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Allele-Level HLA Matching Impacts Key Outcomes Following Umbilical Cord Blood Transplantation for Inherited Metabolic Disorders

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Allogeneic hematopoietic stem cell transplantation has demonstrated efficacy for numerous inherited metabolic disorders (IMDs). Umbilical cord blood transplant (UCBT) is increasingly used as a graft source in IMDs, but little is known of the impact of cord blood unit (CBU)/recipient HLA allelic disparity on key outcomes following UCBT for IMD. We reviewed outcomes of 106 consecutive first, single UCBTs for IMD at the University of Minnesota with regard to CBU/recipient HLA allelic matching (HLA-A, -B, -C, and -DRB1). The median age at UCBT was 1 year, and 87 patients (82%) received myeloablative conditioning. Primary diagnoses were Hurler syndrome (41%), cerebral adrenoleukodystrophy (35%), metachromatic leukodystrophy/globoid cell leukodystrophy (9%), and other (16%). The 5-year overall survival (OS) for the entire cohort was 70% (95% confidence interval, 59% to 79%). Rates of severe acute and chronic graft-versus-host disease were low (6% for each). CBU/recipient HLA conventional matching was based on antigen-level matching at HLA-A and -B, and on allele-level matching at HLA-DRB1. Of 46 conventional matched UCBTs, 20 (43%) were mismatched at 1 or more alleles. Of 49 conventional 5/6 UCBTs, 30 (61%) were mismatched at ≥2 alleles and 19 (39%) were mismatched at ≥3 alleles. Within the 6/6 conventional match stratum, comparisons of key outcomes between allele-matched and allele-mismatched UCBT were as follows: 5-year OS, 88% versus 42% ($P < .01$); 1-year engrafted survival (ES) with ≥90% donor chimerism, 73% versus 60% ($P = .33$); graft failure, 8% versus 30% ($P = .05$); and transplantation-related mortality (TRM), 8% versus 30% ($P = .04$). For patients undergoing conventional 5/6 HLA-matched UCBT, better allelic matching was associated with similar outcomes: 5-year OS, 77% versus 74% ($P = .72$); 1-year ES, 73% versus 47% ($P = .06$); graft failure, 17% versus 42% ($P = .05$); and TRM, 10% versus 16% ($P = .54$). On multivariable analyses, fewer allele-level mismatches within each conventional match stratum continued to predict more favorable outcomes following UCBT. These data provide evidence that allele-level HLA matching considerations within a conventional HLA match stratum may better predict outcomes of interest after UCBT for IMD. Larger studies are warranted to confirm these findings and explore other allele-level HLA match dynamics.

INTRODUCTION

Since Hobbs' first report of allogeneic hematopoietic stem cell transplantation (HCT) for Hurler syndrome, HCT has been explored as therapy for numerous inherited metabolic disorders (IMDs) [1]. Over the past 2 decades, the use of unrelated umbilical cord blood (UCB) allografts has become common for patients with IMD, as the number of publicly available cord blood units (CBU) has skyrocketed and as the desire for rapid HCT in many cases of IMD often precludes the use of volunteer unrelated donors. Notably, UCB is considered the preferred graft source for transplantation in patients with Hurler syndrome [2,3]; however, umbilical cord blood transplantation (UCBT) is still associated with significant risks of graft failure and transplantation-related mortality (TRM). To date, most transplantation centers have followed conventional CBU/recipient HLA matching algorithms (antigen-level matching at HLA-A and -B, allele-level matching at HLA-DRB1) on the basis that salient post-transplantation outcomes for IMD, including survival with high donor chimerism, are dependent on these matching characteristics [2,4–10]. More recently, investigators have retrospectively analyzed the impact of CBU/recipient allele-level HLA matching

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characteristics on outcomes after UCBT. Many of these studies found clearly superior outcomes with increasing allelic matching at various class I and class II loci [11-13]. These studies have almost exclusively analyzed pediatric and adult patients undergoing UCBT for hematologic malignancy, a setting in which some CBU/recipient HLA disparity can be hypothesized to protect against disease relapse. In 2006, Martin et al. analyzed CBU/recipient allele-level matching characteristics at HLA-A, -B, and -DRB1 in 60 patients with IMD undergoing UCBT on the COBLT study. They found a minimal impact of allele-level mismatching on various outcomes [14]. Despite these findings and the relative lack of studies on this important topic in the IMD population, recent expert consensus has recommended minimizing allele-level mismatch for all UCBT [15].

We aimed to analyze, within each conventional HLA match stratum, the impact of CBU/recipient allele-level HLA disparity (considering HLA-A, -B, -C, and -DRB1) on key outcomes following UCBT for IMD at a single institution.

