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Transplantation of Unrelated Donor Umbilical Cord Blood for Nonmalignant Diseases: a Single Institution's Experience with 45 Patients

Tang-Her Jaing,[1] Shih-Hsiang Chen,[1] Ming Horng Tsai,[1] Chao-Ping Yang,[1] Iou-Jih Hung,[1] Pei-Kwei Tsay[2]

The potential benefits of unrelated donor bone marrow transplantation are offset by the immunologic complications of graft-versus-host disease (GVHD) and infection. We used cryopreserved umbilical cord blood (UCB) as a strategy to reduce the risks of GVHD and treatment-related mortality (TRM) and improved survival. Data on 45 patients with median age of 4.5 years who received transplants between October 2003 and February 2009 for the treatment of nonmalignant diseases were evaluated. As of May 15, 2009, the median follow-up was 25 months (range: 3-66). The majority (82%) of patients received an HLA-mismatched graft. The median infused total nucleated cell dose was 7.6×10^7/kg and $CD34^+$ count 4.0×10^5/kg. Primary graft failure was encountered after 4 transplantations (8%). Log-rank tests and Cox regression analyses were used to determine the effects of various demographic, graft-related, and treatment factors on engraftment, GVHD, TRM, graft failure, and survival. Incidences of neutrophil and platelet engraftment were 88% and 82%, respectively. The incidence of severe grade III-IV acute GVHD (aGVHD) was 42%. Five-year overall survival (OS) and disease-free survival (DFS) were 88.1% and 77.1%, respectively. The cumulative incidence of TRM at 2 years was 12.0%. When cell dose and other factors are optimal, unrelated CBT is a promising approach for curative therapy of nonmalignant diseases.

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KEY WORDS: Unrelated cord blood transplantation, Nonmalignant diseases, Overall Survival, Disease-free survival, Indications, Prognosis

INTRODUCTION

Cord blood transplantation (CBT) has emerged as a therapeutic option for a number of nonmalignant diseases affecting the bone marrow (BM) and leading to clinical manifestations, most likely affecting distant organs. Advantages from unrelated donor umbilical cord blood (UCB) donors such as faster availability, tolerance of 1 to 2 HLA mismatches, and low incidence of acute graft-versus-host disease (aGVHD) made UCB transplants attractive for patients with some nonmalignant diseases [1]. We used unrelated donor UCB as a strategy to reduce the risks of GVHD and treatment-related mortality (TRM) in children with nonmalignant diseases. Our study was designed to explore the impact of innovations in transplant source on results of hematopoietic stem cell transplantation.

MATERIALS AND METHODS

Patients and Selection of Appropriate Transplants

The study was in accordance with the principles of the Declaration of Helsinki, and the appropriate ethical committee approved the work and proposed study design. A parent or legal guardian provided informed consent for each child before any trial-related treatment began.

Underlying diseases included transfusion-dependent thalassemia (SAA; n = 32), primary immunodeficiency (n = 5), severe aplastic anemia (n = 3), infantile osteopetrosis (n = 3), and Fanconi's anemia (FA; n = 2).

From the [1]Divisions of Hematology and Oncology, Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung University, Taoyuan, Taiwan, Republic of China; and [2]Department of Public Health and Center of Biostatistics, College of Medicine, Chang Gung University, Taoyuan, Taiwan, Republic of China.

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Correspondence and reprint requests: Tang-Her Jaing, MD, Division of Hematology and Oncology, Department of Pediatrics, Chang Gung University and Children's Hospital, 5 Fu-Shin Street, Kwei-Shan, 333, Taoyuan, Taiwan, R.O.C (e-mail: jaing001@cgmh.org.tw).

