HLA-Mismatch Is Associated With Worse Outcomes After Unrelated Donor Reduced Intensity Conditioning Hematopoietic Cell Transplantation: An Analysis From The CIBMTR

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Abstract

Purpose—Over the past two decades reduced-intensity conditioning allogeneic hematopoietic cell transplantation (RIC HCT) has increased substantially. Many patients do not have fully HLA-matched donors, and the impact of HLA-mismatch on RIC HCT has not been examined in large cohorts.

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Patients and Methods—We analyzed 2,588 recipients of 8/8 HLA-high resolution matched (n=2025) or single-locus mismatched (n=563) unrelated donor (URD) RIC HCT from 1999-2011. Overall survival (OS) was the primary outcome. Secondary endpoints included treatment-related mortality (TRM), relapse, disease-free survival (DFS), and acute/chronic graft-versus-host disease (GVHD).

Results—Adjusted one and three-year OS was better in 8/8 vs. 7/8 matched recipients (54.7% vs. 48.8%, p=0.01 and 37.4% vs. 30.9%, p=0.005, respectively). In multivariate models 7/8 RIC URD HCT recipients had more grade II-IV aGVHD (RR=1.29, p=0.0034), higher TRM (RR=1.52, p<0.0001) and lower DFS (RR=1.12, p=0.0015) and OS (RR=1.25, p=0.0001), with no difference in relapse or chronic GVHD. In subgroup analysis, inferior transplant outcomes were noted regardless of the HLA allele mismatched. Previously reported permissive mismatches at HLA-C (C*03:03/C*03:04) and HLA-DP1 (based on T cell-epitope matching) were not associated with better outcomes.

Conclusion—While feasible, single-locus mismatch in RIC URD HCT is associated with inferior outcomes.

Increasing numbers of patients traditionally considered ineligible for transplantation due to age, performance status or other comorbidities now commonly undergo reduced intensity conditioning followed by unrelated donor hematopoietic cell transplantation (RIC URD HCT). However, only ∼30-75% of patients needing transplantation will have an 8/8 HLA-matched (HLA-A, -B, -C, -DRB1) URD.[1, 2] Frequently a 7/8 single HLA-mismatched donor is available for such patients. However, it is currently unknown whether 7/8 URD RIC HCT recipients experience inferior transplantation outcomes. In the context of myeloablative conditioning (MA) HLA 7/8 mismatches increase the incidence of acute graft vs. host disease (aGVHD) and treatment related mortality (TRM), resulting in inferior overall survival (OS).[3-9] Considering however, that successful RIC transplant procedure relies more upon graft vs. leukemia (GVL) reactions than after myeloablation and that patients undergoing RIC URD HCT are more likely to be older and/or have more comorbidities, it is important to examine whether outcomes differ between 7/8 mismatched and fully HLA-matched (8/8) URD RIC procedures.

A small number of studies have investigated the impact of HLA-mismatch in URD RIC HCT and have noted the importance of HLA-C locus mismatches. A retrospective report from the Dana-Farber Cancer Institute compared HLA-C antigen- and allele-mismatched donors to fully matched donors and showed that mismatched recipients had significantly increased grade II-IV and III-IV acute GVHD (aGVHD), TRM, and worse 2-year OS.[10] In a CIBMTR analysis of HLA-mismatches in URD PB transplantation performed from 1999-2006, a subgroup of 673 URD RIC transplantations was analyzed. Recipients of HLA-C antigen mismatched URD RIC transplants had significantly reduced survival.[11] However, HLA-C allele mismatches and other locus mismatches were not identified as relevant, possibly due to limited sample size. A prospective study of T-replete 1-2 locus HLA-mismatched RIC URD utilizing PBSCs also described high rates of grade II-IV and III-IV aGVHD, NRM and a 2-year OS.[12]