METHODS

Patient Selection, Transplantation Regimens, and Supportive Care

All patients with IMD who underwent their first transplantation using a single-unit UCB graft were identified from the prospectively maintained University of Minnesota Blood and Marrow Transplant Database. Transplantations were included for retrospective analysis if allele-level HLA typing data (at loci -A, -B, -C, and -DRB1) were available for both the recipient and the CBU. Clinical and laboratory data were obtained from the Blood and Marrow Transplant Database and supplemented with a review of medical records. All patients underwent transplantation following Institutional Review Board-approved protocols after providing informed consent. For patients receiving a reduced-intensity conditioning (RIC) regimen (18%), conditioning consisted of alemtuzumab (1.5 mg/kg i.v., divided over days -12 through -8), clofarabine (40 mg/m^2/day i.v. on days -7 through -3), melphalan (140 mg/m^2 i.v. on day -2), and external beam radiation (total body irradiation, 200 cGy on day -1 or total lymphoid irradiation, 500 cGy on day -1). Most patients (82%) in this analysis underwent busulfan-based myeloablative (MA) conditioning, which before 2014 consisted of a conditioning backbone of serotherapy (antithymocyte globulin or alemtuzumab), i.v. cyclophosphamide (200 mg/kg), and i.v. busulfan. Beginning in July 2014, the MA conditioning regimen was changed to busulfan, fludarabine, and thymoglobulin (10 mg/kg i.v., divided on days -8 to -5). Fludarabine 40 mg/m^2/day and busulfan were each administered once daily i.v. for 4 days (days -5 to -2). Beginning in 2004, busulfan pharmacokinetic monitoring was used to target total regimen exposure to ≥70 mg·h/L. Before 2004, the total busulfan dosage was 16 to 19.2 mg/kg, divided every 6 hours for 16 total doses and without pharmacokinetic monitoring.

Graft-versus-host disease (GVHD) prophylaxis consisted of either cyclosporine (CsA) with prednisone or CsA with mycophenolate mofetil (MMF), according to the protocol in place at the time of UCBT. Patients received antimicrobial prophylaxis in accordance with existing institutional guidelines. Following institutional supportive care guidelines, patients received granulocyte colony-stimulating factor at 5 μg/kg/dose i.v. daily beginning on day +1 and continuing until the absolute neutrophil count (ANC) exceeded 2500/μL for 2 consecutive days. Donor hematopoietic chimerism monitoring was performed at 1 year post-UCBT on the myeloid fraction of blood using the standard clinical assay at the time.

CBU Selection

All patients underwent UCBT with a single, sufficiently cell-dosed CBU chosen following the existing institutional selection algorithm. CBU/recipient HLA matching was done by conventional standards: typing for HLA-A and -B at the antigen level and for HLA-DRB1 at the allele level. CBUs were obtained from national and international registries.

HLA Matching Considerations for the Present Study

Allele-level, CBU/recipient HLA typing at HLA-A, -B, -C, and -DRB1 was based on high-resolution molecular testing performed at our center as described previously [16]. The primary aim of this analysis was to determine whether, within a conventional HLA-matching stratum, allele-level HLA matching impacted outcomes after UCBT for IMD. Conventional HLA matching assignment was based on the number of CBU/recipient HLA mismatches at an antigen level for HLA-A and -B and at an allele level for HLA-DRB1 (matched, 6/6; 1 mismatch, 5/6; 2 mismatches, 4/6). High-resolution/allelic HLA match assignment was based on the number of HLA mismatches at 8 loci (HLA-A, -B, -C, and -DRB1) between the patient and the CBU. Within each conventional matching stratum, patients were subclassified based on allele level typing as follows: 6/6 stratum, 8/8 versus 5 to 7/8; 5/6 stratum, 6 to 7/8 versus 4 to 5/8; 4/6 stratum, no allele-level analysis owing to insufficient numbers.

Outcomes

All event times were calculated from the date of transplantation. Graft failure before day +100 was defined as failure to recover an ANC ≥500/μL for 3 consecutive days by day +42, <5% donor myeloid chimerism at any time, or loss of graft function after initial engraftment. Engrafted survival (ES) was defined as being alive and having ≥90% donor myeloid chimerism at 1 year post-transplantation. Neutrophil recovery was defined as the first of 3 consecutive days with an ANC ≥500/μL; platelet recovery, as the first day of a sustained platelet count ≥20,000/μL without transfusion support for 7 consecutive days. TRM was defined as death attributable to complications of HCT, but not from progression of the underlying disease. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were diagnosed and graded according to standard consensus criteria [17,18].

Statistical Analysis

Patient and transplantation characteristics were summarized using descriptive statistics. Overall survival (OS) by 5 years and ES by 1 year (events: death, graft failure, and donor myeloid chimerism <90%) were estimated by the Kaplan-Meier method with 95% confidence intervals (CIs) derived from the standard errors. Associations with graft failure before day +100 were evaluated using the chi-square or Fisher exact test based on expected cell counts. Cumulative incidence was similarly used to estimate neutrophil and platelet engraftment, aGVHD, and cGVHD, treating nonevent death as a competing risk. TRM by 1 year was also estimated by cumulative incidence, but with disease-related events as the competing risk. Cox regression was used to assess the independent effect of HLA disparity (by both conventional matching and allele-level matching within a conventional stratum) on OS and ES. Fine and Gray regression was used to assess the independent effect of HLA disparity (by both conventional matching and allele-level matching within a conventional stratum) on neutrophil recovery, platelet recovery, TRM, aGVHD, and cGVHD. Logistic regression was used to assess the independent effect of HLA disparity on graft failure. Other factors considered in regression models included recipient age (0 to 5 years versus 6 to 27 years), diagnosis (Hurler syndrome versus cerebral adrenoleukodystrophy versus other), year of transplantation (2003 to 2009 versus 2010 to 2015), ABO mismatch (match versus minor mismatch versus major mismatch versus bidirectional mismatch), intensity of the conditioning regimen (MA versus non-MA), GVHD prophylaxis (CsA/prednisone versus CsA/MMF), donor-recipient sex match (match versus mismatch), recipient cytomegalovirus serostatus (positive versus negative), and infused cell dose/kg (total nucleated cell [TNC] dose and CD34$^+$ cell dose). Results generated from the logistic regression model are expressed as odds ratios (ORs); those generated from Cox regression models, as hazard ratios (HRs). All reported *P* values are 2-sided. SAS 9.3 (SAS Institute, Cary, NC) and R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

