Matching at HLA-C improved the outcomes after double umbilical cord blood transplantation for recipients of 2–4/6 HLA-matched grafts

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Abstract

We studied the effect of HLA-C matching in 515 patients after double umbilical cord blood (dUCB) transplantation. After HLA-matching HLA-A, -B, and -DRB1 at the allele level, we scored patients according to number of donor-recipient HLA-C matches at 4 possible loci, 2 from each donor unit, at the allele level. Given a direct interaction between HLA-A, -B, and -DRB1 matching and HLA-C score, we analyzed HLA-C matching in those receiving at least one 2–4/6 HLA-matched unit (n= 389) vs. those receiving only 5–6/6 matched units (n=126). In those with at least one 2–4/6 HLA-matched unit, a better HLA-C matching score was associated with significantly lower risk of death of any cause and non-relapse mortality and better disease-free survival. There was no association with the risk of relapse, acute and chronic graft vs host disease, and hematopoietic recovery. In contrast, among patients receiving only allele-level 5–6/6 HLA-matched UCB units, HLA-C match had no demonstrable effect on any outcome. For patients receiving at least one allele-level 2–4/6 HLA-matched UCB unit, matching at HLA-C reduces non-relapse mortality and improves survival.

INTRODUCTION

One of the advantages of umbilical cord blood (UCB) grafts for allogeneic hematopoietic cell transplantation (HCT) is the less stringent requirement for donor-recipient HLA-matching as compared to unrelated adult donor (URD) HCT. Conventionally, favorable outcomes for URD HCT require allele-level matching at least at HLA-A, -B, -C, and -DRB1 (8/8 allele matching), with some centers also considering HLA-DQB1 and -DPB1.

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CONFLICT OF INTEREST

There are no relevant conflicts of interest to disclose.

Published data demonstrate that increasing degrees of HLA mismatching of URD grafts results in higher risk of non-relapse mortality (NRM) and poorer survival.[1, 2] In contrast, UCB grafts are traditionally selected when matched to the patient at HLA-A and -B at the antigen level and at -DRB1 at the allele level, while not considering HLA-C.

A recent registry-based retrospective analysis studied the effect of HLA-C matching after single UCB unit transplantation[3]. The key observation of that study was that in patients receiving a 5–6/6 HLA-matched unit, further matching at HLA-C also resulted in lower NRM and superior survival[3]. In that study most patients were children, had acute leukemia or myelodysplastic syndrome, and received a myeloablative conditioning regimen. However, in adults and larger adolescents an adequately dosed single UCB unit is often not available, necessitating consideration of a double UCB (dUCB) transplant, using two partially HLA matched units. Moreover, use of reduced intensity conditioning (RIC) is more common in adults because of co-morbidities or older age. Thus, we evaluated the effect of HLA-C matching in the setting of dUCB transplantation and RIC as well as myeloablative conditioning.

PATIENTS AND METHODS

In this retrospective study we included patients with hematological malignancies who received a dUCB transplant between 2003 and 2014 and who had HLA-C data available from the blood and marrow transplant programs at the University of Minnesota, the Massachusetts General Hospital, and the Dana Farber Cancer Institute. This retrospective study was approved by the Institutional Review Board of the participating institutions. Conditioning regimens, immune suppression, graft selection, and supportive care have been previously reported.[4–7] In summary, the myeloablative regimen consisted of cyclophosphamide 60 mg/kg for 2 days, total body irradiation 1320 cGY, and fludarabine 25 mg/m2 for 3 days. There were two RIC regimens that consisted of: 1) cyclophosphamide 50 mg/kg for 1 day, fludarabine 40 mg/m2 for 5 days and total body irradiation 200 cGY with or without equine anti-thymocyte globulin (ATG) 15 mg/kg twice daily for 3 days and 2) fludarabine 30 mg/m2 for 6 days, melphalan 100 mg/kg in 1 day, and rabbit ATG 1.0–1.5 mg/kg for 4 doses on alternating days (Table 1). The immune suppression regimens were cyclosporine-A and mycophenolate mofetil (MMF), tacrolimus with sirolimus and/or MMF, sirolimus and MMF, or cyclosporine/prednisone (Table 1). Disease risk at the time of transplantation was classified into standard risk or high risk based on the ASBMT RFI 2006 risk scoring schema.[8] Acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) in first or second complete remission, chronic myeloid leukemia (CML) in first chronic phase, Hodgkin or non-Hodgkin lymphoma in complete remission or chemotherapy-sensitive partial remission, and chronic lymphocytic leukemia (CLL) in first remission were defined as standard risk; all other diseases were classified as high risk.

HLA-matching

Patients and UCB unit were HLA typed using established molecular techniques. For this analysis HLA-A, -B, -C, and -DRB1 were analyzed at the allele level. We first scored the allele level HLA-matching at HLA-A, -B, and -DRB1. We then scored the allele level

matching at HLA-C considering up to 4 possible loci, 2 from each donor unit. Resulting scores ranged from 0 to 4 out of 4 possible loci (0/4, 1/4, 2/4, 3/4, and 4/4 HLA-C matches). In the group that had 2/4 HLA-C match, the score could have resulted in 1 match from each unit or both matches from one unit. However, only 8 of 211 patients (4%) had a 2/4 HLA-C match score resulting from a single unit matching at both C locus (2/2) and the other unit at none (0/2); thus, these patients were studied as a single group. The final analysis was carried out considering the degree of HLA-match of the graft pair based on the less well matched of the two donor units (worst match) and by the HLA-match of UCB unit that predominated long-term. The predominant unit was defined as the unit accounting for 70% of whole bone marrow or whole blood chimerism, as previously defined.[9] As the analysis considering the predominant unit only studied engrafted patients (n=416), we excluded 58 who had graft failure, 17 early deaths, 3 early relapses, and 21 with no predominant unit.

