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

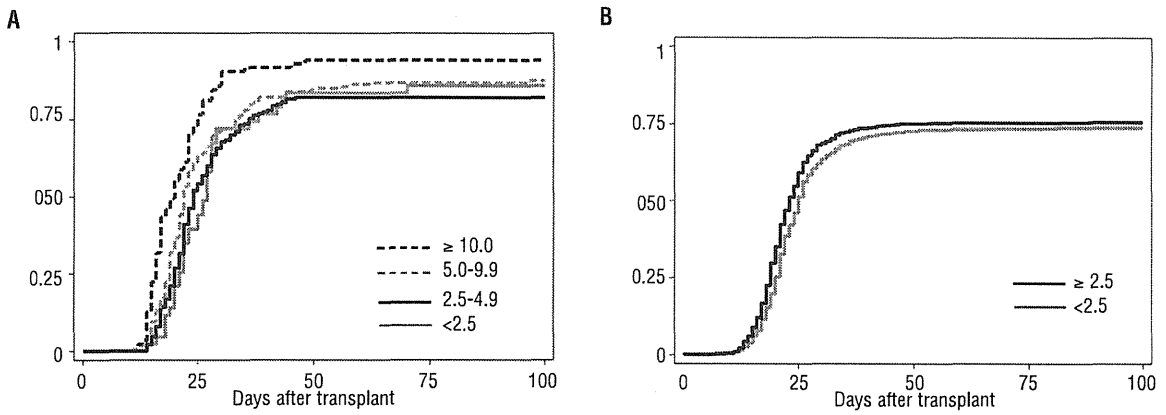

Figure 2. Unadjusted cumulative incidences of neutrophil recovery in total nucleated cell dose groups for pediatric (A) and adult (B) recipients with leukemia. (A) In children, the unadjusted cumulative incidences of neutrophil recovery were 94% for >10x10^7/kg, 88% for 5.0-9.9 x10^7/kg, 82% for 2.5-4.9x10^7/kg,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

Outcome	Children ≤15 years or younger N	RR	95%CI	*P* value		Adults ≥16 years or older 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.

Outcome	Grade 2 to 4 acute GVHD N.	RR	95%CI	P	Grade 3 to 4 acute GVHD RR	95%CI	P	Chronic GVHD N.	RR	95%CI	P	Extensive-type chronic GVHD 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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Comparison of Unrelated Cord Blood Transplantation and HLA-Mismatched Unrelated Bone Marrow Transplantation for Adults with Leukemia

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Recent advances in unrelated cord blood transplantation (UCBT) and high-resolution typing of human leukocyte antigen (HLA) from an unrelated donor have increased choices in alternative donor/stem cell source selection. We assessed HLA-mismatched locus-specific comparison of the outcomes of 351 single-unit UCB and 1,028 unrelated bone marrow (UBM) adult recipients 16 years old or older at the time of transplantation who received first stem cell transplantation with myeloablative conditioning for acute leukemia or myelodysplastic syndromes. With adjusted analyses, HLA 0 to 2 mismatched UCBT showed similar overall mortality (relative risk [RR] = 0.85, 95% confidence interval [CI], 0.68-1.06; $P = .149$) compared with that of single-HLA-DRB1-mismatched UBMT. UCBT showed inferior neutrophil recovery (RR = 0.50, 95% CI, 0.42-0.60; $P < .001$), lower risk of acute graft-versus-host disease (RR = 0.55, 95% CI, 0.42-0.72; $P < .001$), and lower risk of transplantation-related mortality (RR = 0.68, 95% CI, 0.50-0.92; $P = .011$) compared with single-HLA-DRB1-mismatched UBMT. No significant difference was observed for risk of relapse (RR = 1.28, 95% CI, 0.93-1.76; $P = .125$). HLA 0 to 2 antigen-mismatched UCBT is a reasonable second alternative donor/stem cell source with a survival outcome similar to that of single-HLA-DRB1-mismatched or other 7 of 8 UBMT.

