
<td>(35.1)</td>
</tr>
<tr>
<td>B</td>
<td>17</td>
<td>(8.9)</td>
</tr>
<tr>
<td>AB</td>
<td>6</td>
<td>(3.1)</td>
</tr>
<tr>
<td>O</td>
<td>101</td>
<td>(52.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Original HLA Match</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 of 6</td>
<td>17</td>
<td>(8.9)</td>
</tr>
<tr>
<td>5 of 6</td>
<td>58</td>
<td>(30.4)</td>
</tr>
<tr>
<td>4 of 6</td>
<td>111</td>
<td>(58.1)</td>
</tr>
<tr>
<td>3 of 6</td>
<td>5</td>
<td>(2.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final HLA Match</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 of 6</td>
<td>16</td>
<td>(8.9)</td>
</tr>
<tr>
<td>5 of 6</td>
<td>40</td>
<td>(22.3)</td>
</tr>
<tr>
<td>4 of 6</td>
<td>77</td>
<td>(43.0)</td>
</tr>
<tr>
<td>3 of 6</td>
<td>35</td>
<td>(19.6)</td>
</tr>
<tr>
<td>2 of 6</td>
<td>11</td>
<td>(6.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender Combinations (Donor/Patient)</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/F</td>
<td>33</td>
<td>(17.3)</td>
</tr>
<tr>
<td>F/M</td>
<td>52</td>
<td>(27.2)</td>
</tr>
<tr>
<td>M/F</td>
<td>39</td>
<td>(20.4)</td>
</tr>
<tr>
<td>M/M</td>
<td>63</td>
<td>(33.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td>(4.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race Combinations (Patient/Donor)</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian/Caucasian</td>
<td>90</td>
<td>(47.1)</td>
</tr>
<tr>
<td>Black/Black</td>
<td>14</td>
<td>(7.3)</td>
</tr>
<tr>
<td>Hispanic/Hispanic</td>
<td>8</td>
<td>(4.2)</td>
</tr>
<tr>
<td>Asian/Asian</td>
<td>4</td>
<td>(2.1)</td>
</tr>
<tr>
<td>Mixed/Mixed</td>
<td>2</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Mismatch</td>
<td>73</td>
<td>(38.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABO Match (Patient/Donor)</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Match</td>
<td>129</td>
<td>(67.5)</td>
</tr>
<tr>
<td>Mismatch</td>
<td>62</td>
<td>(32.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RH Match (Patient/Donor)</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Match</td>
<td>168</td>
<td>(88.0)</td>
</tr>
<tr>
<td>Mismatch</td>
<td>23</td>
<td>(12.0)</td>
</tr>
<tr>
<td>Total Number of HLA Matches</td>
<td>Original HLA Match (N=191)</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>(%)</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>(8.9)</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>(30.4)</td>
</tr>
<tr>
<td>4</td>
<td>111</td>
<td>(58.1)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>(2.6)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>(0)</td>
</tr>
</tbody>
</table>

* Original HLA match was defined by low/intermediate resolution typing at HLA Class I A and B and high resolution typing at DRB1. Final HLA match was defined by high resolution typing at HLA Class I A and B and DRB1.
Table 3. Multivariate Results