Statistical considerations

Overall and disease-free survival (DFS) were estimated with Kaplan-Meier curves.[10] Relapse, NRM, acute graft-versus-host disease (GVHD), chronic GVHD, and engraftment were estimated using competing risks methods.[11] Cox regression analysis[12] was performed to assess the independent effect of HLA-C match on OS and DFS through five years post transplantation in the presence of other factors. Fine and Gray proportional hazards regression was used to assess the independent effect of the indices on NRM, relapse, acute and chronic GVHD, and engraftment.[13] Backward elimination was used to achieve a final model. Requirement for inclusion in the final model was $p < 0.10$ if clinically significant; however, overall HLA disparity and number of matches at HLA-C were included in all models. All regression models were stratified by center due to disparity in characteristics across centers. The OS and DFS were stratified by conditioning due to violation of the proportional hazards assumption. Also, we attempted to keep similar factors in the final models across OS, DFS, relapse, and NRM as well as between grade II–IV acute GVHD and chronic GVHD. Martingale residuals were used to test against non-proportionality.[14] Logistic regression was employed to investigate the independent influence of HLA-C matching on neutrophil engraftment, excluding deaths prior to day 28 and treating late deaths as graft failures if not already identified as graft failures. SAS 9.3 (SAS Institute, Cary, NC) and R 3.0.2 were used to perform all statistical analyses.

RESULTS

EFFECT OF HLA-C MATCHING SCORE OF THE WORST HLA-MATCHED UNIT ON OUTCOMES

Demographics—Patient, dUCB graft, and transplant characteristics for the 515 HCT are summarized in Table 1. Three-quarters of patients received at least one unit that was 2–4/6 HLA-matched at -A, -B, or -DRB1 to the patient at the allele level. The HLA-C matching score was 4 in 93 (19%), 3 in 90 (18%), 2 in 196 (40%), and 0–1 in 111 (23%) patients. The median patient age was 48 years (range, 2–73). Approximately two-thirds of patients were male, had acute leukemia, were CMV seropositive, and received RIC. The majority (82%) received cyclosporine A/MMF immunosuppression.

Survival and DFS—The point estimates for survival, DFS, relapse, and NRM are summarized in Table 2. In univariate analysis the HLA-C matching score did not affect survival, DFS, or relapse. However, higher HLA-C matching score resulted in lower NRM (Figure 1A–D and Table 2). We recognized an interaction between matching at HLA-A, -B, and -DRB1 and the number of matches at HLA-C regarding survival, DFS, and NRM. Thus, in multivariate analysis for these endpoints the effect of the HLA-C matching score analysis was performed considering two groups based on matching at HLA-A, -B, and -DRB1 at the allele level: those receiving at least one 2–4/6 HLA-matched unit (n=389) versus those receiving only 5–6/6 matched units (5/6 & 5–6/6; n=126). In patients receiving at least one 2–4/6 HLA-matched unit, better matching at HLA-C was associated with significantly lower risk of death of any cause and NRM and better DFS (Table 3). There was no association with the risk of relapse. In contrast, among patients receiving only the 5–6/6 HLA-matched units, HLA-C match had no demonstrable effect on the risk of death, DFS, or NRM (Table 3). However, the relatively small number of patients resulting from the stratification limited the power to detect differences in this group. We found no effect of HLA-C matching score on the risk of relapse (Table 4). We also looked of the effect of on outcomes considering only the worst HLA-C matched of the 2 units resulting in a score 0, 1, or 2. Findings remained the same with improved DFS and NRM, but no effect on relapse for those receiving less well HLA-matched units, and no overall effect on better HLA-matched cases (Table S1 and Table S2).

Graft-vs.-Host Disease—The cumulative incidences of grade II–IV acute (Figure 2A) and chronic GVHD (Figure 2B) were not influenced by HLA-C matching score (Table 2) even when adjusting for other factors in multivariate analysis (Table 4).

Hematopoietic recovery—We found that patients who had a higher HLA-C matching score had improved neutrophil recovery by day +42 and platelet recovery at 6 months (Table 2). However, after adjusting for matching at HLA-A, -B, and -DRB1, conditioning regimen, age of the patient, and CMV serostatus, there was no independent effect of the HLA-C matching score on hematopoietic recovery (Table 4)

EFFECT OF THE HLA-C MATCHING SCORE OF THE PREDOMINANT UNIT ON OUTCOMES

In dUCB transplantation, a single unit will provide long-term hematopoiesis in most patients defined as the predominat unit at day +100. We therefore studied the effect of the HLA-C matching score of the predominant unit on outcomes. This patient subset (n=416) excluded those with graft failure, dual donor chimera (both donor present), and early deaths. The median age was 47 years (range, 2–73), and the majority were male (60%), had acute leukemia (61%), and received CSA/MMF immune suppression (77%). Many also had high-risk disease (36%) and received myeloablative conditioning (32%). Considering the allele level HLA-matching at HLA-A, -B, and -DRB1, the predominant unit was 2/6 in 15 (4%), 3/6 in 33 (8%), 4/6 in 184 (44%), 5/6 in 123 (30%), and 6/6 in 31 (7%). The HLA-C matching score of the predominant unit was zero in 46 (11%), 1 in 50 (12%), 2 in 169 (41%, and 4 in 88 (21%). We observed no independent effect of the HLA-C matching score of the predominant unit on DFS, relapse, or NRM (Table 5).