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KEY WORDS: Unrelated cord blood transplantation, HLA-mismatched unrelated bone marrow transplantation

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a widely used, curative treatment for hematologic malignancies. When available, a human leukocyte antigen (HLA)-identical sibling is the donor of choice. However, only about 30% of candidates eligible for allogeneic HSCT will have such a donor. In addition, older patients with older siblings have more difficulty finding such a donor capable of stem cell donation. High-resolution donor-recipient HLA matching has contributed to the success of unrelated donor marrow transplantation, and the current first recommended alternative donor after an HLA-matched sibling for HSCT is an HLA-A, -B, -C, and -DRB1 8 of 8-allele-matched unrelated donor [1-4]. However, there are still a significant number of patients for which finding an HLA 8 of 8-matched unrelated donor is difficult and for whom a second alternative donor/stem cell source should be found.

The effect of HLA mismatches after bone marrow transplantation from unrelated donors (UBMT) has been well studied, and single mismatched UBM donors are usually selected as a second alternative donor/stem cell source [1-4]. Lee al. [3] showed that a single mismatch, antigen-level, or high-resolution, at HLA-A, -B, -C, or -DRB1 loci was associated with higher mortality and decreased survival. However, the reduction in survival may be acceptable in comparison with the survival rates for currently available alternative treatments. Analyses from the Japan Marrow Donor Program (JMDP) showed better survival in HLA class II mismatched recipients; thus, single-DRB1-mismatched UBM donor is currently a second alternative in Japan [1,2,5].

Recent advances in unrelated cord blood transplantation (UCBT) have provided patients with increased choices for a second alternative donor/stem cell source [6]. Clinical comparison studies of cord blood transplantation and HLA-A, -B, and -DRB1 6 of 6 allele-matched bone marrow transplantation for leukemia from unrelated donors in adult recipients showed comparable results [7-9]. More recently, promising outcomes of UCBT were shown compared with HLA-A, -B, -C, and -DRB1 8 of 8 allele-matched UBMT, the current first alternative donor/stem cell source [10-12].

The aim of this study was to determine the utility of UCBT as a second-alternative donor source in adult patients with acute leukemia or myelodysplastic syndromes. It is common today to perform high-resolution typing of HLA for donor selection of unrelated donors; thus, we performed mismatched-allele-specific analyses for comparison of HLA-mismatched UBMT and UCBT in terms of overall survival (OS) and other HSCT outcomes, setting single-DRB1-mismatched UBMT, the current second alternative, as the reference.

PATIENTS AND METHODS

Collection of Data and Data Source

The recipients' clinical data were provided by the Japan Cord Blood Bank Network (JCBBN) and the JMDP [13]. Peripheral blood stem cell donation from unrelated donors was not permitted in Japan during the study period. All 11 cord blood banks in Japan are affiliated with JCBBN. Both JCBBN and JMDP collect recipients' clinical information at 100 days posttransplantation. Patients' information on survival, disease status, and long-term complications including chronic graft-versus-host (cGVHD) disease and second malignancies is renewed annually using follow-up forms. This study was approved by the institutional review board of Nagoya University Graduate School of Medicine.

Patients

The subjects were adult patients of at least 16 years of age with acute myeloid leukemia, acute lymphoblastic leukemia, and myelodysplastic syndromes, who were recipients of first UBMT or UCBT with myeloablative conditioning. All patients in the UCBT cohort received a single-unit CB. Transplantation years were between 1996 and 2005 for UBMT and between 2000 and 2005 for UCBT to avoid the first 3 years of a pioneering period (1993-1995 for UBMT and 1997-1999 for UCBT). There were no statistically significant differences between UBMT in 1996-1999 and UBMT in 2000-2005 in probabilities of OS (41% versus 44%, at 3 years posttransplantation; $P = .86$) and in relapse-free survival (RFS) (40% versus 40%, at 3 years posttransplantation; $P = .93$).