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Each acceptable cord blood unit (CBU) was a 4/6 HLA match or better with the patient and achieved a minimum precryopreservation cell dose of 2.5×10^7 total nucleated cells (TNC)/kg. Double-unit CBT was done only if no single unit $\geq 2.5 \times 10^7$ TNC/kg of recipient body weight is available. Total cell dose for double-unit transplants (UCB1 + UCB2) was required to be $\geq 3.7 \times 10^7$ TNC/kg of recipient body weight. These patients received unmanipulated grafts without ex vivo expansion or T cell depletion. Cell dose escalation to facilitate engraftment was permitted for patients with previous graft failure. Therefore, UCB grafts used for transplantation in this study contained after thawing a median of 7.6×10^7 TNC (range: 2.8-15.0) and 4.0×10^5 CD34 cells (range: 1.3-19.9) per kilogram recipient body weight.

Searches for unrelated CB donors were processed through the StemCyte Cord Blood Bank. Units of cord blood required a match of at least 4 of 6 HLA loci based on antigen-level HLA-A and -B typing and allele-level HLA-DRB1 typing. Matching at HLA-C, -DQ, and -DP were not considered. Individual data sets were compiled and verified through the audit processes of the Center for International Blood and Marrow Transplant Research (CIBMTR).

Conditioning Regimen

Depending on the underlying disease, patients received an antithymocyte globulin (ATG)-containing conditioning regimen with or without total body irradiation (TBI) followed by UBT transplantation. The specifics of conditioning regimen depends on the nature of the disease for which transplant is being performed, Lansky performance status, and age of the patients. Conditioning consisted of i.v. busulfan (Bu) 14 mg/kg over 4 days (day -9 to -6) plus cyclophosphamide (Cy) 200 mg/kg over 4 days (day -5 to -2) in 37 transplants for thalassemia, 4 for immunodeficiency, and 1 for a 7-month-old infant with osteopetrosis. Three recipients with SAA and 2 with FA received fludarabine (Flu; 30 mg/m^2/day $\times$ 6 days) and Cy (60 mg/kg/day $\times$ 2 days). Regimens including TBI were used for 2 transplants for osteopetrosis; 1 patient with SCID received ATG alone. The conditioning regimens used for retransplant in thalassemic patients consisted of i.v. Bu 14 mg/kg over 4 days (days -7 to -4) plus Cy 120 mg/kg over 2 days (days -3 to -2).

Hematopoietic Recovery and Engraftment

Myeloid engraftment was defined as 3 consecutive days of an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L. The day after the last day of red blood cell (RBC) transfusion was recorded as the first day of RBC transfusion independence. Platelet engraftment was defined as 7 consecutive days of a platelet count of $\geq 20 \times 10^9$/L maintained without transfusion. In thalassemic patients with myeloid engraftment, desferrioxamine was administered intravenously to accelerate the clearance of body iron deposits if serum ferritin levels exceeded 2500 μg/L. Phlebotomy was not justifiable when iron overload and anemia exist simultaneously.

Chimerism Studies

Chimerism status was assessed analyzing short tandem repeat (STR) polymorphisms. Peripheral blood (PB) samples after transplantation were collected for donor chimerism studies. Chimerism analyses of BM erythroblasts were not routinely performed. Serial STR polymerase chain reaction confirmed conversion from mixed chimerism to a predominantly donor profile on the day that the myeloid engraftment occurred, on day +42, +100, +180, +270, and +360, 1.5 years after transplantation, and yearly, thereafter. An additional test was done if clinically indicated. Total leukocyte chimerism was determined by analysis of STR loci (Profiler Plus, Applied Biosystem, Foster City, CA).

GVHD Prophylaxis

GVHD prophylaxis consisted of antithymocyte globulin (ATG), cyclosporine (CsA), and methylprednisolone. The level of CsA was adjusted to between 200 and 400 ng/mL. Patients were evaluated for aGVHD daily during initial hospitalization, at least once weekly after initial discharge during the first 100 days, and at routine follow-up evaluations posttransplant. aGVHD was staged according to Glucksberg's criteria, with histopathologic confirmation when possible, and an overall grade was assigned according to the International Blood and Marrow Transplant Research (IBMTR) severity index. Patients with clinical stage II or later disease were treated initially with methylprednisolone (>48 mg/m^2 intravenously or oral equivalent) daily for a minimum of 2 weeks prior to tapering.