DISCUSSION

Studies on the effect of HLA-related factors in dUCB transplantation represent a unique challenge as both donor units may contribute to outcomes, but only one predominates in the long-term[9]. In many studies, the effect of HLA match on transplant outcomes have often focused on the HLA match of the worst matched of the two UCB units. Studies on the effect of killer immunoglobulin-like receptor (KIR)-matching[15, 16], donor specific HLA antibodies[17–19], and allele level HLA-matching[20, 21] have yielded conflicting results, in particular when comparing data from the single and double UCB transplantation settings. In this study, we considered allele level matching at HLA-A, -B and -DRB1 of the less well matched of the two UCB units composing the graft and separately scored HLA-C matching. Our report contrasts to a previously reported study in single UCB HCT that considered class I HLA loci at the antigen level.[3]

Not unexpectedly, we found an interaction between at HLA-A, -B and -DRB1 and HLA-C matching score on the effect on survival, DFS, and NRM endpoints. Our main finding in this stratified analysis was that for patients receiving a less well HLA-matched dUCB graft with at least one of the units being 2–4/6 matched to the patient at HLA-A, -B and -DRB1, a higher HLA-C matching score was associated with improved survival, DFS, and reduced NRM. Notably, there were no differences in outcomes for 2/6 vs 3/6 vs. 4/6 HLA-matched patients. We speculate that this may have resulted from relative small number of patients or that in the contxt of significant mismatch, any improvement in HLA-matching is beneficial. In contrast, the HLA-C matching score had no effect on these endpoints in patients receiving only 5–6/6 HLA-matched units. However, the smaller number of patients in the better HLA matched group that resulted from the need of stratification reduced our power and may have obscured any differences in outcomes. Notably, this observation differs from the study of HLA-C matching in single UCB transplantation[3] where HLA-C had favorably influenced the outcomes of better HLA-matched HCT (5–6/6), but had no effect in recipients of a 4/6 HLA-matched unit.[3] The discrepancy between these two studies may, at least in part, be explained by differences in patient and transplant characteristics. In the current study, we had an older population and a higher proportion receiving RIC.

In a subgroup analysis, we studied the effect of the HLA-C matching score of the long-term predominant unit, but found no independent effect on DFS, relapse, or NRM. This observation contrasts with our findings for the whole group of patients where the HLA-C score influenced DFS and NRM. While it would have been interesting to have demonstrated that the HLA-C matching score of the long-term predominant UCB unit also predicted long term outcomes, this analytical approach has significant limitations. We speculate that the discrepancy noted above resulted from bias introduced by excluding patients who did not engraft and those who had early deaths, two events that are important determinants of the risk of NRM and consequently DFS. Moreover, as our ability to predict the winning UCB unit remains limited, any effect of HLA-C score of the predominant unit would be difficult to translate into clinical practice.

Consistent with single UCB data,[3] we observed no independent effect of the number of matches in HLA-C on the risk of GVHD and relapse. There was also no independent effect

on hematopoietic recovery. These observations contrast with those in URD bone marrow and peripheral blood grafts where antigen, but not allele, mismatches at HLA-C led to higher risk of GVHD and resulted in higher NRM[1, 2]. The greater immune tolerance even after partially matched UCB transplantation results in a relative low risk of GVHD, but a preserved graft-vs-malignancy effect.

The practical implication of our data is that for dUCB transplantation patients receiving at least one 2–4/6 HLA allele level-matched unit, additional HLA-C antigen-level matching improves survival and reduces NRM and should be pursued whenever possible. However, in patients receiving only well matched units (5/6) as part of a double UCB graft, further matching at HLA-C offers no additional benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key Points

1. In patients receiving at least one 2–4/6 HLA-matched UCB unit, additional matching at HLA-C reduces non-relapse mortality and improves disease-free and overall survival