Among 2,253 UBMT recipients with complete HLA high-resolution data, the following recipients with HLA -A, -B, -C, and -DRB1 8 of 8 allele match (n = 1,079) and more than three mismatches (5 of 8 allele match [n = 117], 4 of 8 allele match [n = 24], 3 of 8 allele match [n = 4], 2 of 8 allele match [n = 1]) were excluded. There were no statistically significant differences in risk of mortality or treatment failure (RFS) associated with single high-resolution (allele) versus single low-resolution (antigen) mismatches (data not shown), so in the analyses, allele and antigen mismatches were considered equivalent. HLA matching of cord blood was performed using low-resolution molecular typing methods for HLA-A and -B, and high-resolution molecular typing for HLA-DRB1. Of 557 recipients of CB with complete HLA data, 105 recipients with three mismatches and nine recipients with four mismatches were excluded. A total of 1,028 UBMT recipients (248 HLA class II locus mismatched, 424 HLA class I locus mismatched, and 356 HLA 2 loci mismatched) and 351 UCBT recipients (20 HLA-A, -B, low-resolution and -DRB1 matched, 87

locus mismatched, and 244 2 loci mismatched) were the subjects for analyses. Both host-versus-graft and graft-versus-host directions were accounted for in terms of HLA mismatch.

HLA Typing

Alleles at the HLA-A, -B, -C, and -DRB1 with unrelated bone marrow donor-recipient pairs and for HLA-DRB1 for unrelated cord blood donor-recipient pairs were identified by the methods described previously [1,5,14]. Serologic or antigen-level typing was performed with a standard two-stage complement-dependent test of microcytotoxicity or low-resolution DNA-based typing usually by collapsing the four-digit typing result back to its first two digits in part.

Definitions

The primary outcome of the analyses was OS, defined as time from transplantation to death from any cause. A number of secondary endpoints were also analyzed. Neutrophil recovery was defined by an absolute neutrophil count of at least 500 cells per cubic millimeter for three consecutive points; platelet recovery was defined by a count of at least 50,000 platelets per cubic millimeter without transfusion support. Diagnosis and clinical grading of acute GVHD (aGVHD) were performed according to the established criteria [15,16]. Relapse was defined as a recurrence of underlying hematologic malignant diseases. Transplantation-related death was defined as death during a continuous remission. RFS was defined as survival in a state of 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 for categoric variables. Cumulative incidence curves were used in a competing-risks setting to calculate the probability of aGVHD and cGHVD, relapse, and transplantation-related mortality (TRM) [17]. Gray's test was used for group comparison of cumulative incidences [18]. Adjusted comparison of the groups on OS and RFS was performed with the use of the Cox proportional-hazards regression model [19]. For other outcomes with competing risks, Fine and Gray's proportional-hazards model for subdistribution of a competing risk was used [20]. For neutrophil and platelet recovery, death before neutrophil or platelet recovery was the competing event; for GVHD, death without GVHD and relapse were the competing events; for relapse, death without relapse was the competing event; and, for TRM, relapse was the competing event [21]. Adjusted probabilities of OS and RFS were estimated using the Cox proportional-hazards regression model, with consideration of other significant clinical variables in the final multivariate models. The variables considered were the patient's age at transplantation, patient's sex, donor-patient sex mismatch, donor-patient ABO mismatch, diagnosis, disease status at conditioning, the conditioning regimen, and the type of prophylaxis against GVHD. Factors differing in distribution between CB and BM recipients and factors known to influence outcomes were included in the final models. Variables with more than two categories were dichotomized for the final multivariate model. Variables were dichotomized as follows: patient age >40 or <40 years at transplantation, recipient's sex, sex-mismatched donor-patient pair versus sex-matched pair, donor-recipient ABO major mismatch versus others for ABO matching, advanced versus standard (first and second complete remission of acute myeloid leukemia, first complete remission of acute lymphoblastic leukemia, or refractory anemia or refractory anemia with ring sidoblasts of myelodysplastic syndromes) risk of the disease, cyclophosphamide, and total-body irradiation (TBI) or busulfan and cyclophosphamide or others for conditioning regimen, and cyclosporine-based versus tacrolimus-based prophylaxis against GVHD. No significant interactions were identified between each variable and HLA disparity/stem cell source groups. All P values were two-sided.