<table>
<thead>
<tr>
<th>Multivariate Results</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
<th>Favorable factor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neutrophil Recovery (using Original HLA Match)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pre-Cryopreserved Nucleated Cell Dose (×10⁷/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.1</td>
<td>1.39</td>
<td>1.02</td>
<td>1.90</td>
<td>Larger TNC</td>
</tr>
<tr>
<td>&lt;=5.1</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original HLA Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/6 of 6</td>
<td>1.39</td>
<td>1.02</td>
<td>1.89</td>
<td></td>
</tr>
<tr>
<td>3/4 of 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neutrophil Recovery (using Retrospective HLA Match)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pre-Cryopreserved Nucleated Cell Dose (×10⁷/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.1</td>
<td>1.42</td>
<td>1.04</td>
<td>1.94</td>
<td></td>
</tr>
<tr>
<td>&lt;=5.1</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective HLA Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/6 of 6</td>
<td>1.34</td>
<td>0.98</td>
<td>1.84</td>
<td></td>
</tr>
<tr>
<td>3/4 of 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Platelet Recovery (20k)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pre-Cryopreserved Nucleated Cell Dose (×10⁷/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.1</td>
<td>1.41</td>
<td>1.04</td>
<td>1.91</td>
<td>Larger TNC</td>
</tr>
<tr>
<td>&lt;=5.1</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Platelet Recovery (50k)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pre-Cryopreserved Nucleated Cell Dose (×10⁷/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.1</td>
<td>1.41</td>
<td>1.04</td>
<td>1.91</td>
<td>Larger TNC</td>
</tr>
<tr>
<td>&lt;=5.1</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate Results</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>P</td>
<td>Favorable factor(s)</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>--------------</td>
<td>----------</td>
<td>-----</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Acute GvHD Grades II-IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(using Original HLA Match)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.78</td>
<td>1.15</td>
<td>2.78</td>
<td>Male</td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original HLA Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 of 6</td>
<td>1.66</td>
<td>1.04</td>
<td>2.63</td>
<td></td>
</tr>
<tr>
<td>5/6 of 6</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute GvHD Grades II-IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(using Retrospective HLA Match)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.61</td>
<td>1.03</td>
<td>2.54</td>
<td>Male</td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective HLA Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/4 of 6</td>
<td>1.90</td>
<td>1.13</td>
<td>3.22</td>
<td></td>
</tr>
<tr>
<td>5/6 of 6</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute GvHD Grades III-IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(using Original HLA Match)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original HLA Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/4 of 6</td>
<td>1.88</td>
<td>0.91</td>
<td>3.89</td>
<td></td>
</tr>
<tr>
<td>5/6 of 6</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute GvHD Grades III-IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(using Retrospective HLA Match)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective HLA Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/3/4 of 6</td>
<td>3.45</td>
<td>1.21</td>
<td>9.80</td>
<td></td>
</tr>
<tr>
<td>5/6 of 6</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute GvHD Grades III-IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(using Retrospective HLA Match)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective HLA Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/4 of 6</td>
<td>3.53</td>
<td>1.23</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>5/6 of 6</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic GvHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=7.7 years</td>
<td>1.90</td>
<td>0.99</td>
<td>3.66</td>
<td>Older Recipients</td>
</tr>
<tr>
<td>&gt;7.7 years</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate Results</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>( P )</td>
<td>Favorable factor(s)</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
<td>--------</td>
<td>--------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Recipient Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.99</td>
<td>1.04</td>
<td>-3.79</td>
<td>Male Recipients</td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient CMV Serostatus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3.17</td>
<td>1.49</td>
<td>-6.76</td>
<td>Negative CMV</td>
</tr>
<tr>
<td>Negative</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABO Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mismatch</td>
<td>2.57</td>
<td>1.31</td>
<td>-5.06</td>
<td>ABO Match</td>
</tr>
<tr>
<td>Match</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.35</td>
<td>1.19</td>
<td>-4.67</td>
<td>Male Recipients</td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Survival (using Original HLA Match)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient CMV Serostatus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.95</td>
<td>1.27</td>
<td>-2.99</td>
<td>Negative CMV</td>
</tr>
<tr>
<td>Negative</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.74</td>
<td>1.15</td>
<td>-2.63</td>
<td>Male Recipients</td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABO Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mismatch</td>
<td>1.68</td>
<td>1.10</td>
<td>-2.57</td>
<td>ABO Match</td>
</tr>
<tr>
<td>Match</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original HLA Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/4 of 6</td>
<td>1.49</td>
<td>0.97</td>
<td>-2.29</td>
<td>5/6 of 6</td>
</tr>
<tr>
<td>5/6 of 6</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pre-Cryopreserved Nucleated Cell Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(( \times 10^7 /kg ))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=2.5</td>
<td>1.97</td>
<td>1.04</td>
<td>-3.73</td>
<td>Higher TNC</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Survival (using Retrospective HLA Match)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient CMV Serostatus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.94</td>
<td>1.24</td>
<td>-3.04</td>
<td>Negative CMV</td>
</tr>
<tr>
<td>Negative</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.76</td>
<td>1.15</td>
<td>-2.70</td>
<td>Male Recipient</td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABO Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mismatch</td>
<td>1.68</td>
<td>1.08</td>
<td>-2.59</td>
<td>ABO Match</td>
</tr>
<tr>
<td>Match</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective HLA Match</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/3/4 of 6</td>
<td>1.68</td>
<td>1.02</td>
<td>-2.75</td>
<td>5/6 of 6</td>
</tr>
<tr>
<td>5/6 of 6</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pre-Cryopreserved Nucleated Cell Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(( \times 10^7 /kg ))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=2.5</td>
<td>2.04</td>
<td>1.04</td>
<td>-4.00</td>
<td>Higher TNC</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