2. In patients receiving 5–6/6 HLA-matched UCB units, further matching at HLA-C offers no additional benefit.
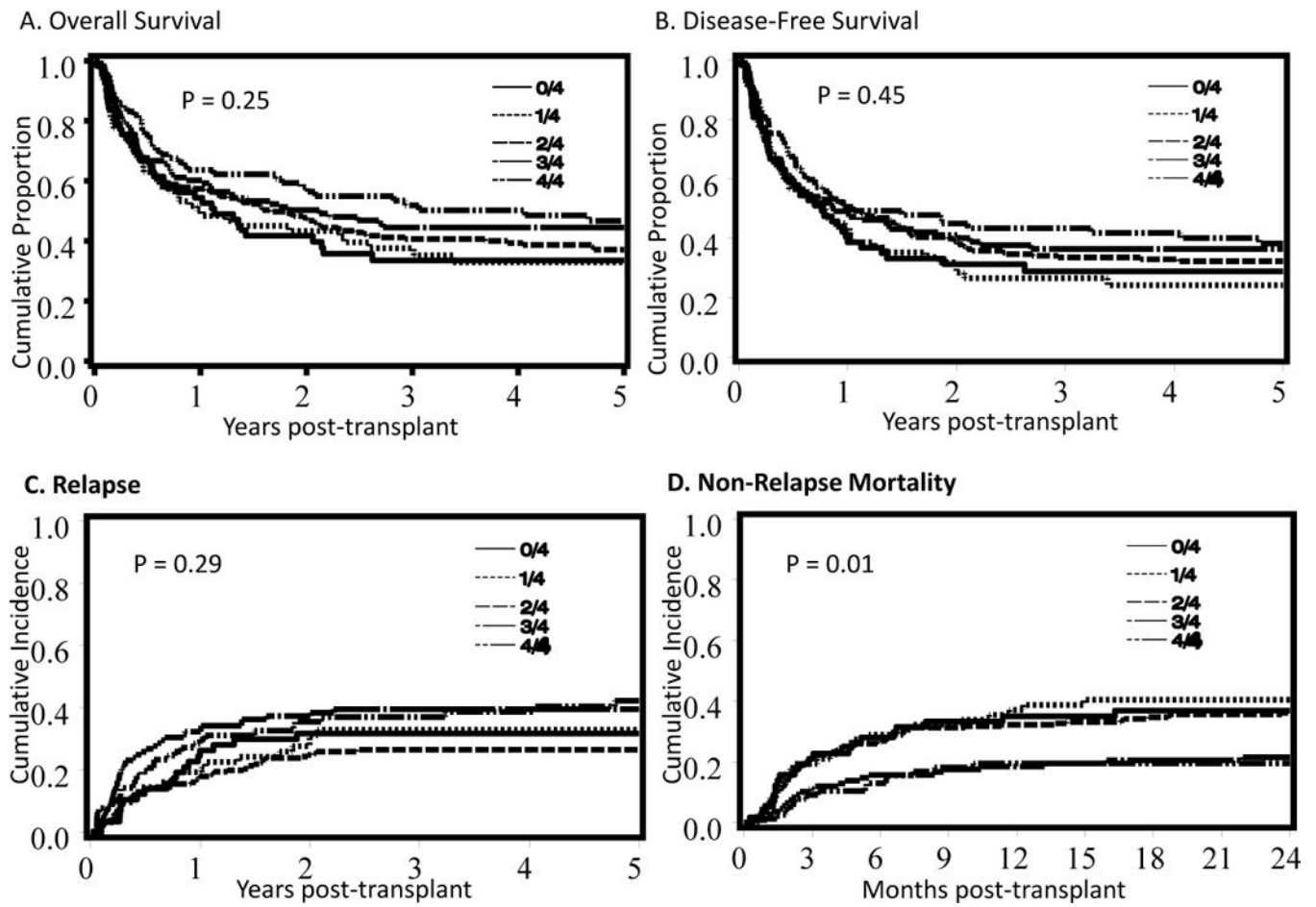
Figure 1.
Estimates of (A) Overall survival and (B) disease-free survival, and cumulative incidence of (C) relapse and (D) non-relapse mortality according to HLA-C matching score group.
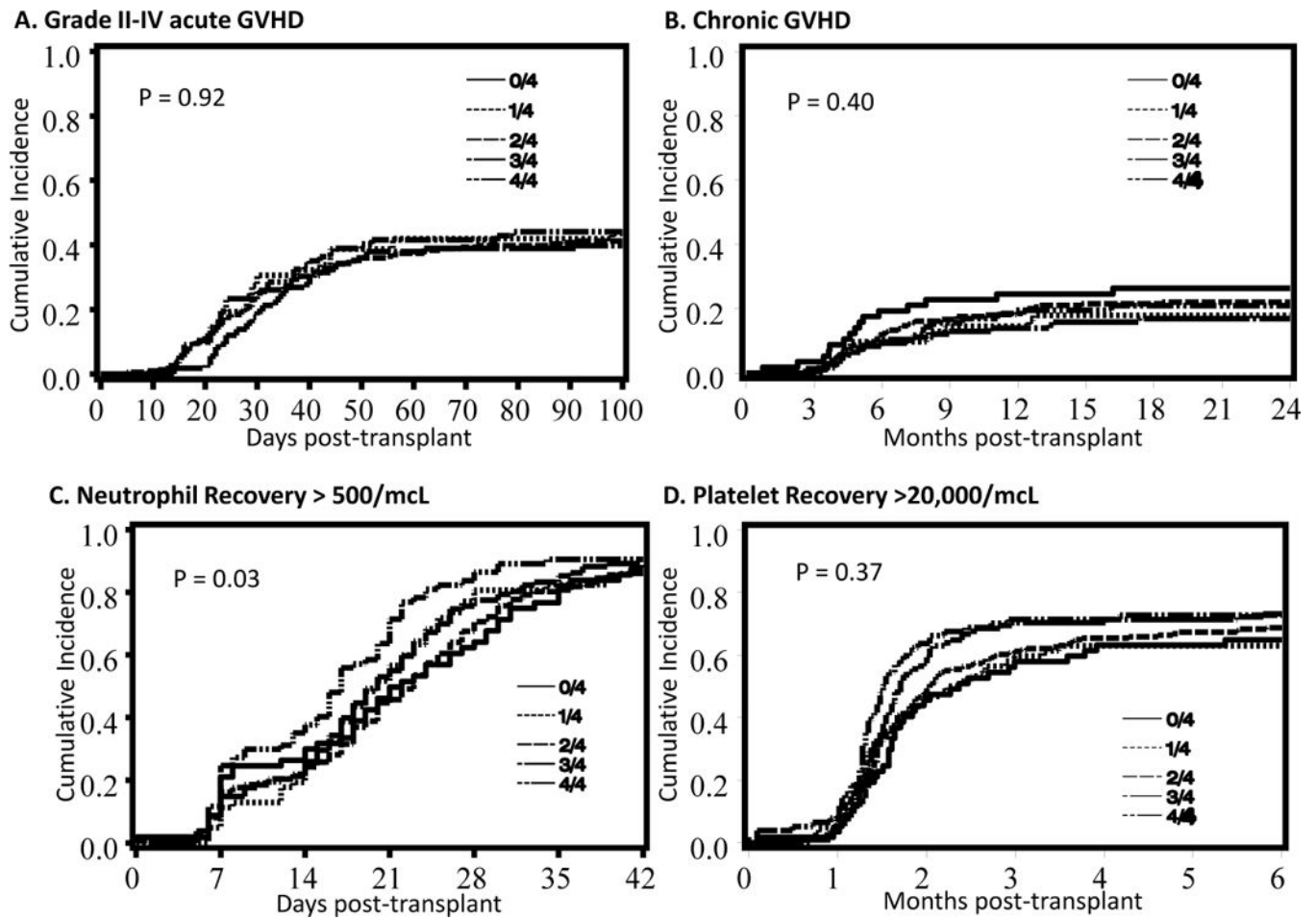
Figure 2.
Cumulative incidences of (A) grade II–IV acute graft-vs-host disease, (B) chronic graft-vs-host disease, (C) neutrophil recovery > 500/mcL and (D) plaleted recovery > 20,000/mcL according to HLA-C matching score group.