RESULTS

Patient Characteristics

Table 1 shows characteristics of patients, their disease, and transplantation regimens. Proportions of females, sex-mismatched donor-recipient pairs, and ABO mismatched donor recipient pairs were larger in cord blood recipients ($P < .001$, $P < .001$, and $P < .001$, respectively). UCB recipients were older than recipients of UBM (median age, 37 years versus 34 years; $P < .001$). A preparative regimen with TBI and cyclophosphamide was used in the majority of patients in all groups, and cytosine arabinoside was supplemented for CB recipients in addition to TBI and cyclophosphamide in about half the recipients with cyclophosphamide and TBI. For GVHD prophylaxis, tacrolimus and short-term methotrexate was used preferentially in BM recipients (61% of DRB1-one-mismatched BM recipients), while cyclosporine A and short-term methotrexate was used preferentially in CB recipients (61%). The median follow-up period for survivors was 2.1 years (range, 0.1-6.2) for CB recipients and 5.5 (range, 0.3-11.6) years for BM recipients.

Table 1. Patient, Disease, and Transplantation Characteristics According to Stem Cell Source and Number of Mismatched Loci

	Bone Marrow Transplant			
	Class II One Locus Mismatch	Class I One Locus Mismatch	Two Loci Mismatch	Cord Blood Transplantation
	N (%)	N (%)	N (%)	N (%)
Number of transplantations	248	424	356	351
Patient age at transplantation				
Median (range)	36 (16-60)	34 (16-67)	34 (16-59)	37 (16-58)
Patient sex				
Male	151 (61)	241 (57)	210 (59)	162 (46)
Female	97 (39)	183 (43)	146 (41)	189 (54)
Sex matching				
Matched	145 (58)	268 (63)	217 (61)	170 (48)
Male to female	52 (21)	82 (19)	73 (21)	97 (28)
Female to male	50 (20)	71 (17)	64 (18)	84 (24)
Unknown	1 (<1)	3 (1)	2 (1)	0 (0)
Diagnosis				
AML	135 (54)	204 (48)	172 (48)	193 (55)
ALL	78 (31)	149 (35)	135 (38)	113 (32)
MDS	35 (14)	71 (17)	49 (14)	45 (13)
Disease status				
Standard	124 (50)	214 (50)	168 (47)	147 (42)
Advanced	114 (46)	195 (46)	169 (47)	174 (50)
Unknown	10 (4)	15 (4)	19 (5)	30 (9)
ABO matching				
Matched	119 (48)	184 (43)	153 (43)	114 (32)
Minor mismatch	53 (21)	108 (25)	85 (24)	99 (28)
Major mismatch	67 (27)	116 (27)	97 (27)	73 (21)
Bidirectional	8 (3)	12 (3)	14 (4)	64 (18)
Unknown	1 (<1)	4 (1)	7 (2)	1 (<1)
HLA-mismatched number and direction				
Matched				20 (6)
One locus mismatched				87 (25)
HVG direction	16 (6)	38 (9)		8 (9)
GVH direction	17 (7)	30 (7)		8 (9)
Both directions	215 (87)	356 (84)		71 (82)
Two loci mismatched				244 (70)
Two HVG direction			4 (1)	2 (1)
One HVG direction and one GVH direction			6 (2)	4 (2)
Two GVH direction			4 (1)	3 (1)
One both directions and one HVG direction			42 (12)	40 (16)
One both directions and one GVH direction			29 (8)	28 (11)
Two both directions			271 (76)	167 (68)
No. of nucleated cells infused ($\times 10^7$/kg)				
Median	25.0	24.5	23	2.46
Range	2.40-59.8	2.10-97.5	1.5-66.0	1.41-6.01
Preparative regimen				
CY + TBI	94 (38)	168 (40)	151 (42)	109 (31)
CY + CA + TBI	46 (19)	78 (18)	74 (21)	124 (35)
CY + BU + TBI	20 (8)	39 (9)	27 (8)	15 (4)
Other TBI regimen	45 (18)	70 (17)	61 (17)	80 (23)
BU + CY	34 (14)	54 (13)	30 (8)	21 (6)
Other non-TBI regimen	9 (4)	15 (4)	13 (4)	2 (1)
GVHD prophylaxis				
Cycrosporine A + sMTX	87 (35)	221 (52)	150 (42)	213 (61)
Cyclosporine A ± other	1 (<1)	5 (1)	5 (1)	24 (7)
Tacrolimus + sMTX	152 (61)	191 (45)	193 (54)	76 (22)
Tacrolimus ± other	8 (3)	5 (1)	6 (2)	35 (10)
Others	0 (0)	2 (<1)	2 (<1)	3 (1)

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BU, oral busulfan; CA, citarabine; CY, cyclophosphamide; GVH, graft-versus-host; HVG, host-versus-graft; MDS, myelodysplastic syndomes; sMTX, short-term methotrexate.