RESULTS

Patient Characteristics

We identified 106 patients with an IMD undergoing their first single-unit UCBT and with available allele-level HLA data at the University of Minnesota between February 2003 and May 2015. Patient characteristics and demographic data are summarized in Table 1. The median recipient age at the time of UCBT was 1 year, and 60% of the recipients were male. The most common diagnoses were Hurler syndrome (41%) and cerebral adrenoleukodystrophy (35%). Eighty-seven patients (82%) received MA conditioning, and 19 patients (18%) underwent RIC UCBT. GVHD prophylaxis was CsA/prednisone in 75 patients (71%) and CsA/MMF in 31 patients (29%). The median time to follow-up (using the reverse Kaplan-Meier curve) was 4 years.

CBU Graft Characteristics and HLA Disparity

By conventional HLA matching, 46 patients (43.3%) underwent 6/6 matched UCBT, 49 patients (46.3%) underwent 5/6 matched UCBT, and 11 patients (10.4%) underwent 4/6 matched UCBT. Additional CBU graft characteristics for the cohort are presented in Table 1. The degree of HLA disparity by allele-level typing within each conventional match stratum is summarized in Table 2. Among the 46 conventional 6/6

Table 1
Patient-Related and Transplantation-Related Characteristics

Characteristic	Value
Number of patients	106
Primary disease, n (%)	
Hurler syndrome	43 (41)
Cerebral adrenoleukodystrophy	37 (35)
Metachromatic leukodystrophy	5 (5)
Globoid cell leukodystrophy	4 (4)
Other*	17 (16)
Age, yr, median (range), (IQR)	1 (0.1-27), (1-7)
Age group, yr, n (%)	
0-5	71 (67)
6-10	30 (28)
11-15	3 (3)
16-27	2 (2)
Male sex, n (%)	64 (60)
Era of UCBT, n (%)	
2003-2009	56 (53)
2010-2015	50 (47)
Conditioning regimen, n (%)	
MA	87 (82)
RIC	19 (18)
GVHD prophylaxis, n (%)	
CsA/prednisone	75 (71)
CsA/MMF	31 (29)
CMV serostatus positive, n (%)	29 (27)
ABO blood match, n (%)	
Match	34 (32)
Minor mismatch	34 (32)
Major mismatch	30 (28)
Bidirectional mismatch	8 (8)
TNC count ($\times 10^7$/kg), median (range), (IQR)	8 (2-27), (5-11)
CD34$^+$ cell count ($\times 10^5$/kg), median (range), (IQR)	8 (1-97), (4-15)
Time to follow-up, yr, median (range), (IQR)	4.0 (0.6-11.9), (1.8-6.8)
Donor type by conventional HLA matching, n (%)	
Matched single UCB	46 (43)
Mismatched single UCB	60 (57)

IQR indicates interquartile range; UCBT, umbilical cord blood transplantation; MA, myeloablative; RIC, reduced-intensity conditioning; GVHD, graft-versus-host disease; CsA, cyclosporine; MMF, mycophenolate mofetil; CMV, cytomegalovirus; UCB, umbilical cord blood.

* Includes mannosidosis, I-cell mucolipidosis, Niemann-Pick disease type B, Wolman disease, Maroteaux-Lamy syndrome, gangliosidosis, and Batten disease.

matched UCBTs, 26 (57%) were 8/8 allele matched and 20 (43%) were mismatched at 1 or more alleles. Among the 49 conventional 5/6 matched UCBTs, 30 (61%) were mismatched at 1 or 2 alleles and 19 (39%) were disparate at ≥3 alleles.

OS

The 5-year estimated OS for the entire cohort was 70% (95% CI, 59% to 79%). Analysis by conventional HLA matching stratum revealed a 5-year OS of 70% (95% CI, 53% to 82%) for the 6/6 matched cohort, 76% (95% CI, 58% to 87%) for the 5/6 matched cohort, and 45% (95% CI, 17% to 71%) for the 4/6 matched cohort ($P = .06$) (Figure 1A). Within the 6/6 conventional stratum, the 5-year OS after 8/8 allele-matched UCBT was 88% (95% CI, 68% to 96%), which was statistically superior

Table 2
Scrutiny of Conventional HLA Matching at High-Resolution Allele-Level Typing

Conventional HLA- Matched		Allele-Level HLA-Matched						
	Total patients	8/8	7/8	6/8	5/8	4/8	3/8	2/8
6/6	46	26	13	6	1	--	--	--
5/6	49	—	15	15	14	5	--	--
4/6	11	--	—	—	3	5	2	1

Table 3
Comparison of Outcomes Based on Conventional HLA-Matching Disparity and Allele-Level HLA-Matching Disparity