Table 1

Patient, graft and transplant characteristics

Variable	N
Number of patients	515
Median age in years (range), (IQR)	48 (2–73), (33–59)
Males	307 (60%)
Diagnosis	
Acute lymphoblastic leukemia	90 (17%)
Acute myeloid leukemia	213 (41%)
Chronic myeloid leukemia	15 (3%)
Other Leukemia	23 (4%)
Myelodysplastic syndrome	70 (14%)
Hodgkin's & Non-Hodgkin's lymphoma	94 (18%)
Other Malignancy[1]	10 (2%)
High risk disease	204 (40%)
CMV Seropositive	303 (59%)
Conditioning regimen intensity[2]	
Myeloablative	166 (33%)
Reduced intensity	349(77%)
GvHD Prophylaxis[3]	
Cyclosporine A/mycophenolate mofetil	383 (74%)
Tacrolimus/sirolimus	69 (13%)
Sirolimus/MMF	39 (8%)
Other	24 (4%)
Worst HLA Allele Match at -A, -B and -DRB1	
2/6	27 (5%)
3/6	106 (21%)
4/6	256 (50%)
5/6	102 (20%)
6/6	24 (5%)
HLA-C Matching Score	
0 matches	57 (11%)
1 match	62 (12%)
2 matches	211 (41%)
3 matches	108 (21%)
4 matches	77 (15%)
Gender mismatch of at least one unit	373 (76%)
TNC Infused ($\times 10^7$/kg) Median (range), (IQR)	4 (2–20), (3–5)
Variable	N

Variable	N
Year of Transplantation	
2003–2005	127 (25%)
2006–2009	231 (45%)
2010–2014	157 (30%)
Follow-up in years Median (range), (IQR)	5.9 (1.0–12.4), (3.2–8.2)

Abbreviations: IQR, inter-quartile range; CMV, cytomegalovirus; GVHD, graft-vs-host disease; HLA, human leukocyte antigen; TNC, total nucleated cell dose.

[1]Myeloma (n=7), plasma cell leukemia (n=2), and renal cell carcinoma (n=1)

[2]Myeloablative regimen consisted of cyclophosphamide 60 mg/kg for 2 days and total body irradiation 1320 cGY (n=3) and fludarabine 25 mg/m2 for 3 days (n=168). The RIC regimens were: 1) cyclophosphamide 50 mg/kg for 1 day, fludarabine 40 mg/m2 for 5 days and total body irradiation 200 cGY with (n=81) or without equine anti-thymocyte globulin 15 mg/kg twice daily for 3 days (n=152), and 2) fludarabine 30 mg/m2 for 6 days and melphalan 100 mg/kg in 1 day and rabbit anti-thymocyte globulin 1.5 mg/kg for 4 doses in alternating days (n=86).

[3]The other immune suppression regimens were tacrolimus/mycophenolate mofetil (n=15), sirolimus/ mycophenolate mofetil (n=5), tacrolimus/ sirolimus/mycophenolate mofetil (n=3), and cyclosporine/prednisone (n=4).