Statistical Analysis

Baseline characteristics of all patients were summarized using descriptive statistics. Overall survival (OS) was measured from transplantation until death from any cause or last date of follow-up. Disease-free survival (DFS) was defined as the time from transplantation to relapse or death from any cause. Probabilities of survival and TRM were evaluated by Kaplan-Meier analysis. Patients who died without evidence of engraftment were censored at the time of death (n = 1). Patients who had very slow engraftment (after day 42) or failed to have BM reconstitution of donor origin were scored as having primary graft failure (n = 4). Those with autologous recovery after primary engraftment were scored as having secondary graft failure

(n = 2). Pearson's correlation coefficient was used to estimate a correlation between nucleated cell dose and CD34 cell dose. All statistical were performed using SPSS for Windows (release 11.0.1; SPSS Inc., Chicago, IL).

RESULTS

Patient and Cord Blood Characteristics

A total of 50 UCB transplants were performed between August 2003 and February 2009. Patient characteristics and treatment of the 45 recipients are shown in Table 1. Among donor-recipient matches, 36 matched at 5 or 6 HLA loci and 26 matched at 4 HLA loci. One matched at 3 HLA loci with 2 GVHD mismatches. Reduced-intensity conditioning (RIC) regimens were used in 7 patients (5 with primary immunodeficiency and 2 with FA). In 32 patients with thalassemia, 21 patients were classified as Pesaro I, 9 were Pesaro II, and 2 were previously unavailable. There are 27 patients (84%) who are alive and transfusion-independent after a median follow-up of 27 months (range: 3-66 months). Five patients with thalassemia underwent retransplantation for graft failure. Three patients had primary graft failure and the other 2 had secondary graft failure. Table 2 summarized the 5 patients' characteristics and outcome.

Of the 45 patients, 12 received 2 UCB units. One of these 12 patients received a second transplant 10 months after first transplantation because of secondary graft failure. Forty-four patients achieved neutrophil engraftment at a median of day 16 (range: 10-46 days). Incidence of neutrophil engraftment by day 42 was 88% (95% confidence interval [CI] = 0.76-0.94). Median time to platelet engraftment was 48 days (range: 24-117 days). Incidence of platelet engraftment by day 60 was 82% (95% CI = 0.67-0.91) in 39 evaluable patients. There is a positive linear correlation between CD34 and nucleated cell doses, but the correlation was not statistically significant (R = 0.267; P = .06).

aGVHD and Chronic GVHD (cGVHD)

aGVHD occurred in 42 patients and was scored as grade I (n = 8), grade II (n = 15), grade III (n = 16), or grade IV (n = 3) disease. By day 100 after transplantation, incidences of grade II-IV and grade III-IV aGVHD was 76% (95% CI = 0.65-0.82) and 42% (95% CI = 0.33-0.51), respectively. Skin was the organ most likely to be affected, with mild to moderate disease in the majority of patients (Table 3).

Of the evaluable patients, the incidence of cGVHD was 35% (95% CI = 0.29-0.42) at 1 year after transplantation. Of the 14 patients who developed cGVHD, extensive disease was found in 1 patient compared with limited disease in 13. Of the 45 total patients, 40 (89%) were alive and disease-free with a Lansky performance score >80% at last follow-up (range: 3 and 66 months; median, 25 months).