Outcome	Conventional Match, % (95% CI)		Allele-Level Match, % (95% CI)		*P* Value*	Conventional Match, % (95% CI)		Allele-Level Match, % (95% CI)		*P* Value*	Conventional Match, % (95% CI)		Allele-Level Match, % (95% CI)		*P* Value*
	6/6		**8/8**			**5/6**		**6-7/8**			**4-5/8**				
ES at 1 yr	67	(52-79)	73	(52-86)	.33	63	(48-75)	73	(54-86)	.06	47	(24-67)	.06	36	(11-63)
OS at 5 yr	70	(53-82)	88	(68-96)	*<.01*	76	(58-87)	77	(54-89)	.72	74	(41-90)	.72	45	(17-71)
TRM at 1 yr	17	(7-28)	8	(0-18)	*.04*	12	(3-21)	10	(0-21)	.54	16	(0-32)	.54	45	(16-75)
Neutrophil recovery	89	(78-96)	92	(78-99)	.71	82	(70-91)	90	(76-97)	.17	68	(48-87)	.17	64	(37-89)
Platelet recovery	80	(64-97)	92	(70-100)	*.01*	63	(47-79)	67	(46-87)	.62	58	(34-82)	.62	36	(9-64)
Grade III-IV aGVHD	4	(0-10)	4	(0-11)	.80	6	(0-13)	10	(0-21)	0	--		.17	9	(0-25)
cGVHD	5	(0-11)	0	-	*.05*	6	(0-13)	7	(0-15)	5	(0-15)	.89	9	(0-25)	
	5-7/8														
ES at 1 yr	60	(36-78)													
OS at 5 yr	42	(14-68)													
TRM at 1 yr	30	(10-50)													
Neutrophil recovery	85	(67-96)													
Platelet recovery	65	(41-89)													
Grade III-IV aGVHD	5	(0-14)													
cGVHD	12	(0-26)													

CI indicates confidence interval; ES, engrafted survival; OS, overall survival; TRM, transplantation-related mortality; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.

* *P* values shown represent statistical comparisons of outcomes between the specified allele-level subgroups. Significant values are in italics.