Figure 1. Cumulative incidence of engraftment and GvHD. (A) Cumulative incidences and 1-KM probability of neutrophil recovery. (B) Cumulative incidences and 1-KM probability of platelet engraftment of 50K. (C) Cumulative incidences and 1-KM probability of acute GvHD grades III-IV. (D) Cumulative incidences and 1-KM probability of chronic GvHD.

Figure 2. Cumulative incidence of relapse. (A) Overall cumulative incidence and 1-KM probability of relapse. (B) Cumulative incidence and 1-KM probability of relapse by stage of disease (1st and 2nd CR vs. other).

Figure 3. Survival for patients with pediatric malignancies. (A) Overall survival; (B) Survival by recipient CMV pre-transplant serostatus; (C) and (D) Survival by disease status for patients with AML and ALL; (E) and (F) Survival by original and final HLA match.
Figure 1. Cumulative incidence of engraftment and GvHD.

A
Cumulative Incidence and 1-Kaplan-Meier Estimate
Neutrophil Recovery

B
Cumulative Incidence and 1-Kaplan-Meier Estimate
Platelet Engraftment (>50k/mm^3)

C
Cumulative Incidence and 1-Kaplan-Meier Estimate
Acute GvHD Grades III-IV

D
Cumulative Incidence and 1-Kaplan-Meier Estimate
Chronic GvHD (Limited or Extensive)

Note: [1] Death is a competing risk.
Figure 2. Cumulative incidence of relapse.

A

Cumulative Incidence and Kaplan–Meier Estimate
Relapse

- CINC [1]
- KM [2]

1-KM at 1 year: 54.3% (95% CI, 17.5%, 31.4%)
CINC at 1 year: 18.6% (95% CI, 13.3%, 24.3%)

Note: [1] Death is a competing risk.

B

Cumulative Incidence and Kaplan–Meier Estimate
Relapse by Stage of Disease

- CINC of 1st and 2nd CR [1]
- CINC of Other [1]
- 1-KM of 1st and 2nd CR [2]
- 1-KM of Other [2]

Note: [1] Death is a competing risk.
Figure 3. Survival for patients with pediatric malignancies.

A. Overall Survival

- At 180 days, 67.4% (95% CI, 60.7%, 74.1%)
- At 1 year, 57.3% (95% CI, 50.2%, 64.3%)

B. Survival by Recipient CMV Serostatus

- Positive (N=98)
- Negative (N=92)

C. Survival by ALL Disease Status

- First Complete Remission (N=17)
- Second Complete Remission (N=65)
- Third Complete Remission (N=20)
- First or Second Relapse (N=6)

D. Survival by AML Disease Status

- Primary Induction Failure (N=6)
- First Complete Remission (N=13)
- Second Complete Remission (N=21)
- First or Second Relapse (N=11)

p = 0.32

p = 0.02
Figure 3 (continued)

E
Survival by Original HLA Match
- 3 of 6 (N=5)
- 4 of 6 (N=56)
- 5 of 6 (N=17)
- 6 of 6 (N=17)

F
Survival by Final HLA Match
- 2/3 of 6 (N=46)
- 4 of 6 (N=77)
- 5 of 6 (N=40)
- 6 of 6 (N=16)

p = 0.10

p = 0.22
Results of the Cord Blood Transplantation Study (COBLT): Clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies