Different effects of HLA disparity on transplant outcomes after single-unit cord blood transplantation between pediatric and adult patients with leukemia

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ABSTRACT

Recent advances in unrelated cord blood transplantation have increased chances and options available in allogeneic stem cell transplantation. The effect of HLA disparity on outcomes after cord blood transplantation was studied recently in mainly pediatric populations. Results showed that HLA matching in combination with total nucleated cell dose positively affects survival. The effect of HLA disparity after single-unit cord blood transplantation may be different in adults because their total nucleated cell dose is much lower compared to pediatric patients. We investigated the effect of HLA disparity on the outcome of single-unit unrelated cord blood transplantation separately in 498 children aged 15 years or under (HLA-A, HLA-B low-resolution, and HLA-DRB1 high-resolution matched [6/6], n=82, and one locus- [5/6], n=222, two loci- [4/6], n=158, three loci- [3/6] mismatched, n=36) and 1,880 adults (6/6, n=71; 5/6, n=309; 4/6, n=1,025; 3/6, n=475) with leukemia. With adjusted analyses, in children, 4/6 showed significantly increased risks of overall mortality (relative risk [RR]=1.61, *P*=0.042) and transplant-related mortality (RR=3.55, *P*=0.005) compared to 6/6. The risk of grade 2 to 4 acute GVHD was increased in 5/6 (RR=2.13, *P*=0.004) and 4/6 (RR=2.65, *P*<0.001). In adults, the risk of mortality did not increase with the number of mismatched loci (RR=0.99, *P*=0.944 for 5/6; RR=0.88, *P*=0.436 for 4/6). The risk of relapse was significantly decreased in 4/6 (RR=0.67, *P*=0.034). The risk of transplant-related mortality (TRM) or acute GVHD was not increased in 5/6 or 4/6. The effect of HLA disparity on transplant outcome differed between children and adults. In children, an increased number of mismatched HLA loci correlated with an increased risk of mortality. In adults, there was no increase in mortality with an increase in the number of mismatched HLA loci.

Introduction

Recent advances in unrelated cord blood transplantation (UCBT) have provided increased opportunities for patients with hematologic malignancies to receive hematopoietic stem cell transplantation (HSCT). This has led to an increased number of UCBT procedures over the past decade.[1,2] Clinical comparison studies of cord blood and bone marrow from unrelated donors have shown comparable results, which indicates that cord blood is a reasonable alternative donor / stem cell source.[3-12] These studies support the use of HLA-A, HLA-B, low-resolution and HLA-DRB1 zero- to two-loci-mismatched UCB for patients with leukemia in the absence of an HLA-A, HLA-B, HLA-C, and HLA-DRB1 allele matched unrelated adult donor, and the use of UCB as a first-line option when a transplant is urgently required.

The effect of HLA mismatches after bone marrow transplantation from unrelated donors (UBMT) has been well studied, and HLA-A, HLA-B, HLA-C, and HLA-DRB1 allele matched bone marrow is currently the first alternative for HLA-identical sibling donors.[13-16] An increase in the number of HLA mismatches, antigen-level, or high-resolution, at HLA-A, HLA-B, HLA-C, or HLA-DRB1 loci from 8/8 to 7/8, or 7/8 to 6/8 was associated with higher mortality with an approximately 10% reduction in survival in UBM recipients.[12,13,15] Since HLA mismatches are better tolerated after UCB with a lower incidence of severe graft-*versus*-host disease (GVHD), up to two HLA antigen mismatches of HLA-A, HLA-B, low resolution and HLA-DRB1 high resolution are considered in the current CB selection algorithm. Several reports have recently described the effect of HLA disparity on the transplant outcomes after UCBT.[9,17,18] Eapen *et al.* reported the pos-

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sibility of a better outcome in HLA 6/6 matched UCB in 35 recipients, and Barker *et al*. confirmed these results with a larger number of UCB recipients.[9,18] However, these studies, which assessed the effect of HLA disparity on the outcome of single-unit CBT, were mainly conducted in pediatric populations in which the infused cell dose is much greater than that in adult recipients.

The aim of this study was to assess the effect of HLA disparity on the transplant outcomes after single-unit UCBT in pediatric and adult recipients. The accumulation of single-unit CBT in adult recipients has enabled us to assess separately the effect of HLA disparity on CBT outcomes in children and adults.

Design and Methods

Study design and data source

For this retrospective observational study, recipients' clinical data were provided by the Japan Cord Blood Bank Network (JCBBN). All 11 cord blood banks in Japan are affiliated with the JCBBN. JCBBN collected the recipients' clinical information at 100 days post-transplant through the Transplant Registry Unified Management Program (TRUMP) of the Japan Society of Hematopoietic Cell Transplantation (JSHCT).[19] Information on survival, disease status, and long-term complications including chronic graft-*versus*-host disease and second malignancies is renewed annually. Patient consent is not required for TRUMP registration of the JSHCT for the registry data consists of anonymized clinical information. This study was approved by the data management committees of the JSHCT and the JCBBN, and by the institutional review boards of Saitama Medical Center, Jichi Medical University and Nagoya University Graduate School of Medicine, Japan.

Patients

The subjects were patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), or myelodysplastic syndrome (MDS), who were recipients of their first UCBT between January 2000 and December 2009. Among 2,461 recipients of single-unit UCB with complete HLA-A, HLA-B, low-resolution and HLA-DRB1 high-resolution data, 51 recipients with 4 HLA mismatches were excluded. Thirty recipients who did not receive GVHD prophylaxis and 2 recipients for whom information regarding the conditioning regimen was missing were excluded. A total of 2378 single-unit UCB recipients (498 children aged 15 years or under at transplant, and 1880 adults aged 16 years or over at transplant) were subjects for analysis.

HLA typing

Histocompatibility data for low-resolution typing for the HLA-A, HLA-B, and HLA-DR loci and high-resolution typing for HLA-DRB1 were obtained from the TRUMP database which includes HLA information provided by cord blood banks or transplant centers. The level of HLA typing in the present study was HLA-A, HLA-B, low-resolution, and HLA-DRB1 high-resolution, as in other studies in Europe and North America. However, according to current practice in Japan, mismatches in HLA-DR loci were counted at the low-resolution level at UCB unit selection. Therefore, results regarding the effect of HLA mismatches in HLA-A, HLA-B, and HLA-DR low-resolution are also provided (*Online Supplementary Table S1*). Analyses from the Japan Marrow Donor Program (JMDP) showed better survival in HLA class II mismatched recipients compared to HLA class I mismatched recipients. Thus, in Japan, a single-DRB1-mismatched UBM donor is preferred over a single-A-mismatched UBM or single-B-mismatched UBM donor.[15,20] This background affected HLA typing strategy of HLA-DR low-resolution typing instead of high-resolution typing for selection of cord blood units in Japan. This observation may explain the fact that the frequency of 4/6 grafts is higher in this cohort than in cohorts in Europe and the USA.

Definitions

The primary outcome of the analyses was overall survival, defined as time from transplant to death from any cause. Several secondary end points were also analyzed. Neutrophil recovery was defined as an absolute neutrophil count of at least $0.5x10^9$/L cells per cubic millimeter for three consecutive points; platelet recovery was defined as a count of at least $50x10^9$ platelets per cubic millimeter without transfusion support. The recipients of reduced-intensity conditioning were also defined with the criteria above, according to the previous report that confirmed complete donor chimeras of all engrafted patients after CBT with reduced-intensity conditioning.[21] Diagnosis and clinical grading of acute GVHD were performed according to the established criteria.[22,23] Relapse was defined as the recurrence of underlying hematologic malignant diseases. Transplant-related death was defined as death during a continuous remission.

Statistical analysis

Descriptive statistical analysis was performed to assess patient baseline characteristics, diagnosis, disease status at conditioning, donor-patient ABO mismatches, preparative regimen, and GVHD prophylaxis. Medians and ranges are provided for continuous variables and percentages are shown for categorical variables. Cumulative incidence curves were used in a competing-risks setting to calculate the probability of acute and chronic GVHD, relapse and transplant-related mortality (TRM).[24] Gray's test was used for group comparisons of cumulative incidences.[25] An adjusted comparison of the groups with regard to overall survival (OS) was performed with the use of the Cox's proportional-hazards regression model.[26] For other outcomes with competing risks, Fine and Gray's proportional-hazards model for the subdistribution of a competing risk was used.[27] For neutrophil and platelet recovery, death before neutrophil or platelet recovery was the competing event. For GVHD, death without GVHD and relapse were competing events. For relapse, death without relapse was the competing event, and for transplant-related mortality (TRM), relapse was the competing event.[28] For acute GVHD, subjects were limited to those who engrafted, and for chronic GVHD, subjects were limited to those who engrafted and survived at least 100 days after transplantation.

The variables considered were the patient's age at transplant (5 years or over *vs.* under 5 years for pediatric recipients, and 50 years or over *vs.* under 50 years for adult recipients; cut-off points were around the median in each group), patient's sex, donor-patient sex mismatch (matched *vs.* male to female *vs.* female to male), donor-patient ABO mismatch (major mismatch *vs.* matched or minor mismatch), diagnosis (AML, ALL, CML or MDS), disease status at conditioning (first or second complete remission (CR) of AML, 1CR of ALL, first chronic phase of CML, and refractory anemia or refractory anemia with ringed sideroblasts as standard-risk diseases *vs.* advanced for all others), the conditioning regimen (reduced-intensity conditioning *vs.* myeloablative conditioning), and the type of prophylaxis against GVHD (tacrolimus-based *vs.* cyclosporine-based). Conditioning regimens were classified as myeloablative if total-body irradiation >8 Gy, oral busulfan ≥9 mg/kg, intravenous busulfan ≥7.2 mg/kg, or melphalan >140 mg/m^2 was used based on the report from the Center for International Blood and Marrow Transplant Research.[29,30] We cat-

egorized patients for whom there was insufficient information regarding the doses of agents or radiation used for the conditioning regimen according to information on the conditioning intensity (i.e. whether or not the conditioning regimen was intended to be myeloablative) as reported by the treating clinicians. The cryopreserved total nucleated cell dose was categorized as >10.0x10^7/kg, 5.0-9.9 x 10^7/kg, 2.5-4.9x10^7/kg, or <2.5 x 10^7/kg for children, and >3.0x10^7/kg, 2.5-2.9x10^7/kg, 2.0-2.4x10^7/kg, or <2.0x10^7/kg for adults. HLA disparity and nucleated cell dose were maintained in the model. Since patient age was highly correlated with the total nucleated cell dose in children, age was excluded from multivariate analyses for pediatric recipients. Other variables were selected in a backward stepwise manner with a variable retention criterion of P<0.05. Interaction between HLA disparity and adult (patient age at transplant 16 years or over) or child (patient age at transplant 15 years or under) was tested for overall survival by using a Cox's proportional-hazards regression model adjusted by other significant covariates in the final model for adult and pediatric recipients except for patient age. All P values were two-sided.

Results

Patients' characteristics

Table 1 shows patients' characteristics, their disease, and transplant regimens. Median age at transplant was five years (range 0-15) in 498 pediatric and 49 years (range 16-82) in 1880 adult recipients of single-unit CBT. The proportion of females was 45% in both children and adults. Among children, the proportion of patients with ALL was greatest (58%) followed by that of patients with AML (34%). Among adults, the most frequent disease was AML (59%), followed by ALL (22%) and MDS (13%). The median number of cryopreserved total nucleated cells received in children was 5.30 x 10^7/kg, which was significantly greater (approximately double) than the number of nucleated cells received in adult patients (2.52 x 10^7/kg). In adults, only 33 patients (2%) received CB with a total nucleated cell dose greater than or equal to 5.0 x 10^7/kg. In children, 82 patients (16%) received HLA-matched (6/6) UCB, 222 (45%) received one-locus-mismatched (5/6), 158 (32%) received two-loci-mismatched (4/6), and 36 (7%) received three-loci-mismatched (3/6) UCB. For adults, the numbers and proportions of recipients were 71 (4%) for 6/6, 309 (16%) for 5/6, 1025 (55%) for 4/6, and 475 (25%) for 3/6. Among those who received 3/6 UCB, only 2 pediatric and 11 adult patients received three HLA-A, HLA-B, HLA-DR low-resolution mismatched UCB. Eighty-eight percent (TBI regimen 62%, non-TBI regimen 26%) and 62% (TBI regimen 56%, non-TBI regimen 6%) of children and adults, respectively, received myeloablative conditioning. Fludarabine-based reduced-intensity conditioning was given to 34% of adult recipients. T-cell depletion *in vivo* with antithymocyte globulin or antilymphocyte globulin was performed in only 6 (2%) child recipients and 26 (1%) adult recipients. The median follow-up period for survivors was 2.4 years (range 0.1-9.5) for pediatric recipients and 2.1 (range 0.1-9.0) years for adult recipients.

Outcome

Overall survival, relapse, and transplant-related mortality: among children, overall mortality in 4/6 UCB recipients was significantly higher than that in 6/6 UCB recipients (RR=1.61, 95% confidence interval [CI], 1.02-2.56, P=0.042) (Table 2). Overall mortality increased with the number of mismatched loci in children (P for trend 0.043). The increased mortality in 4/6 UCB recipients was mainly affected by increased transplant-related mortality (TRM) (RR=3.55, 95%CI: 1.47-8.58, P=0.005) (P for trend 0.002) but not by the risk of relapse (RR=0.77, 95%CI: 0.48-1.24, P=0.392) in children. Among children, there were no differences in the risks of mortality and relapse between 5/6 UCB recipients (RR=1.07, P=0.765 for overall mortality; RR=1.06, P=0.794 for relapse; and RR=1.29, P=0.58 for TRM) and 6/6 UCB recipients (Table 2).

In adults, the number of HLA mismatches was not significantly associated with increased mortality (for overall mortality: RR=0.99, P=0.944 for 5/6; RR=0.88, P=0.436 for 4/6; RR=0.95, P=0.751 for 3/6; for TRM, RR=1.41, P=0.205 for 5/6; RR=1.24, P=0.408 for 4/6; RR=1.29, P=0.339 for 3/6). A two-loci mismatch was associated with a decreased risk of relapse in adult recipients (RR=0.70, P=0.075 for 5/6; RR=0.67, P=0.034 for 4/6; RR=0.70, P=0.07 for 3/6) (Table 2). The risks of mortality were similar when subjects were limited to those with standard risk disease status or to those with advanced risk disease status at transplant, to those who received myeloablative conditioning or to those who received reduced-intensity conditioning (*Online Supplementary Table S2*). A decreased risk of relapse was more prominent in patients with acute myeloid leukemia, and those who received reduced-intensity conditioning (*Online Supplementary Table S2*).)

Figure 1 shows unadjusted overall survival curves in children and adults. In children, the unadjusted probabilities of survival at three years post-transplant were 66% for 6/6, 62% for 5/6, 45% for 4/6, and 62% for 3/6 (P=0.032) (Figure 1A). In adults, the survival probabilities in all of the HLA disparity groups were similar (38% for 6/6, 37% for 5/6, 39% for 4/6, and 40% for 3/6 at three years post-transplant, P=0.567) (Figure 1B). A similar trend was seen when subjects were limited to standard-risk disease status at transplant (81% for 6/6, 76% for 5/6, 57% for 4/6, and 81% for 3/6 at three years post-transplant, P=0.035, for children; 51% for 6/6, 57% for 5/6, 58% for 4/6, and 55% for 3/6 at three years post-transplant, P=0.375, for adults) (*Online Supplementary Figure S1*).

A test of the interaction between HLA disparity and age (adult *vs.* child) revealed that the effect of HLA disparity on overall survival differed significantly between the pediatric and adult patient groups (P=0.009 for HLA disparity of 0-1 mismatches *vs.* 2-3 mismatches).

Hematologic recovery

The cryopreserved total nucleated cell dose significantly affected neutrophil and platelet recovery in children and neutrophil recovery in adults (Table 3). HLA disparity did not significantly affect neutrophil or platelet recovery in adults or children for neutrophil recovery: RR=1.03, P=0.823 for 5/6; RR=0.96, P=0.799 for 4/6; RR=0.67, P=0.068 for 3/6 in children; RR=0.89, P=0.436 for 5/6; RR=0.92, P=0.576 for 4/6; RR=0.84, P=0.243 for 3/6 in adults; for platelet recovery: RR=0.89, P=0.438 for 5/6; RR=0.75, P=0.09 for 4/6; RR=0.71, P=0.164 for 3/6 in children; RR=1.05, P=0.775 for 5/6; RR=1.05, P=0.791 for 4/6; RR=0.99, P=0.951 in 3/6 in adults (Table 3).