Outcome

OS and RFS

OS and RFS for CB recipients were similar when compared with that of single-HLA-DRB1-mismatched BM recipients (relative risk [RR] = 0.85, 95% confidence interval [CI], 0.68-1.06; P = .149 for OS and RR = 0.97, 95% CI, 0.92-1.35; P = .747) (Table 2).

The adjusted probabilities of survival at 3 years posttransplantation of CB recipients (47%) were not different from those of single HLA-DRB1 mismatched BM recipients (41%; P = .19) or single HLA class I-mismatched BM recipients (47%; P = .96), but superior to those of 6 of 8 BM recipients (38%; P = .014) (Figure 1A). Figure 1B shows adjusted RFS curves (42% for CB recipients, 36% for single HLA-DRB1-mismatched BM, 44% for single HLA class I-mismatched BM, and 36% for 6 of 8 BM recipients, at 3 years posttransplant) (P values of comparison between CB and single HLA-DRB1-mismatched BM, CB, and single HLA

Table 2. Multivariate Analyses of Overall Survival, Relapse-Free Survival, Relapse, and Transplant-Related Mortality

	Degree of HLA Mismatch	N	Overall Survival			Relapse-Free Survival			Relapse			Transplant-Related Mortality		
			RR	(95% CI)	P value	RR	(95% CI)	P value	RR	(95% CI)	P value	RR	(95% CI)	P value
Bone marrow transplant	Single DRB1 (7/8)	248	1.00			1.00			1.00			1.00		
	Single A or B (7/8)	137	0.84	(0.64-1.11)	.216	0.82	(0.63-1.08)	.158	0.65	(0.41-1.01)	.056	1.07	(0.77-1.49)	.698
	Single C (7/8)	287	0.89	(0.72-1.12)	.324	0.86	(0.69-1.07)	.170	0.60	(0.41-0.87)	.007	1.13	(0.86-1.48)	.391
	C + DRB1 (6/8)	144	0.97	(0.74-1.27)	.831	0.95	(0.73-1.24)	.726	0.76	(0.49-1.17)	.208	1.10	(0.78-1.55)	.600
	A/B + C (6/8)	122	1.22	(0.94-1.59)	.143	1.15	(0.88-1.49)	.300	0.70	(0.44-1.10)	.12	1.42	(1.03-1.96)	.032
	Other two loci (6/8)	90	1.25	(0.92-1.68)	.146	1.13	(0.84-1.53)	.409	0.60	(0.35-1.02)	.061	1.48	(1.03-2.13)	.035
Cord blood transplant		351	0.85	(0.68-1.06)	.149	0.97	(0.92-1.35)	.747	1.28	(0.93-1.76)	.125	0.68	(0.50-0.92)	.011

RR indicates relative risk; CI, confidence interval.
Adjusted by patient age at transplantation >40 versus ≤40, patient sex, donor-patient sex mismatch versus matched, ABO major mismatch versus others, advanced versus standard disease status at transplantation, cyclophosphamide and total-body irradiation or busulfan and cyclophosphamide for conditioning versus other conditioning regimen, and cyclosporine-based versus tacrolimus-based prophylaxis against graft-versus-host disease.

class I-mismatched BM, and CB and 6 of 8 BM recipients were 0.80, 0.12, and 0.43, respectively).

Relapse and TRM

There was no significant increase of relapse rates among CB recipients when compared with DRB1 single-mismatched BM recipients (RR = 1.28, 95% CI, 0.93-1.76; $P = .125$). The risk of TRM was lower in CB recipients compared with that of single HLA-DRB1-mismatched BM recipients (RR = 0.68, 95% CI, 0.50-0.92; $P = .011$) (Table 2). The risk of TRM was also lower in CB recipients when compared with 6 of 8 BM recipients (RR = 0.52, 95% CI, 0.39-0.68; $P < .001$).