Table 1. Demography of 45 Patients with Nonmalignant Diseases for CBT

Characteristics of patients undergone UCB transplant	Number of patient (%) or median (range)
Number of patients	45
Median age in years (range)	4.5 (0.1-16.2)
Male: Female	27:18 (60%:40%)
Diagnosis	
Transfusion-dependent thalassemia	32 (71%)
Severe aplastic anemia	3 (7%)
Fanconi anemia	2 (4%)
Infantile osteopetrosis	3 (7%)
Primary immunodeficiency	5 (11%)
Matching at antigen-level for HLA-A and -B and allele-level for HLA-DRB1	
Fully matched	11 (17%)
One mismatch	25 (40%)
Two mismatches	26 (41%)
Three mismatches	1 (2%)
ABO compatibility	
Full match	25 (40%)
Minor mismatch	18 (28%)
Major mismatch	20 (32%)
Number of infused cells	
Nucleated cells (10^7/kg)	7.6 (2.8-15.0)
CD34 cells (10^5/kg)	4.0 (1.3-19.9)
Conditioning regimen	
Myeloablative	43 (86%)
Reduced intensity	7 (14%)
Cord blood units	
Single-unit	37 (74%)
Double-unit	13 (26%)

UCB indicates umbilical cord blood; CBT, cord blood transplantation.

Disease Response and Survival Analysis

The estimated 5-year OS and PFS rates were 88.1% and 77.1%, respectively. The incidence of TRM 2 years posttransplant was 12.0 % (Figure 1). Initial multivariate analysis looked for differences between transplant-related parameters and the intention of finding no significant differences. Therefore, univariate analyses were not conducted.

At the time of writing, 40 of the 45 patients are alive after UBT transplants. Three patients died during the hospital stay, with 2 dying from bleeding complications that developed from thrombocytopenia and 1 from sepsis. At 11 months posttransplant, 1 patient died of alveolar hemorrhage secondary to Evans' syndrome. At 14 months posttransplant, 1 patient died from an accidental head injury.

DISCUSSION

This trial involved 45 pediatric patients with nonmalignant diseases, 40 of whom were transfusion-dependent at study entry. The Chang Gung Pediatric Hematopoietic Stem Cell Transplantation

Table 2. Characteristics of Five Patients with Thalassemia Undergoing Retransplant for First Graft Failure

UPN	23	24	27	29	63
Characteristics of first transplants					
Diagnosis	β/β thalassemia	β-thalassemia/Hb E	β-thalassemia/Hb E	β/β thalassemia	β/β thalassemia
Donor type	Single unrelated donor UCB	2 unrelated donor UCB	Single unrelated donor UCB	2 unrelated donor UCB	Single UCB
Conditioning regimen for first SCT	Bu 14/Cy 200 /ATG	Bu 14/Cy 200 /ATG	Bu 14/Cy 200 /ATG	Bu 14/Cy 200 /ATG	Bu 14/Cy 200 /ATG
Number of HLA mismatching (loci)					
HLA-A, B antigen	1	0	0	1 (donor 1) 0 (donor 2)	2
HLA-DRB1 allele	0	0	1	0 (donor 1) 1 (donor 2)	0
Infused TNC ($\times 10^7$/kg)	6.95	6.31	4.80	15.95	5.36
Infused CD34$^+$ ($\times 10^5$/kg)	2.47	3.95	1.74	7.21	2.56
First graft failure	Primary	Secondary	Primary	Primary	Secondary
Interval between transplants (mo)	7	10	10	1.5	8
Characteristics of second transplants					
Donor type	2 unrelated donor UCB	2 unrelated donor UCB	2 unrelated donor UCB	G-PBSC from haploidentical mother	2 UCB
Conditioning regimen for second SCT	Bu 14/Cy 120 /ATG	Bu 14/Cy 120 /ATG	Bu 14/Cy 120 /ATG	Bu 14/Cy 120	Bu 14/Cy 120 /ATG
Number of HLA mismatching (loci)					
HLA-A, B antigen	0 (donor 1) 0 (donor 2)	0 (donor 1) 0 (donor 2)	1 (donor 1) 2 (donor 2)	2	2 (donor 1) 2 (donor 2)
HLA-DRB1 allele	1 (donor 1) 1 (donor 2)	1 (donor 1) 1 (donor 2)	1 (donor 1) 2 (donor 2)	0	0 (donor 1) 0 (donor 2)
Infused TNC ($\times 10^7$/kg)	7.16	8.07	14.3	364	9.72
Infused CD34$^+$ ($\times 10^5$/kg)	4.02	5.07	7.58	161	5.04
Neutrophil engraftment	Day +15	Day +23	Day +26	Day +11	Day +17
Platelet engraftment	Day +33	Day +61	Day +53	Day +65	Day +61
Acute GVHD					
Maximum clinical grade	II	I	II	II	I
Site(s) involved	Skin	Skin	Skin	Skin, GI	Skin
Chronic GVHD	Limited	Limited	Limited	Extensive	Limited
Transplantation-related complications	Evans' syndrome	BKV-associated HC	No	CMV reactivation	No
Outcome	Transfusion -independent	Transfusion -independent	Transfusion -independent	Transfusion -independent	Transfusion -independent
Chimerism status					
Day of neutrophil engraftment	93.5% donor 1	96.6% donor 1	85.4% donor 1	100% donor	60.9% donor 1 30.1% donor 2
Latest follow-up	100% donor 1	100% donor 1	100% donor 1	100% donor	60.1% donor 1 39.9% donor 2

