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

Characteristics	Children (age<16)		Adult (age>16)	
	N.	(%)	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 (x10⁷/kg)				
Median	5.30		2.52	
Range	0.81-38.7		0.71-9.98	
N. of cryopreserved CD34-positive cells (x10⁵/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)

continued from the previous page

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)

*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 10⁷/kg, 88% for 5.0-9.9 x 10⁷/kg, 82% for 2.5-4.9 x 10⁷/kg, and 86% for <2.5 x 10⁷/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 10⁷/kg, 3 years for 5.0-9.9 x 10⁷/kg, 8 years for 2.5-4.9 x 10⁷/kg, and 12 years for <2.5 x 10⁷/kg). The cumulative incidences of neutrophil recovery were 76% for >2.5 x 10⁷/kg and 74% for <2.5 x 10⁷/kg in adults (P=0.007) (Figure 2B). The cumulative incidences of TRM at three years post-transplant were 13% for >10 x 10⁷/kg, 14% for 5.0-9.9 x 10⁷/kg, 14% for 2.5-4.9 x 10⁷/kg, and 14% for <2.5x10⁷/kg in children (P=0.98) and 29% for >2.5x10⁷/kg and 28% for <2.5 x 10⁷/kg in adults (P=0.77) (Online Supplementary Figure S2). The probabilities of overall survival at three years post-transplant were 68% for >10x10⁷/kg, 53% for 5.0-9.9 x 10⁷/kg, 57% for 2.5-4.9 x 10⁷/kg, and 55% for <2.5x10⁷/kg in children (P=0.30) and 36% for >2.5 x 107/kg and 41% for <2.5x10⁷/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

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incidence of TRM at three years post-transplant, 8% for 6/6, 11% for 5/6 and >5 x 10⁷/kg, 11% for 5/6 and 2.5-4.9 x 10⁷/kg, 0% for 5/6 and <2.5 x 10⁷/kg, 23% for 4/6 and >5 x 10⁷/kg, 24% for 4/6 and 2.5-4.9 x 10⁷/kg, 25% for 4/6 and <2.5 x 10⁷/kg in children, and 23% for 6/6, 29% for 5/6 and >2.5 x 10⁷/kg, 30% for 5/6 and <2.5 x 10⁷/kg, 27% for 4/6 and >2.5 x 10⁷/kg, 27% for 4/6 and <2.5 x 10⁷/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.

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										
≥10.0x10⁷/kg	85	1.00			1.00			1.00		
5.0-9.9x10⁷/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
2.5-4.9x10⁷/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
<2.5x10⁷/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										
≥3.0x10⁷/kg	439	1.00			1.00			1.00		
2.5-2.9x10⁷/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
2.0-2.4x10⁷/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
<2.0x10⁷/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.
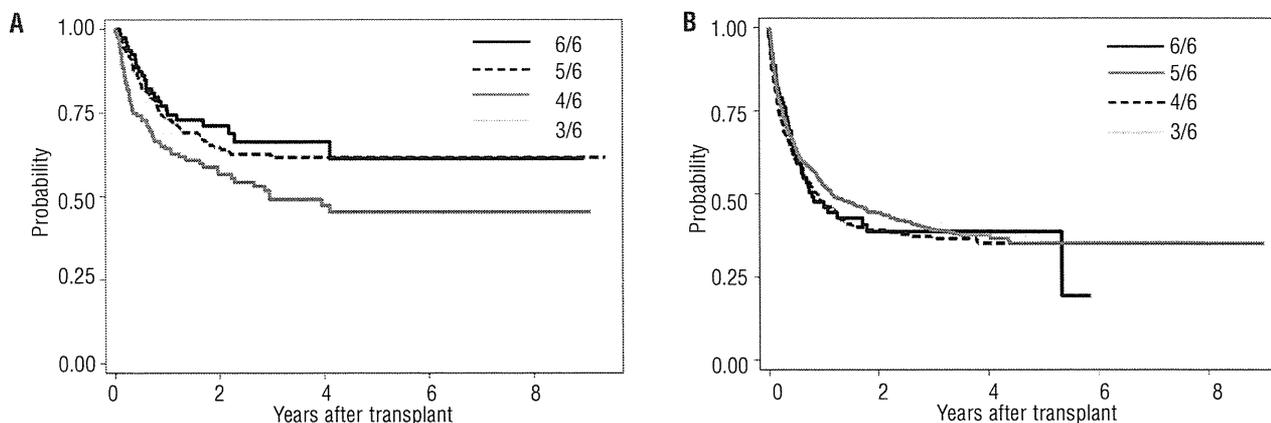
Figure 1. Unadjusted probabilities of overall survival in HLA disparity groups for pediatric (A) and adult (B) recipients with leukemia. (A) In children, the unadjusted probabilities of survival at three years post-transplant were 66% for recipients of HLA matched (6/6), 62% for one-locus-mismatched (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).

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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
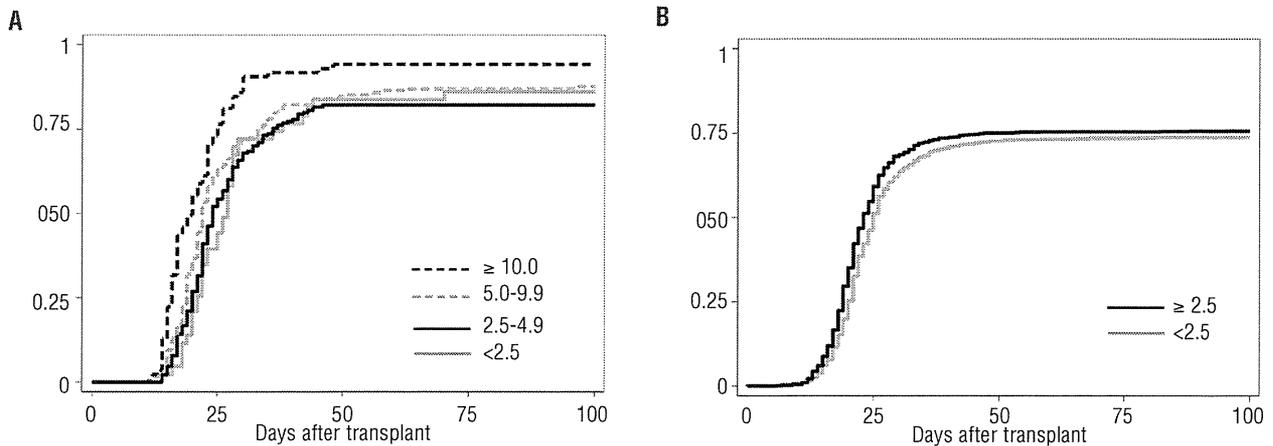
A

B

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.

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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 (>10x10⁷/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 <2.5x10⁷/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 10⁷/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 10⁷/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 HLA antigen-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 the HLA-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.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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