Table 1. Patients', disease, and transplant characteristics of pediatric and adult recipients of single-unit cord blood.

Characteristics	Children (age<16) N.	(%)	Adult (age>16) N.	(%)
N. of transplants	498		1880	
Patient age at transplant				
Median (range)	5 (0-15)		49 (16-82)	
0-9 years	378	(76)		
10-19 years	120	(24)	88	(5)
20-29 years			236	(13)
30-39 years			317	(17)
40-49 years			351	(19)
50-59 years			492	(26)
≥60 years or older			396	(21)
Patient sex				
Male	275	(55)	1039	(55)
Female	223	(45)	841	(45)
Sex matching				
Matched	207	(42)	696	(37)
Male to female	114	(23)	391	(21)
Female to male	125	(25)	485	(26)
Unknown	52	(10)	308	(16)
Diagnosis				
AML	170	(34)	1115	(59)
ALL	290	(58)	418	(22)
CML	7	(1)	106	(6)
MDS	31	(6)	241	(13)
Disease status				
Standard	247	(50)	673	(36)
Advanced	236	(47)	1127	(60)
Unknown	15	(3)	80	(4)
ABO matching				
Matched	182	(37)	602	(32)
Minor mismatch	127	(26)	522	(28)
Major mismatch	113	(23)	451	(24)
Bidirectional	75	(15)	301	(16)
Unknown	1	(<1)	4	(<1)
HLA mismatched number				
Matched (6/6)	82	(16)	71	(4)
One locus mismatched (5/6)	222	(45)	309	(16)
Two loci mismatched (4/6)	158	(32)	1025	(55)
Three loci mismatched (3/6)	36	(7)	475	(25)
N. of cryopreserved nucleated cells (x10^7/kg)				
Median	5.30		2.52	
Range	0.81-38.7		0.71-9.98	
N. of cryopreserved CD34-positive cells (x10^5/kg)				
Median	1.68		0.83	
Range	0.072-65.66		0.07-14.02	
Preparative regimen*				
MAST				
CY+TBI	216	(43)	891	(47)
Other TBI regimen	93	(19)	162	(9)
BU+CY	86	(17)	65	(3)
Other non-TBI regimen	41	(8)	47	(3)
RIST				
FL+BU+other	6	(1)	172	(9)
FL+CY+other	12	(2)	119	(6)
FL+Mel+other	21	(4)	357	(19)
Other RIST	23	(5)	67	(4)
T-cell depletion *in vivo***				
ATG or ALG use	9	(2)	26	(1)
GVHD prophylaxis***				
Cyclosporine A + sMTX	157	(32)	748	(40)
Cyclosporine A + MMF/steroid	37	(7)	99	(5)
Cyclosporine A alone	31	(6)	142	(8)
Tacrolimus + sMTX	216	(43)	434	(23)
Tacrolimus + MMF/steroid	24	(5)	132	(7)
Tacrolimus alone	20	(4)	304	(16)
Others	13	(3)	21	(1)

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**CY: cyclophosphamide; CA: citarabine; BU: busulfan; TBI: total body irradiation; FL: fludarabine; Mel: melphalan, **ATG: antithymocyte globulin; ALG: antilymphocyte globulin; ***sMTX: short-term methotrexate; MMF: mycophenolate mofetil.*

Acute and chronic graft-versus-host disease

The risk of grade 2 to 4 acute GVHD was significantly higher in HLA-mismatched UCB pediatric recipients (RR=2.13, *P*=0.004 for 5/6; RR=2.65, *P*<0.001 for 4/6; RR=2.39, *P*=0.0015 for 3/6; P for trend 0.001) (Table 4). The risk of chronic GVHD and extensive-type chronic GVHD was also significantly higher in 4/6 UCB recipients (RR=2.99, *P*=0.005 for chronic GVHD, and RR=7.62, *P*=0.047 for extensive-type chronic GVHD), and the risks increased according to the number of mismatches (P for trend, 0.002 for chronic GVHD, 0.005 for extensive-type chronic GVHD). In adults, in contrast to the results in children, there were no differences in the risks of grade 2 to 4 acute GVHD in 5/6 and 4/6 UCB recipients (for grade 2 to 4 acute GVHD, RR=1.03, *P*=0.916 for 5/6, RR=1.27, *P*=0.276 for 4/6). The risk of grade 2 to 4 acute GVHD was higher for 3/6 (RR=1.72, *P*=0.017). In adult recipients, the risk of chronic GVHD was increased in recipients of 4/6 UCB (RR=1.90, *P*=0.04), however, there were no differences in the risk of extensive-type chronic GVHD (RR=1.15, *P*=0.758 for 5/6; RR=1.62, *P*=0.253 for 4/6; RR=1.28, *P*=0.574 for 3/6) (Table 4).

Effect of total nucleated cell dose on outcome

An increase in the cryopreserved total nucleated cell dose increased the incidence of neutrophil recovery in both children and adults, as well as the incidence of platelet recovery in children (Table 3). The cumulative incidences of neutrophil recovery were 94% for >10 x 10^7/kg, 88% for 5.0-9.9 x 10^7/kg, 82% for 2.5-4.9 x 10^7/kg, and 86% for <2.5 x 10^7/kg in children (*P*<0.001) (Figure 2A). The cell dose was significantly correlated with the recipient's age at transplant in children (the median ages were one year for >10 x 10^7/kg, 3 years for 5.0-9.9 x 10^7/kg, 8 years for 2.5-4.9 x 10^7/kg, and 12 years for <2.5 x 10^7/kg). The cumulative incidences of neutrophil recovery were 76% for >2.5 x 10^7/kg and 74% for <2.5 x 10^7/kg in adults (*P*=0.007) (Figure 2B). The cumulative incidences of TRM at three years post-transplant were 13% for >10 x 10^7/kg, 14% for 5.0-9.9 x 10^7/kg, 14% for 2.5-4.9 x 10^7/kg, and 14% for <2.5x10^7/kg in children (*P*=0.98) and 29% for >2.5x10^7/kg and 28% for <2.5 x 10^7/kg in adults (*P*=0.77) (*Online Supplementary Figure S2*). The probabilities of overall survival at three years post-transplant were 68% for >10x10^7/kg, 53% for 5.0-9.9 x 10^7/kg, 57% for 2.5-4.9 x 10^7/kg, and 55% for <2.5x10^7/kg in children (*P*=0.30) and 36% for >2.5 x 107/kg and 41% for <2.5x10^7/kg in adults (*P*=0.13). A lower total nucleated cell dose was neither associated with increased mortality in children or adults in multivariate analyses (Table 2). Thus, there was no combined effect of HLA disparity and total nucleated cell dose on mortality neither in children nor in adults (cumulative

incidence of TRM at three years post-transplant, 8% for 6/6, 11% for 5/6 and >5 x 10^7/kg, 11% for 5/6 and 2.5-4.9 x 10^7/kg, 0% for 5/6 and <2.5 x 10^7/kg, 23% for 4/6 and >5 x 10^7/kg, 24% for 4/6 and 2.5-4.9 x 10^7/kg, 25% for 4/6 and <2.5 x 10^7/kg in children, and 23% for 6/6, 29% for 5/6 and >2.5 x 10^7/kg, 30% for 5/6 and <2.5 x 10^7/kg, 27% for 4/6 and >2.5 x 10^7/kg, 27% for 4/6 and <2.5 x 10^7/kg in adults (*Online Supplementary Figure S3*).

Association of outcomes with the type of HLA mismatches for 4/6 adult recipients

The large number of adult recipients of 4/6 CB enabled us to analyze association of outcomes with the type of HLA mismatches in this population. The number of recipients were 7 for HLA-A double mismatch, 170 for HLA-A and HLA-B mismatch, 190 for HLA-A and HLA-DRB1 mismatch, 36 for HLA-B double mismatch, 581 for HLA-B and HLA-DRB1 mismatch, and 41 for HLA-DRB1 double mismatch. With adjusted analyses, adjusted with same variables in the final model of all adult recipients, there was no significant effect of HLA mismatch types on overall mortality with HLA-A and HLA-B mismatch as the reference (*Online Supplementary Table S3*). The risk of relapse was significantly decreased in HLA-A and HLA-DRB1

Table 2. Multivariate analyses of overall survival, relapse, and transplant-related mortality.

		Overall mortality			Relapse			Transplant-related mortality		
Outcome	N.	RR	95%CI	*P*	RR	95%CI	*P*	RR	95%CI	*P*
Children 15 years or younger										
HLA disparity										
Matched (6/6)	82	1.00			1.00			1.00		
5/6	222	1.07	(0.68-1.69)	0.765	1.06	(0.68-1.65)	0.794	1.29	(0.52-3.23)	0.58
4/6	158	1.61	(1.02-2.56)	0.042	0.77	(0.48-1.24)	0.282	3.55	(1.47-8.58)	0.005
3/6	36	1.25	(0.65-2.42)	0.498	0.91	(0.45-1.86)	0.802	1.56	(0.43-5.63)	0.497
Total nucleated cell dose										
≥10.0x10^7/kg	85	1.00			1.00			1.00		
5.0-9.9x10^7/kg	169	1.14	(0.72-1.79)	0.579	1.10	(0.69-1.75)	0.684	0.82	(0.40-1.68)	0.592
2.5-4.9x10^7/kg	190	0.92	(0.58-1.45)	0.707	0.90	(0.56-1.44)	0.651	0.90	(0.45-1.80)	0.77
<2.5x10^7/kg	43	0.88	(0.47-1.67)	0.701	0.98	(0.53-1.83)	0.961	0.67	(0.24-1.88)	0.443
Adults 16 years or older										
HLA disparity										
Matched (6/6)	71	1.00			1.00			1.00		
5/6	309	0.99	(0.71-1.38)	0.944	0.70	(0.47-1.04)	0.075	1.41	(0.83-2.41)	0.205
4/6	1025	0.88	(0.65-1.21)	0.436	0.67	(0.47-0.97)	0.034	1.24	(0.75-2.04)	0.408
3/6	475	0.95	(0.69-1.31)	0.751	0.70	(0.48-1.03)	0.07	1.29	(0.77-2.16)	0.339
Total nucleated cell dose										
≥3.0x10^7/kg	439	1.00			1.00			1.00		
2.5-2.9x10^7/kg	492	0.99	(0.83-1.17)	0.876	0.86	(0.70-1.06)	0.167	1.10	(0.86-1.42)	0.445
2.0-2.4x10^7/kg	705	0.86	(0.72-1.01)	0.06	0.79	(0.65-0.97)	0.021	1.05	(0.83-1.33)	0.694
<2.0x10^7/kg	183	0.93	(0.73-1.18)	0.562	0.79	(0.59-1.07)	0.126	1.00	(0.70-1.45)	0.983

For overall mortality, other predictive variables were advanced disease status at transplant in children, and age at transplant over 50 years, male sex, advanced disease status at transplant, chronic myeloid leukemia (associated with a lower risk of mortality), and reduced-intensity conditioning in adults. For relapse, other predictive variables were advanced disease status at transplant, and acute lymphoblastic leukemia or myelodysplastic syndrome (associated with a lower risk of relapse) in children, and advanced disease status at transplant and myelodysplastic syndrome (associated with a lower risk of relapse) in adults. For transplant-related mortality, there was no other predictive variable in children. Other predictive variables for adults were age at transplant over 50 years and female to male donor-recipient sex mismatch.