Hematologic recovery

Neutrophil and platelet recovery was inferior in CB recipients, as shown in Table 3 (RR = 0.50, 95% CI, 0.42-0.60; $P < .001$ for neutrophil recovery, RR = 0.52, 95% CI, 0.42-0.63; $P < .001$ for platelet recovery).

Acute GVHD and chronic GVHD

The risk of grade 2 to 4 or severe (grades 3-4) aGVHD was lower in CB recipients than that of single HLA-DRB1-mismatched BM recipients (RR = 0.55, 95% CI, 0.42-0.72; $P < .001$ for grade 2 to 4 aGVHD and RR = 0.43, 95% CI, 0.27-0.58; $P < .001$ for severe aGVHD) (Table 4). Unadjusted cumulative incidence of severe aGVHD was 9% for CB, 19% for single HLA-DRB1-mismatched BM, 18% for single HLA

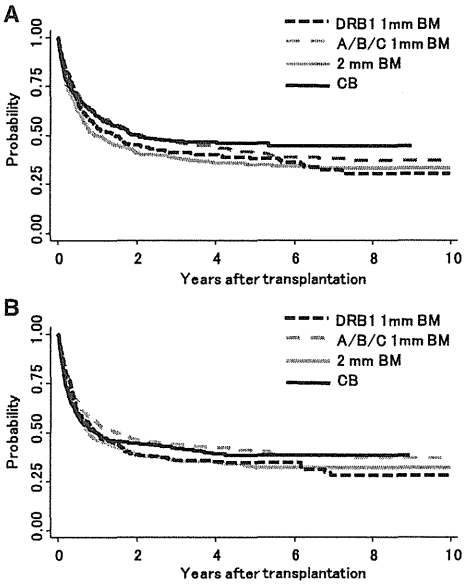

Figure 1. Adjusted probabilities of OS (A) and RFS (B). The adjusted 3-year probabilities of OS for unrelated cord blood recipients, single-HLA-DRB1-mismatched unrelated bone marrow (UBM) recipients, single-HLA-class-I-mismatched UBM, and 6 of 8 UBM recipients were 47%, 41%, 47%, and 38%, respectively (A). The adjusted 3-year probabilities of RFS were 42%, 36%, 44%, and 36%, respectively (B).

Table 3. Multivariate Analyses of Neutrophil and Platelet Recovery

			Neutrophil Recovery			Platelet Recovery		
	Degree of HLA Mismatch	N	RR	(95% CI)	*P* value	RR	(95% CI)	*P* value
Bone marrow transplantation	Single DRB1 (7/8)	248	1.00			1.00		
	Single A or B (7/8)	137	1.31	(1.04-1.65)	.021	1.31	(1.01-1.70)	.039
	Single C (7/8)	287	1.19	(0.98-1.43)	.069	0.98	(0.79-1.21)	.840
	C + DRB1 (6/8)	144	0.96	(0.77-1.20)	.735	0.79	(0.62-1.02)	.065
	A/B + C (6/8)	122	1.14	(0.89-1.45)	.307	0.84	(0.63-1.13)	.255
	Other two loci (6/8)	90	0.89	(0.68-1.14)	.346	0.80	(0.58-1.10)	.174
Cord blood transplantation		351	0.50	(0.42-0.60)	<.001	0.52	(0.42-0.63)	<.001

RR indicates relative risk; CI, confidence interval.
Adjusted by patient age at transplantation >40 versus <40, patient sex, donor-patient sex mismatch versus matched, ABO major mismatch versus others, advanced versus standard disease status at transplant, cyclophosphamide, and total-body irradiation or busulfan and cyclophosphamide for conditioning versus other conditioning regimen, and cyclosporine-based versus tacrolimus-based prophylaxis against graft-versus-host disease.

class I-mismatched BM, and 22% for 6 of 8 BM at 100 days posttransplantation ($P < .001$ between CB and single HLA-DRB1-mismatched BM) (Figure 2A).