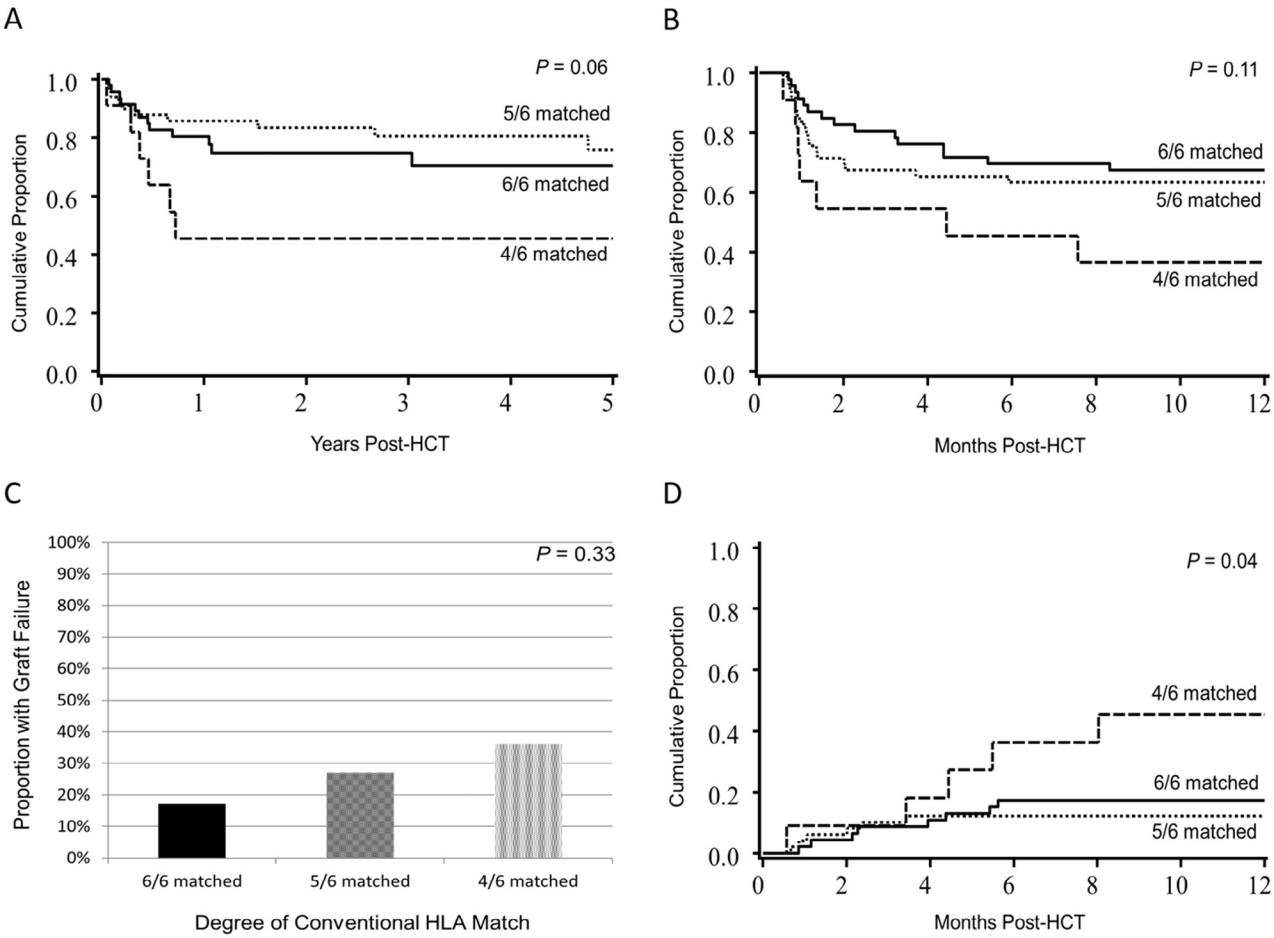

Figure 1. Outcomes of UCBT in the IMD cohort based on conventional HLA matching. Conventional HLA matching between the CBU and recipient is based on antigen-level typing at HLA-A and -B, and allele-level typing at -DRB1. (A) 5-year OS. (B) ≥90% donor ES at 1 year. (C) Graft failure rate by day +100. (D) TRM at 1 year.

to that for 5 to 7/8 allele-mismatched UCBT (42%; 95% CI, 14% to 68%; $P < .01$) (Table 3 and Figure 2A). Within the 5/6 conventional stratum, there was no difference in 5-year OS between the 6 to 7/8 allele-mismatched UCBT cohort (77%; 95% CI, 54% to 89%) and the 4 to 5/8 allele-mismatched UCBT cohort (74%; 95% CI, 41% to 90%; $P = .72$) (Table 3 and Figure 3A). In multivariable analysis, the 5-year OS within the 6/6 cohort continued to be inferior for recipients of allele-mismatched UCBT compared with recipients of 8/8 matched UCBT (HR for death, 5.1; 95% CI, 1.4 to 19; $P = .01$).

ES

Survival with >90% donor-derived chimerism at 1 year (ES) by conventional HLA matching was 67% (95% CI, 52% to 79%) for the 6/6 cohort, 63% (95% CI, 48% to 75%) for the 5/6 cohort, and 36% (95% CI, 11% to 63%) for the 4/6 cohort ($P = .11$) (Figure 1B). Within the 6/6 conventional matched group, allele-matched patients had a 1-year ES of 73% (95% CI, 52% to 86%), compared with 60% (95% CI, 36% to 78%) for the 5-7/8 allelic matched group ($P = .33$) (Table 3 and Figure 2B). Within the 5/6 conventional matched group, the 1-year ES for 6-7/8 allele-matched patients was 73% (95% CI, 54% to 86%), whereas that for the 4-5/8 allele-matched group was 47% (95% CI, 24% to 67%; $P = .06$) (Table 3 and Figure 3B). On multivariate analysis, a trend toward superior ESl was observed within the 6/6 strata among allele-matched UCBT recipients (HR for allele-mismatched recipients, 2.2; 95% CI, 0.8 to 6.1; $P = .14$). In addition, undergoing RIC UCBT was associated with inferior 1-year ES (HR, 6.2; 95% CI, 2.7 to 14.0; $P < .01$).

TRM

The cumulative incidence of TRM at 1 year for the whole cohort was 18% (95% CI, 11% to 25%). By conventional HLA matching, 1-year TRM was 17% (95% CI, 7% to 28%) for the 6/6 cohort, 12% (95% CI, 3% to 21%) for the 5/6 cohort, and 45% (95% CI, 16% to 75%) for the 4/6 cohort ($P = .04$) (Figure 1D). Within the 6/6 stratum, allele-matched UCBT had a 1-year TRM of 8% (95% CI, 0 to 18%), which was superior to the 1-year TRM of 30% (95% CI, 10% to 50%) observed in the 5-7/8 allele-matched group ($P = .04$) (Table 3 and Figure 2D). Within the 5/6 conventional stratum, allele-level matching did not appear to impact the likelihood of TRM (Table 3 and Figure 3D). On multivariable regression analysis of the 6/6 stratum, a trend toward higher TRM was observed for recipients of allele-mismatched UCBT compared with recipients of 8/8 matched UCBT (HR for TRM, 4.5; 95% CI, 0.9 to 22.4; $P = .07$).

Graft Failure and Hematopoietic Recovery

The frequency of graft failure by day +100 for the entire IMD cohort was 24%, and the rate for patients who received MA conditioning was 15%, compared with 63% in those who