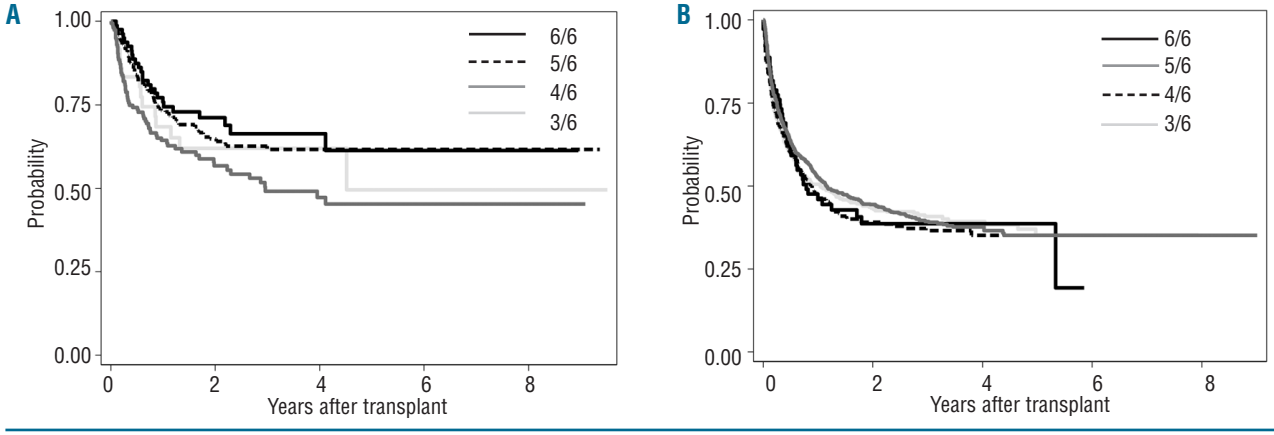

Figure 1. Unadjusted probabilities of overall survival in HLA disparity groups for pediatric (A) and adult (B) recipients with leukemia. (A) In children, the unadjusted probabilities of survival at three years post-transplant were 66% for recipients of HLA matched (6/6), 62% for one-locus-mismatched (5/6), 45% for two-loci-mismatched (4/6), and 62% for three-loci-mismatched (3/6) single-unit unrelated cord blood (*P*=0.032). (B) In adults, these probabilities were 38% 37%, 39%, and 40% respectively (*P*=0.567) (B).

mismatch, HLA-B and HLA-DRB1 mismatch, and HLA-DRB1 double mismatch recipients (RR=0.70, *P*=0.045; RR=0.76, *P*=0.047; and RR=0.46, *P*=0.03, respectively). The risk of transplant-related mortality was significantly increased in HLA-DRB1 double mismatch recipients (RR=2.06, *P*=0.025). There was no significant effect of HLA mismatch types for risks of grade 2 to 4 and grade 3 to 4 acute GVHD (*Online Supplementary Table S3*).

Discussion

Our main objective was to assess the effect of HLA disparity on survival after single-unit UCBT in children and adults, and to obtain data that could be useful for the selection of an appropriate cord blood unit for patients with leukemia. Our study is the first to assess the effect of UCB HLA-matching on the transplant outcome in a large

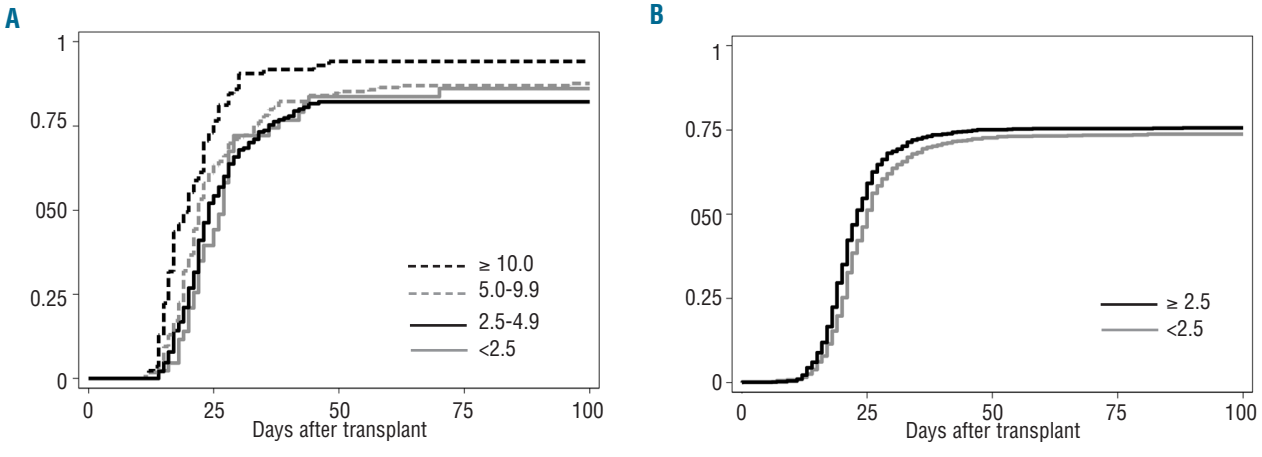

Figure 2. Unadjusted cumulative incidences of neutrophil recovery in total nucleated cell dose groups for pediatric (A) and adult (B) recipients with leukemia. (A) In children, the unadjusted cumulative incidences of neutrophil recovery were 94% for >10x10^7/kg, 88% for 5.0-9.9 x10^7/kg, 82% for 2.5-4.9x10^7/kg, and 86% for <2.5x10^7/kg (*P*<0.001). (B) In adults, these incidences were 76% for >2.5x10^7/kg and 74% for <2.5 x10^7/kg (*P*=0.007).