Among recipients who survived at least 100 days posttransplantaton, the risk of developing cGVHD and extensive-type cGVHD was not significantly increased in all HLA disparity groups of CB recipients when compared with that of HLA-DRB1-allele/antigen-mismatched BM recipients (RR = 1.36, 95% CI, 0.99-1.88; $P = .057$ for cGVHD, and RR = 0.86, 95% CI, 0.55-1.34; $P = .500$ for extensive-type cGVHD). The unadjusted cumulative incidence of extensive-type cGVHD was 17% for CB recipients, 20% for single HLA-DRB1-mismatched BM, 25% for single HLA class I-mismatched BM, and 30% for 6 of 8 BM recipients at year posttransplantation ($P = .34$ between CB and single HLA-DRB1-mismatched BM) (Figure 2B).

DISCUSSION

Our main objective was to compare OS after transplantation of UCBT and single-HLA-mismatched UBMT and to provide useful data for selection of an appropriate donor and graft source in second stem cell source/donor selection for adults with hematologic malignancy. To the best of our knowledge, this is the first study to involve mismatched allele/antigen-specific analyses including CB for the process of donor selection. Our results suggest that 0 to 2 HLA-mismatched UCB is a reasonable second alternative of choice for adult patients with leukemia, with similar survival to that of single DRB1-mismatched or other 7 of 8 UBM recipients, the current first choice for second alternative donor/stem cells.

Neutrophil and platelet recovery was slower in CB recipients than BM recipients, consistent with the results of previous reports [7-10,12]. This is the major limitation of the use of UCB, and several strategies have been studied to reduce the neutropenic period, such as screening for patients' pretransplantation anti-HLA antibodies and their specificity, transplantation of 2 UCB units if a single UCB unit with an adequate cell dose is not available, or direct infusion of UCB into bone marrow [22-26].

Despite higher HLA disparity at the antigen level (69% 2 antigen mismatch, 25% antigen mismatch, and 6% matched), UCB recipients showed lower incidence of severe aGVHD than single DRB1-mismatched UBM recipients, consistent with other reports that compared UCB with single-mismatched UBM (7 of 8) [8,11,12]. In our study, tacrolimus and short-term methotrexate were used preferentially in BM recipients, whereas cyclosporine A was used in 68% of CB recipients. Prior studies have shown reduced severe aGVHD with tacrolimus, and this difference may have underscored the improved aGVHD control of UCB over mismatched BM in unadjusted analyses [27,28]. It is likely that decreased risk of grade 2 to 4 aGVHD in UCB recipients contributed to decreased risk of TRM among UCB recipients.

Increasing the number of HLA mismatches from 7 of 8 to 6 of 8 was associated with an approximately 10% reduction in survival in UBM recipients, which was quite similar to the results from the National Marrow Donor Program [3]. Because we eliminated data from the first 3 pioneering years of unrelated BMT, most of the bone marrow recipients and donors were allele-typed for at least HLA-A, -B, and -DRB1 before transplantation. Survival outcomes of single class I mismatch were not significantly different from those of single class II mismatch in the current analyses. We believe that allele typing of HLA-A, -B, and -DRB1 before transplantation led to better selection of the donor compared with that in the first several years of UBMT. This study includes a large number of fully typed BM and CB recipients, but there are limitations. The choice of stem cell source is influenced by many unmeasured factors that can affect outcome. It is also influenced by the availability of acceptable HLA disparity for unrelated donors and mainly cell dose for cord blood units. Although we have adjusted for known risk factors and disparities between groups, we cannot rule out the influence of potential selection bias, which can only be excluded in a randomized controlled trial. Transplantation years

Table 4. Multivariate Analyses of Acute (Grades 2 to 4 and Grades 3 to 4), Chronic, and Extensive-Type Chronic Graft-versus-Host Disease