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Table 2

Point estimates of outcomes considering the HLA-C matching score

HLA-C Score	N	Overall Survival at 5 years		Disease-Free Survival at 5 years		Relapse at 5 years		Non-Relapse Mortality at 2 years	
		Estimate (CI 95%)	P-value	Estimate (CI 95%)	P-value	Estimate (CI 95%)	P-value	Estimate (CI 95%)	P-value
0/4	57	34% (21–46%)	0.25	29% (18–41%)	0.45	32% (19–45%)	0.29	37% (24–50%)	0.01
1/4	62	33% (21–45%)		24% (14–36%)		33% (20–46%)		40% (28–53%)	
2/4	211	37% (30–44%)		32% (26–39%)		27% (20–33%)		36% (29–43%)	
3/4	108	45% (35–54%)		36% (27–46%)		40% (30–50%)		22% (14–30%)	
4/4	77	47% (35–58%)		38% (27–49%)		42% (30–55%)		19% (11–28%)	

HLA-C Score	N	Acute GVHD 100 days		Chronic GVHD 2 years		Neutrophil Recovery 42 days		Platelet Recovery 6 months	
		Estimate (CI 95%)	P-value	Estimate (CI 95%)	P-value		P-value	Estimate (CI 95%)	P-value
0/4	57	40% (27–54%)	0.92	26% (14–38%)	0.40	87% (77–94%)	0.01	65% (49–80%)	0.05
1/4	62	44% (31–56%)		18% (8–28%)		89% (80–96%)		63% (48–78%)	
2/4	211	41% (34–48%		22% (16–28%)		86% (81–90%)		69% (60–77%)	
3/4	108	40% (30–49%)		17% (10–24%)		89% (82–94%)		73% (62–84%)	
4/4	77	44% (33–56%)		21% (12–30%)		90% (83–96%)		73% (59–86%)	

Abbreviations: HLA, human leukocyte antigen; CI, confidence interval; GVHD, graft-vs.-host disease.

Table 3

Multiple regression analysis of the effect of HLA-C matching score on the outcomes after dUCB transplantation in which there was an interaction with conventional HLA-matching at HLA-A,-B, and -DRB1.

Match at HLA-A,B and DRB1	HLA 2–4/6			HLA 5–6/6		
	N	HR (95% CI)	P-value	N	HR (95% CI)	P-value
OVERALL SURVIVAL [&]						
HLA-C match score						
4/4 [*]	29	1.0 (ref)		48	1.0 (ref)	
3/4	77	2.4 (1.1–5.1)	**0.03**	31	0.9 (0.5–1.6)	0.63
2/4	171	2.9 (1.4–5.9)	**<0.01**	40	0.8 (0.4–1.4)	0.41
1/4	59	2.8 (1.3–6.1)	**0.01**	7 [**]	0.7 (0.2–2.5)	0.57
0/4	53	3.3 (1.5–7.1)	**<0.01**			
Worst HLA-A,-B and -DRB1 Match						
6/6 [*]				24	1.0 (ref)	
5/6				102	1.1 (0.6–2.1)	0.85
4/6 [*]	256	1.0 (ref)				
3/6	106	1.1 (0.8–1.4)	0.81			
2/6	27	0.8 (0.5–1.4)	0.47			
Age						
<18	26	1.0 (ref)		21	1.0 (ref)	
18–34	77	1.6 (0.8–3.3)	0.22	20	0.5 (0.2–1.3)	0.15
35+	286	2.8 (1.4–5.8)	0.01	85	0.3 (0.1–0.7)	**0.01**
Disease Risk						
Standard risk [*]	227	1.0 (ref)		84	1.0 (ref)	
High risk	162	1.6 (1.2–2.1)	<0.01	42	1.1 (0.6–1.8)	0.74
Patient CMV						
Negative [*]	158	1.0 (ref)		NA		
Positive	231	1.6 (1.2–2.2)	<0.01	NA		

Match at HLA-A,B and DRB1	HLA 2–4/6			HLA 5–6/6		
	N	HR (95% CI)	P-value	N	HR (95% CI)	P-value
DISEASE-FREE SURVIVAL &						
HLA-C match score						
4/4 *	29	1.0 (ref)		48	1.0 (ref)	
3/4	77	1.8 (1.0–3.3)	0.07	31	0.9 (0.5–1.6)	0.67
2/4	171	1.9 (1.1–3.4)	**0.03**	40	0.8 (0.4–1.5)	0.47
1/4	59	2.1 (1.1–3.9)	**0.02**	7 **	0.5 (0.1–1.8)	0.30
0/4	53	2.2 (1.2–4.2)	**0.02**			
Worst HLA-A,-B and -DRB1 Match						
6/6 *				24	1.0 (ref)	
5/6				102	0.9 (0.7–1.7)	0.79
4/6 *	256	1.0 (ref)				
3/6	106	1.0 (0.8–1.4)	0.83			
2/6	27	0.8 (0.5–1.4)	0.52			
Age						
<18	26	1.0 (ref)		21	1.0 (ref)	
18–34	77	1.8 (0.9–3.6)	0.12	20	0.6 (0.3–1.5)	0.32
35+	286	2.7 (1.4 (5.5)	**<0.01**	85	0.3 (0.1–0.8)	0.01
Disease Risk						
Standard risk *	227	1.0 (ref)		84	1.0 (ref)	
High risk	162	1.5 (1.2–2.0)	**<0.01**	42	1.2 (0.8–2.1)	0.40
Patient CMV						
Negative *	158	1.0 (ref)		NS	NS	NS
Positive	231	1.5 (1.2–2.0)	**<0.01**	NS	NS	NS
aGVHD						
No	235	1.0 (ref)			1.0 (ref)	
Yes	154	0.6 (0.5–0.8)	**<0.01**		0.9 (0.6–1.5)	0.79