Table 3. Multivariate analyses of neutrophil and platelet recovery.

	Children 15 ≤years or younger					Adults ≥16 years or older			
Outcome	**N**	**RR**	**95%CI**	***P* value**		**N**	**RR**	**95%CI**	***P***
Neutrophil recovery									
HLA disparity									
Matched (6/6)	82	1.00				71	1.00		
5/6	222	1.03	(0.77-1.39)	0.823		309	0.89	(0.66-1.19)	0.436
4/6	158	0.96	(0.71-1.30)	0.799		1025	0.92	(0.70-1.22)	0.576
3/6	36	0.67	(0.44-1.03)	0.068		475	0.84	(0.64-1.12)	0.243
Total nucleated cell dose									
≥>10.0x10^7/kg	85	1.00			≥3.0x10^7/kg	439	1.00		
5.0-9.9x10^7/kg	169	0.66	(0.49-0.89)	0.007	2.5-2.9x10^7/kg	492	0.84	(0.72-0.97)	0.021
2.5-4.9x10^7/kg	190	0.50	(0.37-0.67)	<0.001	2.0-2.4x10^7/kg	705	0.79	(0.68-0.90)	0.001
<2.5x10^7/kg	43	0.54	(0.38-0.77)	0.001	<2.0x10^7/kg	183	0.78	(0.64-0.94)	0.009
Platelet recovery									
HLA disparity									
Matched (6/6)	82	1.00				71	1.00		
5/6	222	0.89	(0.66-1.20)	0.438		309	1.05	(0.73-1.52)	0.775
4/6	158	0.75	(0.54-1.05)	0.09		1025	1.05	(0.74-1.48)	0.791
3/6	36	0.71	(0.44-1.15)	0.164		475	0.99	(0.69-1.41)	0.951
Total nucleated cell dose									
≥10.0x10^7/kg	85	1.00			≥3.0x10^7/kg	439	1.00		
5.0-9.9x10^7/kg	169	0.93	(0.68-1.29)	0.681	2.5-2.9x10^7/kg	492	0.84	(0.70-1.01)	0.058
2.5-4.9x10^7/kg	190	0.70	(0.51-0.97)	0.03	2.0-2.4x10^7/kg	705	0.86	(0.73-1.02)	0.078
<2.5x10^7/kg	43	0.70	(0.45-1.07)	0.101	<2.0x10^7/kg	183	0.72	(0.57-0.91)	0.007

For neutrophil recovery, other predictive variables were acute lymphoblastic leukemia in children (with a higher neutrophil recovery), and advanced disease status at transplant in adults. For platelet recovery, other predictive variables were advanced disease status at transplant in children, and age at transplant over 50 years, male sex, and advanced disease status at transplant in adults.

Table 4. Multivariate analyses of grade 2 to 4/grade 3 to 4 acute graft-*versus*-host disease, and chronic/extensive-type chronic graft-*versus*-host disease.

	Grade 2 to 4 acute GVHD				Grade 3 to 4 acute GVHD				Chronic GVHD				Extensive-type chronic GVHD			
Outcome	N.	RR	95%CI	*P*	RR	95%CI	*P*	N.	RR	95%CI	*P*	RR	95%CI	*P*
Children 15 years or younger														
HLA disparity														
Matched (6/6)	72	1.00			1.00			67	1.00			1.00		
5/6	196	2.13	(1.28-3.58)	0.004	1.75	(0.73-4.24)	0.212	186	1.79	(0.85-3.75)	0.123	4.15	(0.54-31.81)	0.17
4/6	136	2.65	(1.55-4.52)	<0.001	2.25	(0.94-5.41)	0.07	114	2.99	(1.42-6.30)	0.004	7.62	(1.03-56.63)	0.047
3/6	28	2.39	(1.18-4.84)	0.015	2.60	(0.82-8.26)	0.105	23	2.61	(0.96-7.11)	0.061	7.49	(0.81-69.63)	0.077
Adults 16 years or older														
HLA disparity														
Matched (6/6)	56	1.00			1.00			49	1.00			1.00		
5/6	227	1.03	(0.64-1.65)	0.916	0.95	(0.38-2.37)	0.919	193	1.58	(0.83-3.02)	0.161	1.15	(0.47-2.80)	0.758
4/6	765	1.27	(0.82-1.97)	0.276	1.27	(0.55-2.94)	0.573	650	1.90	(1.03-3.51)	0.04	1.62	(0.71-3.72)	0.253
3/6	341	1.72	(1.10-2.70)	0.017	1.13	(0.47-2.68)	0.788	288	1.81	(0.96-3.38)	0.065	1.28	(0.54-3.02)	0.574

For grade 2 to 4 acute GVHD, other predictive variables were total nucleated cell dose (>10x10^7/kg as the reference, RR=1.94 P=0.009 for 5.0-9.9x107/kg, RR=1.73 P=0.028 for 2.5-4.9x107/kg, and R=1.68 P=0.094 for <2.5x10^7/kg) in children, and cyclosporine-based GVHD prophylaxis (vs. tacrolimus-based) in adults. For grade 3 to 4 acute GVHD, male sex and advanced disease status in children, and male sex and male to female donor-recipient sex mismatch and reduced-intensity conditioning in adults. For chronic GVHD, no other predictive variables in children, and other predictive variable for adults was ABO major mismatch, and male to female sex mismatch and advanced risk disease status for decreased risk. For extensive-type chronic GVHD, no other predictive variables in children, and other predictive variable for adults was ABO major mismatch.

number of adult recipients. Our findings in children were similar to those in previous reports.[9,17,18,31,32] An increase in the number of HLA mismatches resulted in an increased risk of acute and chronic GVHD, which led to an increased risk of overall and transplant-related mortality. In contrast to the results in children, the probability of overall or relapse-free survival did not decrease with the number of mismatched antigens in adults. An increase in the number of HLA mismatches in UCB increased the incidence of cGVHD in 4/6 CB recipients; however, there was no increase in the risk of grade 2 to 4 or severe acute GVHD, or extensive-type chronic GVHD. These differences may have contributed to the decreased incidence of relapse without affecting TRM after HLA-mismatched UCBT in adults.