UCB indicates umbilical cord blood; HLA, human leucocyte antigen; G-PBPC, granulocyte colony stimulating factor mobilized peripheral blood stem cell; Bu, busulfan; Cy, cyclophosphamide; GVHD, graft-versus-host disease; BKV-associated HC, BK virus-associated hemorrhagic cystitis; CMV, cytomegalovirus; ATG, antithymocyte globulin.

Table 3. Clinical Grade of Acute GVHD by Organ System

Severity	Skin	GI	Liver	Overall
Grade I	8	0	0	8
Grade II	15	1	1	15
Grade III	16	3	2	16
Grade IV	3	3	3	3
Total	42	7	6	42

GI indicates gastrointestinal tract; GVHD, graft-versus-host disease.

(HSCT) Program has an active protocol for using unrelated donor UCB for transplantation as an alternative source of stem cells when matched unrelated donor marrow is not available. For patients with transfusion-dependent thalassemia, the approach was based on the assumption that the risks associated with UCB transplantation could be counteracted by iron overload leading to organ dysfunction and by transfusion-associated viral infection.These hazards are particularly objectionable in young patients with potential for a long life span. Older patients generally have more advanced disease with both disease- and treatment-related organ complications, mainly because of prolonged iron overload. In our study, all graft failures occurred in patients with thalassemia (6/32, 19%) who were above the age of 6 years. It has been suggested that HSCT has generally been unsuccessful when applied to patients with thalassemia who have a history of multiple transfusions [2]. Therefore, it was decided for this study that early transplantation of unrelated donor UCB could be conducted in young patients who had received few transfusions.

BM transplantation has emerged as a major therapeutic option for a number of nonmalignant diseases affecting BM and leading to significant clinical manifestations affecting other organs. In most instances, the goal of transplantation is to provide stable long-term engraftment and amelioration of disease phenotype [3]. Although delayed or failed engraftment may be attributable to the lower nucleated cell dose in UCB graft, other characteristics of UCB progenitor cells may affect homing and maturation in the recipient and confound correlations with engraftment [4]. When high cell doses are used, UCB transplantation has been shown to achieve outstanding survival in patients with nonmalignant diseases such as thalassemia [5,6]. The results of our study keenly imply that successful outcome reported for a large number of such serious, nonmalignant disorders.

The main limitation of unrelated donor BMT is that, using stringent criteria, only about one-third of patients who started the search find a suitable donor in a median of 3 to 4 months. One possibility to increase donor pools would be to adopt less stringent criteria for HLA matching so donor acceptability would allow disparity in 1 or 2 alleles.