Match at HLA-A,B and DRB1	HLA 2-4/6			HLA 5-6/6		
	N	HR (95% CI)	P-value	N	HR (95% CI)	P-value
Non-Relapse Mortality£						
HLA-C match score						
4/4 *	29	1.0 (ref)		48	1.0 (ref)	
3/4	77	3.8 (0.8–16.6)	0.08	31	0.5 (0.2–1.6)	0.24
2/4	171	6.3 (1.5–26.7)	**0.01**	40	1.3 (0.5–3.2)	0.53
1/4	59	6.2 (1.4–26.7)	**0.01**	7 **	1.1 (0.2–5.6)	0.95
0/4	53	6.5 (1.5–28.2)	**0.01**			
Worst HLA-A,-B and -DRB1 Match						
6/6 *		1.0 (ref)		24	1.0 (ref)	
5/6				102	1.1 (0.4–3.4)	0.82
4/6 *	256	1.0 (ref)				
3/6	106	0.8 (0.5–1.3)	0.46			
2/6	27	0.9 (0.5–2.0)	0.89			
Age						
<18	26	1.0 (ref)		NS	NS	NS
18–34	77	1.6 (0.7–3.6)	0.22	NS	NS	NS
35+	286	2.1 (1.0–4.3)	**0.05**	NS	NS	NS
Disease Risk						
Standard risk *	227	1.0 (ref)		84	1.0 (ref)	
High risk	162	2.1 (1.4–3.0)	**<0.01**	42	1.7 (0.8–3.7)	0.15
Patient CMV						
Negative *	158	1.0 (ref)		NS	NS	NS
Positive	231	1.6 (1.1–2.3)	**0.02**	NS	NS	NS
Conditioning						
MA *	123	1.0 (ref)		54	1.0 (ref)	
RIC	266	0.3 (0.2–0.5)	**<0.01**	72	0.4 (0.2–1.0)	**0.05**

Abbreviations: HLA, human leukocyte antigen; dUCB, double umbilical cord blood; N, number of patients; CI, confidence interval; CMV, cytomegalovirus; MA, myeloablative conditioning; RIC, reduced intensity conditioning; GVHD, graft-vs-host disease.

*
Reference group

**
Combined 0 and 1 HLA-C matching score

&
Overall survival and disease-free survival among 4/6 +4–6/6 were stratified by transplant center and intensity of the conditioning regimen, while for 5/6+–5–6/6 these outcomes were stratified by transplant center.

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Stratified by transplant center

Table 4

Multivariate regression analysis of the effect of HLA-C matching score after dUCB transplantation in endpoints in which there was no interaction with conventional HLA-matching at HLA-A,-B, and -DRB1.

	N	HR (95% Confidence interval)	P-value
RELAPSE[£]			
HLA-C match score			
4/4[*]	77	1.0	
3/4	108	1.0 (0.6–1.6)	0.92
2/4	211	0.7 (0.4–1.1)	0.15
1/4	62	1.0 (0.5–1.7)	0.87
0/4	57	0.9 (0.5–1.7)	0.80
Worst HLA Match –A, -B, and –DRB1			
6/6[*]	24	1.0	
5/6	102	0.5 (0.3–1.1)	0.09
4/6	256	0.6 (0.3–1.2)	0.16
3/6	106	0.6 (0.3–1.3)	0.22
2/6	27	0.5 (0.2–1.5)	0.24
Disease Risk			
Standard risk[*]	311	1.0	
High risk	204	1.0 (0.7–1.4)	0.89
Conditioning			
MAC[*]	166	1.0	
RIC	349	3.0 (1.9–4.7)	**<0.01**
Grade II–IV aGVHD			
No[*]	305	1.0	
Yes	210	0.6 (0.4–0.9)	**0.01**
Grade II–IV Acute GVHD[£]			
HLA-C match score			
4/4[*]	77	1.0	
3/4	108	0.9 (0.6–1.5)	0.68
2/4	211	0.9 (0.6–1.4)	0.70
1/4	62	1.0 (0.6–1.8)	0.94
0/4	57	0.8 (0.5–1.5)	0.54
Worst HLA Match -A, -B, and -DRB1			
6/6[*]	24	1.0	
5/6	102	1.1 (0.5–2.2)	0.81
4/6	256	0.8 (0.4–1.7)	0.65
3/6	106	1.4 (0.7–2.9)	0.38