	Degree of HLA Mismatch	N	Grade 2-4 acute GVHD			Grade 3-4 acute GVHD			Chronic GVHD			Extensive cGVHD		
			RR	(95% CI)	P-value	RR	(95% CI)	P-value	N	RR	(95% CI)	RR	(95% CI)	P value
Bone marrow transplantation	Single DRB1 (7/8)	248	1.00			1.00			199	1.00		1.00		
	Single A or B (7/8)	137	0.76	(0.55-1.06)	.103	0.91	(0.56-1.47)	.698	111	0.91	(0.61-1.36)	0.89	(0.52-1.50)	.651
	Single C (7/8)	287	0.93	(0.72-1.20)	.584	0.91	(0.61-1.35)	.635	227	1.56	(1.15-2.10)	1.79	(1.22-2.63)	.003
	C + DRB1 (6/8)	144	0.85	(0.60-1.18)	.320	0.88	(0.54-1.44)	.610	109	1.44	(1.01-2.05)	1.47	(0.93-2.32)	.097
	A/B + C (6/8)	122	1.40	(1.04-1.90)	.028	1.90	(1.25-2.87)	.003	87	1.64	(1.14-2.34)	2.26	(1.46-3.50)	<.001
	Other two loci (6/8)	90	0.88	(0.60-1.28)	.501	0.65	(0.34-1.22)	.183	60	1.35	(0.86-2.12)	1.15	(0.62-2.13)	.652
Cord blood transplantation		351	0.55	(0.42-0.72)	<.001	0.43	(0.27-0.58)	<.001	252	1.36	(0.99-1.88)	0.86	(0.55-1.34)	.500

GVHD indicates graft-versus-host disease; cGVHD, chronic graft-versus-host disease.
Adjusted by patient age at transplantation >40 versus <40, patient sex, donor-patient sex mismatch versus matched, ABO major mismatch versus others, advanced versus standard disease status at transplantation, cyclophosphamide, and total-body irradiation or busulfan and cyclophosphamide for conditioning versus other conditioning regimen, and cyclosporine-based versus tacrolimus-based prophylaxis against graft-versus-host disease.

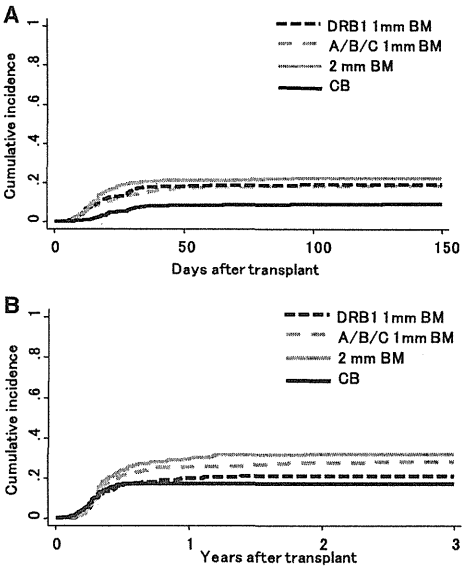

Figure 2. Cumulative incidence of grade 3 to 4 aGVHD (A) and extensive-type cGVHD (B). The cumulative incidences of grade 3 to 4 aGVHD at 100 days posttransplantation for unrelated cord blood recipients, single HLA-DRB1-mismatched unrelated bone marrow (UBM) recipients, and single HLA class I-mismatched UBM were 9%, 19%, 18%, and 22% (A). The cumulative incidences of extensive-type cGVHD at 1-year posttransplantation were 17%, 20%, 25%, and 30% (B).

of UBM recipients included from 1996 and 1999, for which there were no significant outcome differences between UBMT performed in 1996 to 1999 and after 2000. In these periods, there were advances including in supportive care and nutritional management, introduction of new antifungal agents, and more frequent use of tacrolimus, which may have affected transplantation outcomes [27-32].

In conclusion, we suggest that 0 or 2 HLA-mismatched UCB is a comparable second alternative for adult patients with leukemia in the absence of the first alternative, an 8 of 8 UBM donor, with survival similar to that of single DRB1-mismatched or other 7 of 8 UBM recipients. UCB may be preferred over single mismatched UBM when a transplantation is needed urgently, considering the short time needed for UCBT.

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AUTHORSHIP STATEMENT

Contributions: Y.A., Y.M., R.S., and S. Kato designed the study, and wrote the article; Y.A. analyzed results and created the figures; T.N.I., H.A, and M. Takanashi reviewed and cleaned the Japan Cord Blood Bank Network data, and reviewed the results; S. Taniguchi, S. Takahashi, S. Kai., H.S., Y. Kouzai., N.K., T.M., T.F., and Y. Kodera submitted and cleaned the data; M. Tsuchida, K.K., T.K., and Y.M. reviewed and cleaned the Japan Marrow Donor Program data, and reviewed the results.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2011.10.008.

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