At present, most banks match UCB donors for respective recipients by HLA-A, -B low-resolution

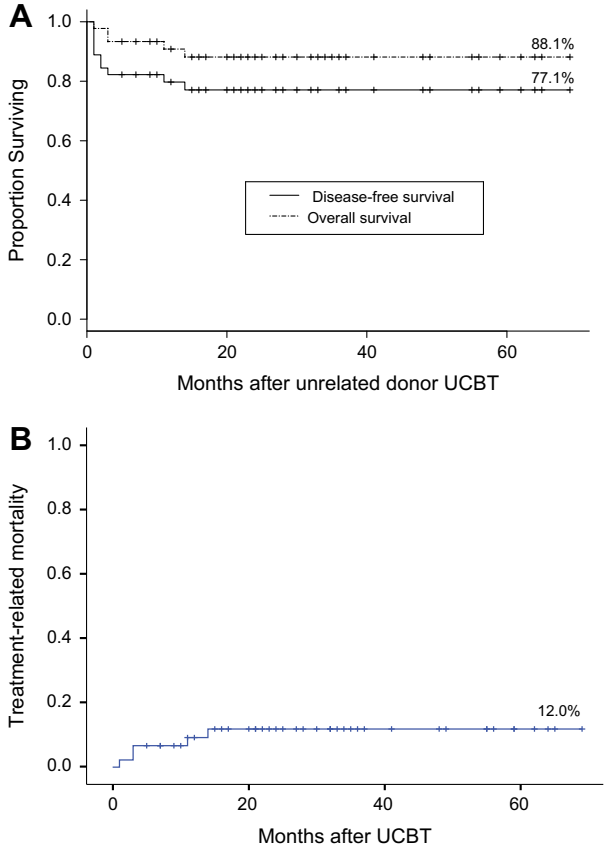

Figure 1. Kaplan-Meier analyses of 45 patients who underwent unrelated cord blood transplantation. (A) Five-year disease-free survival and (B) 2-year treatment-related mortality.

typing and -DRB1 high-resolution typing [1,7]. With such a large supply and flexibility of HLA matching, collecting more CBU should pose no difficulty in finding compatible donors. Cell number seems to be quite important; perhaps more so than a high degree of HLA match. In our previous study, it has been shown that higher prefreeze TNC and $CD34^+$ cell doses were associated with cord predominance [8]. However, CD34 count seems to be a better quantitative indicator of success than nucleated cell count [9]. Our study has demonstrated a higher cell dose supports higher levels of engraftment. Furthermore, double-unit transplants may reduce the time to engraftment and thus reduce TRM [10-12]. High-resolution HLA typing has enabled physicians to perform transplants from unrelated volunteer donors for thalassemic patients with results comparable with those obtained employing an HLA-identical sibling [13].

Improved RBC transfusion schedules and iron chelation therapy have allowed children with thalassemia to avoid serious deformities and to have an improved life expectancy. When a matched-related or matched-unrelated adult donor cannot be found, it is debated that matched unrelated donor UCB should be used. The result of discussion is always that there are many clinical variables to create rules, such as

universally poor outcome with conventional treatment for patients with increasing age [14] and the optimal indication for transplantation in young children with transfusion-dependent thalassemia.

Improvements in conservative treatment have considerably improved the prognosis of patients with nonmalignant diseases such as thalassemia. However, disease- and treatment-related complications progress over time in many patients, causing severe morbidity and shortening life expectancy even in patients with access to good medical treatment [15,16]. There is no reason to deny these patients the advantages of a life free from daily tedious, expensive, and uncomfortable therapy. Delaying transplantation until the patient is in a risk category substantially reduces the probability of transplant success and jeopardizes reversibility of organ damage. Patients without an HLA-identical related donor who have a well-selected unrelated donor should also be considered for transplantation with UCB.

CONCLUSIONS

In experienced hands and highly specialized centers, use of unrelated donor UCB transplantation may create fundamental new opportunities for treatment of nonmalignant diseases requiring expedient HSCT to prevent irreversible disease progression.

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