	N	HR (95% Confidence interval)	P-value
2/6	27	1.1 (0.5–2.6)	0.80
Conditioning			
MAC[*]	166	1.0	
RIC	349	0.6 (0.5–0.8)	**<0.01**
Chronic GVHD[£]			
HLA-C match score			
4/4[*]	77	1.0	
3/4	108	1.0 (0.5–1.9)	0.89
2/4	211	1.3 (0.7–2.5)	0.44
1/4	62	1.0 (0.4–2.4)	0.95
0/4	57	1.5 (0.7–3.5)	0.31
Worst HLA Match -A, -B, and -DRB1			
6/6[*]	24	1.0	
5/6	102	0.5 (0.2–1.1)	0.09
4/6	256	0.5 (0.2–1.1)	0.09
3/6	106	0.6 (0.2–1.5)	0.30
2/6	27	0.5 (0.2–1.7)	0.29
Conditioning			
MAC[*]	166	1.0	
RIC	349	0.9 (0.6–1.4)	0.68
Neutrophil Engraftment by Day +42[£]			
HLA-C match score			
4/4[*]	77	1.0	
3/4	108	0.8 (0.5–1.1)	0.13
2/4	211	0.8 (0.6–1.1)	0.15
1/4	62	1.0 (0.7–1.5)	0.90
0/4	57	0.9 (0.6–1.3)	0.52
Worst HLA Match -A, -B, and -DRB1			
6/6[*]	24	1.0	
5/6	102	1.0 (0.6–1.6)	0.93
4/6	256	0.9 (0.5–1.4)	0.53
3/6	106	0.7 (0.4–1.2)	0.21
2/6	27	0.7 (0.4–1.3)	0.23
Conditioning			
MAC[*]	166	1.0	
RIC	349	1.9 (1.5–2.4)	**<0.01**
Age			
<18[*]	47	1.0	

	N	HR (95% Confidence interval)	P-value
18–34	97	0.7 (0.5–1.0)	0.08
35+	371	0.9 (0.6–1.2)	0.42
CMV serostatus			
Negative *	212	1.0	
Positive	303	0.8 (0.7–1.0)	0.06
Platelet Engraft £			
HLA-C match score			
4/4 *	77	1.0	
3/4	108	1.0 (0.6–1.4)	0.81
2/4	211	0.8 (0.6–1.2)	0.36
1/4	62	0.8 (0.5–1.3)	0.43
0/4	57	0.7 (0.5–1.2)	0.19
Worst HLA Match -A, -B, and -DRB1			
6/6 *	24	1.0	
5/6	102	0.9 (0.5–1.7)	0.92
4/6	256	0.8 (0.4–1.4)	0.78
3/6	106	0.8 (0.4–1.5)	0.53
2/6	27	0.7 (0.3–1.5)	0.32
Conditioning			
MAC *	166	1.0	
RIC	349	1.7 (1.3–2.1)	**<0.01**
CMV serostatus			
Negative *	212	1.0	
Positive	303	0.8 (0.7–1.0)	**0.05**

Abbreviations: HLA, human leukocyte antigen; dUCB, double umbilical cord blood; N, number of patients; CI, confidence interval; GVHD, graft-vs-host disease.

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Reference group

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Stratified by transplant center

Table 5

Multivariate analysis of the effect of HLA-C matching score after dUCB transplantation considering the predominant cord blood unit.

	N	HR (95% Confidence interval)	P-value
Disease-Free Survival			
HLA-C match score			
2/2 *	117	1.0	
1/2	232	1.0 (0.8–1.4)	0.83
0/2	67	1.1 (0.8–1.7)	0.52
HLA Match -A, -B, and -DRB1			
5–6/6 *	154	1.0	
4/6	184	0.9 (0.6–1.3)	0.72
2–3/6	78	1.0 (0.7–1.5)	0.91
Risk			
Standard *	268	1.0	
High	148	1.3 (1.0–1.7)	0.08
CMV			
No *	175	1.0	
Yes	241	1.4 (1.1–1.8)	**0.01**
Relapse			
HLA-C match score			
2/2 *	117	1.0	
½	232	0.9 (0.6–1.3)	0.44
0/2	67	1.0 (0.6–1.7)	0.93
HLA Match -A, -B, and -DRB1			
5–6/6 *	154	1.0	
4/6	184	0.9 (0.6–1.4)	0.60
2–3/6	78	0.9 (0.5–1.6)	0.73
Conditioning			
MA *	136	1.0	
RIC	280	2.6 (1.6–4.2)	**<0.01**
Grade II–IV AGVHD			
No *	217	1.0	
Yes	199	0.7 (0.5–1.0)	0.06
Non-Relapse Mortality			
HLA-C match score			
2/2 *	117	1.0	
1/2	232	1.4 (0.8–2.3)	0.20

	N	HR (95% Confidence interval)	P-value
0/2	67	1.4 (0.7–2.7)	0.31
HLA Match -A, -B, and -DRB1			
5–6/6 *	154	1.0	
4/6	184	0.9 (0.6–1.5)	0.72
2–3/6	78	1.2 (0.7–2.0)	0.61
Conditioning			
MA *	136	1.0	
RIC	280	0.5 (0.3–0.7)	**<0.01**
Disease Risk			
Standard	268	1.0	
High	148	1.7 (1.1–2.5)	**0.01**
CMV			
Negative *	175	1.0	
Positive	241	1.5 (1.0–2.2)	0.07

HLA, human leukocyte antigen; dUCB, double umbilical cord blood; N, number of patients; CI, confidence interval; GVHD, graft-vs-host disease; CMV cytomegalovirus.

*
Reference group

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Stratified by transplant center