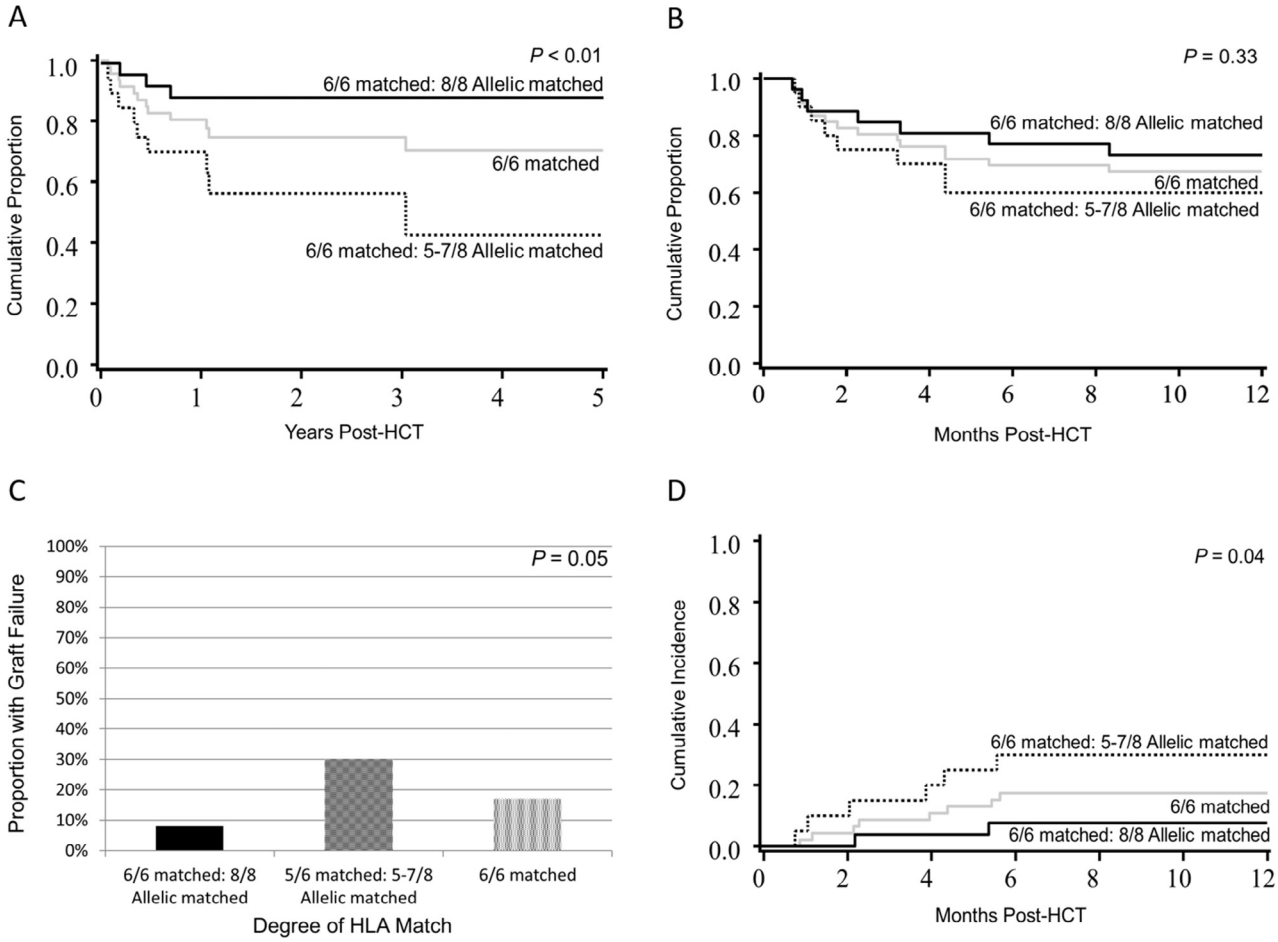

Figure 2. Outcomes by allele-level HLA disparity within the 6/6 UCBT conventional match stratum. Conventional HLA matching between the CBU and recipient is based on antigen-level typing at HLA-A and -B, and allele-level typing at -DRB1. Patients were then further subdivided by the number of allele-level HLA mismatches observed at HLA-A, -B, -C, and -DRB1. (A) 5-year OS. (B) ≥90% donor ES at 1 year. (C) Graft failure rate by day +100. (D) TRM at 1 year.

received RIC regimens ($P < .01$). The graft failure rate by conventional HLA matching was 17% for the 6/6 matched cohort, 27% for the 5/6 cohort, and 36% for the 4/6 cohort ($P = .33$) (Figure 1C). Within the 6/6 conventional stratum, allele-matched UCBT had a graft failure rate of 8%, compared with the 30% seen in the 5 to 7/8 allele-matched group ($P = .05$) (Figure 2C). Within the 5/6 conventional stratum, the graft failure rate for recipients of 6 to 7/8 UCBT was 17%, compared with the 42% seen in the 4 to 5/8 allele-matched group ($P = .05$) (Figure 3C). On multivariable analysis within the 6/6 stratum, allelic mismatch continued to correlate with a higher frequency of graft failure compared with 8/8 UCBT (OR, 10.2; 95% CI, 1.3 to 77.9; $P = .03$). In addition, RIC UCBT was associated with more graft failure compared with MA UCBT (OR, 15.8; 95% CI, 4.0 to 62.5; $P < .01$).

The median time to neutrophil and platelet recovery for the entire cohort was 20.5 and 60 days, respectively. The incidence of neutrophil recovery by day +42 was 89% (95% CI, 78% to 96%) in recipients of a 6/6 matched conventional UCBT, 82% (95% CI, 70% to 91%) in recipients of a 5/6 matched conventional UCBT, and 64% (95% CI, 37% to 89%) in recipients of a 4/6 conventional matched UCBT ($P = .35$) (Table 3). The incidence of platelet recovery in these cohorts was 80% (95% CI, 64% to 97%), 63% (95% CI, 47% to 79%), and 36% (95% CI, 9% to 64%), respectively ($P = .02$) (Table 3). The cumulative incidence of neutrophil and platelet recovery within each conventional stratum by allele-level matching was not statistically significantly different (Table 3). In multivariable analysis, neutrophil recovery did not depend on allele-level matching considerations within either the 6/6 or the 5/6 conventional stratum; however, within the 6/6 stratum, platelet recovery did correlate significantly with allele-matched UCBT (HR for recovery among allele-mismatched recipients, 0.4; 95% CI, 0.2 to 0.7; $P < .01$). Both neutrophil and platelet recovery were significantly associated with conditioning intensity (RIC inferior) and $CD34^+$ dose infused (inferior recovery in recipients of the lowest-quartile dose).