A major potential contributor to the different findings in children and adults is the difference in the nucleated cell dose. There was a dramatic difference in the nucleated cell dose between children and adults. TNC dose in adults is highly concentrated in a very small, low-dose area that is quite different from the doses used in children in our study and from the doses in previous reports, mainly in pediatric recipients.[9,18,32] A positive effect on the transplant outcome with a decreased incidence of acute GVHD and lower mortality with HLA matching might only be seen in the setting of pediatric recipients who receive cord blood with a larger cell dose compared to adults. A report from Eurocord of 171 adult recipients of single-unit CBT did not see a decrease in the probability of overall or relapse-free survival with the number of mismatched antigens.[33] A more recent collaborative study by the Center for International Blood and Marrow Transplant Research, the New York Blood Center National Cord Blood Program, and the Eurocord-Netcord registry with 514 adult recipients did not observe an increase in mortality after HLA-mismatched UCBT.[34]

Another potential cause of different findings in children and adults is differences in diagnosis. Adult recipients had a significantly greater proportion of patients with myeloid malignancy. The incidence of a graft-*versus*-leukemia effect is reportedly higher in myeloid malignancy.[35-37] The decreased risk of relapse with a significant graft-*versus*-leukemia effect in HLA-mismatched UCB recipients was also more prominent in adult recipients with acute myeloid leukemia in our study. Furthermore, there were differences in disease risk between children and adults. Only 36% of adults were in a standard-risk disease status at transplant, while this value was 50% in children. Although we had adjusted for the disease status at transplant, we cannot rule out the possibility that these differences influenced the results.

An increase in the total nucleated cell dose increased the neutrophil recovery rate in both children and adults, consistent with other reports.[18,31-33] A lower total nucleated cell dose was not associated with increased transplant-related or overall mortality in our cohort, thus, we did not see a combined effect of HLA disparity and total nucleated cell dose. This differs from the findings of a recent report from New York Cord Blood Bank.[18] In our cohort, a lower cell dose was associated with a slower recovery; however, the differences in the overall incidences of neutrophil recovery between cell dose groups were small, especially in the adult cohort. This may explain our finding that a lower total nucleated cell dose was not associated with increased mortality. Another probable reason for the different findings is that for our analyses we separated children and adults. A small percentage of older adults who received lower cell dose CB included in the subjects of previous studies may have affected increased mortality with lower cell doses. Lastly, TNC dose in adults is highly concentrated in a very small, low-dose area (nearly 70% lie in the range of 2.0-3.0 x 10^7/kg) which is a unique finding for adult recipients of single-unit cord blood in Japan. Therefore, differences in cell doses between the TNC dose groups is quite small, which is suspected to be one of the reasons for these findings. The results of our study support the current recommended cut-off TNC dose for cord blood search in Japan, which is 2.0 x 10^7/kg.

Although information is still limited because of the limited number of 6/6 and 5/6 CB adult recipients, the large number of adult recipients of 4/6 CB enabled us to analyze the association of outcomes with the type of HLA mismatches in this population. There was no effect of HLA mismatch type on overall mortality; therefore, there is no

preference recommendation for HLA mismatch types from our study. The increase in the number of HLA-DRB1 mismatch was associated with decreased mortality; however, it is important to note that HLA-DRB1 double mismatch was associated with increased transplant-related mortality.

This study included a large number of HLA-A, HLA-B, low-resolution and HLA-DRB1 high-resolution typed CB recipients, but there are limitations. UCB selection is mainly influenced by the availability of an acceptable cell dose, but is also influenced by many unmeasured factors that can affect the outcome. Although we adjusted for known risk factors and disparities between groups, we cannot rule out the influence of a potential selection bias. Another limitation involves the results for 3/6. Since, in current practice in Japan, HLA-DR typing for UCB unit selection is performed at low resolution, with a preference of up to two HLAantigen-mismatched UCB units, most (97%) of the HLA-A, HLA-B, low-resolution and HLA-DRB1 high-resolution 3/6 UCB in the present study were selected as one- or two-antigen-mismatched for theHLA-A, HLA-B, and HLA-DR low-resolution level. If we consider the effect of the current practice for UCB unit selection regarding 3/6 UCB, our conclusions should only apply to HLA-A, HLA-B, and HLA-DRB1 or HLA-A, HLA-B, and HLA-DR zero- to two-mismatched UCBT. Furthermore, we may have underestimated the impact of HLA-matching, since we did not have enough data to include low- or high-resolution information on HLA-C matching, which was recently reported to affect mortality.[38]

In conclusion, we found that the effects of HLA disparity on transplant outcome differed between children and adults. In children, an increased number of mismatched HLA loci correlated with an increased risk of mortality. These findings support the selection of a UCB unit with HLA 6/6 followed by 5/6, consistent with the recommendations from the US and Europe. In adults, there was no increase in mortality with an increase in the number of mismatched HLA loci. In this case, a UCB unit with up to 4/6 can be selected if transplant is urgently needed.

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Authorship and Disclosures

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