aGVHD and cGVHD

Overall rates of severe aGVHD and any cGVHD were low, at 6% each. The incidence of grade III-IV aGVHD was also similar among the conventional HLA-matched groups, at 4% (95% CI, 0 to 10%) in recipients of a 6/6 conventional matched UCBT, 6% (95% CI, 0 to 13%) in recipients of a 5/6 conventional matched UCBT, and 9% (95% CI, 0 to 25%) in recipients of a 4/6 conventional matched UCBT ($P = .79$) (Table 3). Similarly, the respective incidence of any cGVHD in these cohorts was 5% (95% CI, 0 to 11%), 6% (95% CI, 0 to 13%), and 9% (95% CI, 0 to 25%) ($P = .02$) (Table 3). The cumulative incidence of severe aGVHD by allele-level matching within the 6/6 and

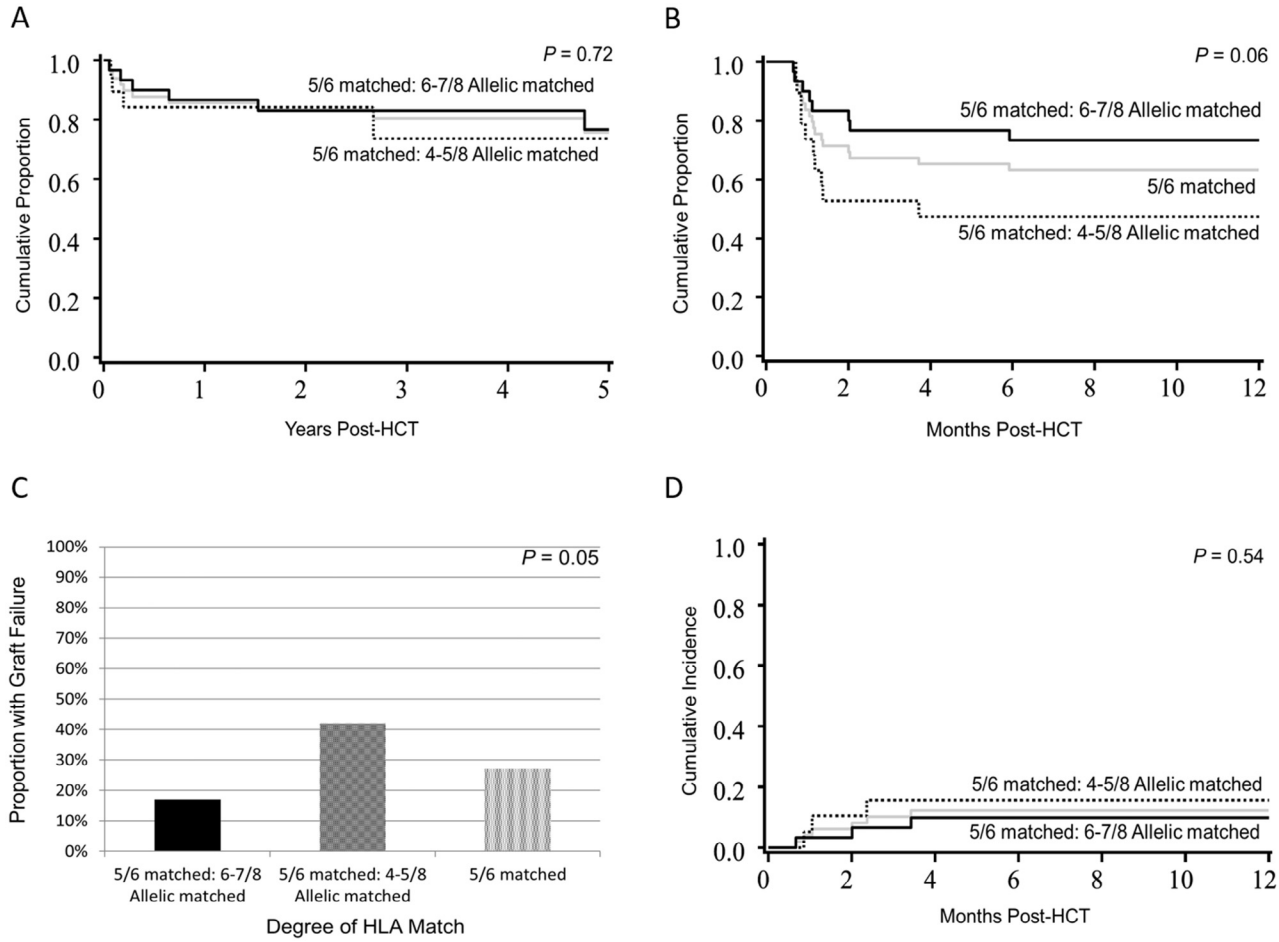

Figure 3. Outcomes by allele-level HLA disparity within the 5/6 UCBT conventional match stratum. Conventional HLA matching between the CBU and recipient is based on antigen-level typing at HLA-A and -B, and allele-level typing at -DRB1. Patients were then further subdivided by the number of allele-level HLA mismatches observed at HLA-A, -B, -C, and -DRB1. (A) 5-year OS. (B) ≥90% donor ES at 1 year. (C) Graft failure rate by day +100. (D) TRM at 1 year.

5/6 conventional matched groups was not statistically significantly different (Table 3). Although the difference in incidence of cGVHD by allele-level typing within the 6/6 and 5/6 conventional strata are reported to have a statistical significance ($P = .05$) (Table 3), the very low number of actual events call the validity of this finding into question. No significant differences were detected on multivariable analysis.

DISCUSSION

UCBT is established therapy for various rare IMDs, because it has been shown to both prolong survival and favorably alter the natural history of disease in specific populations. The use of UCB as a graft source has improved access to transplantation, decreased the time to transplantation compared with unrelated donor grafts, and achieved high levels of donor chimerism and enzyme levels in disorders such as Hurler syndrome [2,7]. To date, most transplantation centers have followed conventional CBU/recipient HLA matching algorithms (antigen-level matching at HLA-A and -B, and allele-level matching at HLA-DRB1) based on the fact that relevant post-transplantation outcomes for IMD are dependent on these matching characteristics [2,4-10].

Recently, investigators have reported significant associations between allele-level HLA matching on outcomes after UCBT for malignant disease, and consensus opinion has recommended minimizing allelic mismatch in all UCBTs [13,19]. Eapen et al. [13] evaluated 1568 single UCBTs for hematologic malignancy and found that only 7% of the units were allele-matched at HLA-A, -B, -C, and -DRB1. The risk of nonrelapse mortality was independently correlated with the overall degree of allele-level HLA mismatch, and mismatching at ≥3 alleles was associated with a higher risk of primary graft failure. The unit TNC content was the only other donor characteristic associated with nonrelapse mortality, and was independent of HLA matching. The authors suggested that single CBU should have a minimum cryopreserved TNC of 3×10^7/kg, and that thereafter the best allele-level HLA-matched unit should be selected [13]. In contrast, Brunstein et al. [16] found no apparent correlation between allele-level matching and salient outcomes after double UCBT for hematologic malignancies when considering the "worst-matched" unit; however, within a subgroup of patients with acute leukemia, greater allele-level HLA disparity (when considering the engrafted unit) was correlated with less relapse and less overall treatment failure. Importantly, data on the significance of allele-level HLA matching on outcomes after UCBT for IMD are lacking. In the COBLT study, Martin et al. [14] reported no impact on engraftment, GVHD, or OS after scrutinizing CBU/recipient HLA allele disparity at loci HLA-A, -B, and -DRB1 in 60 patients with IMD undergoing UCBT. We sought to analyze our experience at a single institution with a larger IMD population, while considering HLA-C allele matching as well.

Owing to the rarity of IMDs, our analysis was constrained to the impact of allelic HLA disparity within the conventional 6/6 and 5/6 match strata. Applying this greater scrutiny to the conventional 6/6 stratum revealed clear trends, often reaching strong statistical significance, in various key outcomes, including OS, ES with high donor chimerism, graft failure, and TRM. Although a greater degree of allelic mismatch in the conventional 5/6 stratum led to greater graft failure and inferior ES after first UCBT, this did not equate to significantly higher TRM or worse OS. This finding reflects both better transplantation supportive care measures, as well as increasing success with subsequent transplantation in the modern era. Thus, our data suggest that within a stratum defined by conventional HLA-matching characteristics, minimizing allelic disparity in UCBT for IMD is advisable. As public UCB banking expands, transplantation physicians will have increasing opportunities to select more closely matched CBUs for their patients with an IMD. A recent retrospective analysis of UCBT in adults with malignant disease found that a 33% change in historical allograft selection would have occurred (without compromising cell dose) had the scrutiny of allele-level matching been used [19]. Furthermore, it is now estimated that nearly all children in the United States have access to 1 or more sufficiently HLA-similar CBUs by conventional matching algorithms [20]. Finally, advances in UCB expansion technologies may provide more opportunities to consider other intrinsic properties of UCB (eg, HLA genotype) in CBU selection.

This analysis supports allele-level HLA-matching considerations in UCBT for IMD; however, there may be other important allelic HLA-matching dynamics relevant to this patient population that are beyond the scope of this analysis. For example, we cannot determine whether better outcomes would be expected for a conventional 5/6, allelic 7/8 UCBT than for a conventional 6/6, allelic 6/8 UCBT. In addition, loci-specific allelic-mismatch considerations are warranted; for example, we cannot determine whether a single class I locus mismatch is associated with more (or less) favorable outcomes compared with another class I or a class II locus mismatch. These important questions may best be answered by analyzing a larger IMD UCBT cohort.

In conclusion, high-resolution allele-level matching at HLA-A, -B, C-, and -DRB1 appears to optimize outcomes within a conventional HLA-matching stratum following UCBT for IMD. In scenarios where multiple suitable conventional matched 6/6 or 5/6 CBUs are available, our data suggest that allelic-mismatch characteristics should be considered in final CBU selection. Future studies of large IMD cohorts are needed to confirm these findings, as well as to assess other allelic HLA-matching dynamics on outcomes after UCBT.

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