To date, the question of whether HLA mismatching impacts upon the success of URD RIC HCT has not been fully addressed. This information is critical to optimize donor selection and perhaps extend the utility of transplantation. As well, data addressing this topic could constitute a baseline comparator for any novel conditioning or GVHD regimens for RIC URD recipients. Moreover, it is formally possible that HLA mismatching may be beneficial with respect to relapse, especially in RIC. Therefore, a large registry analysis was undertaken using the CIBMTR database to compare RIC URD transplant in recipients of HLA 7/8 antigen or allele matched transplants to recipients of 8/8 fully matched (HLA-A, -B, -C and DRB1) transplants. In subgroup analysis, we determined whether outcomes varied based on individual HLA locus mismatch. Secondary aims were to determine whether there was an interaction between disease risk and HLA mismatch and whether mismatching between specific HLA-C alleles (C*03:03/C*03:04) or HLA-DP (based on T cell-epitope matching) was permissive based on existing models in the MA setting.[7, 8, 13, 14]

Methods

Study population

This study included patients reported to the National Marrow Donor Program (NMDP)/ CIBMTR who received a reduced intensity or non-myeloablative transplant from an URD between 1999 and 2011. Patients receiving MA conditioning were excluded. MA conditioning was defined as the following: single-dose total body irradiation (TBI) greater than 500cGy or more than 800cGy total in fractionated doses, busulfan at least 9mg/kg, melphalan with dose greater than 150mg/m^2, or thiotepa dose > 10mg/kg. The study population consisted of recipients who received their first BM or PB URD transplantation for the treatment of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML) or myelodysplastic syndrome (MDS). Early stage disease was defined as AML or ALL in first complete remission, CML in first chronic phase, and MDS subtype refractory anemia. Intermediate stage disease was defined as AML or ALL in second or subsequent complete remission and CML in accelerated phase or second chronic phase. Advanced phase disease was defined as AML in first or higher relapse or primary induction failure, CML in blast phase and MDS subtypes refractory anemia with excess blasts or in transformation.

All surviving recipients included in this analysis provided informed consent for participation in the NMDP research program. Research was approved and conducted under the supervision of the NMDP Institutional Review Board. A modeling process was used as previously described to adjust for any bias introduced by exclusion of non-consenting survivors.[5, 15] This adjustment is standard for all studies using NMDP data.

HLA Typing and Permissive Mismatch Analysis

High-resolution typing was performed as previously described for HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1.[16] Low-resolution (serologic or antigen-level) disparities were derived through conversion of DNA-based typing to serologic equivalent according to the 2010 WHO nomenclature for factors of the HLA system.[17] Mismatch at HLA-DQ (and –DP) included only –DQB1 (and –DPB1), as there is strong linkage disequilibrium between the

alpha and beta subunits (> 98%), and –DQA1 and –DPA1 typing data was limited (not available for the majority of cases in the dataset). DQB1 and DPB1 data was available for 97% and 53% of the population, respectively. As previously described,[18] the directionality of HLA mismatch was considered for the analysis of GVHD and engraftment. Mismatches at homozygous alleles were considered single mismatches. Donor-recipient high-resolution HLA matching at HLA-A, -B, -C, and –DRB1 defined an 8/8 matched pair. Allele- or antigen-level mismatch at one (7/8) of these loci defined the mismatch group of interest in the main analysis. Secondary analyses examined the following: Mismatch at HLA-DPB1 or –DQB1, HLA-C*03:03/03:04 vs. other -C allele or antigen mismatch,[19] and -DPB1 permissive vs. non-permissive mismatches according to T-cell epitope grouping, as previously reported.[20] The –DPB1 permissive mismatch analysis was performed separately in 8/8 and 7/8 cases. These analyses did not consider –DQB1, as –DQB1 mismatch was infrequent (allele matched in 89% of cases).

Outcome definitions

OS was defined as time from HCT to death from any cause. Engraftment was defined as achieving an absolute neutrophil count of 500/μl for three consecutive days. Treatment-related mortality (TRM) was death in continuous remission from the primary malignancy. Disease free survival (DFS) and relapse were defined per Center for International Blood and Marrow Transplant Research (CIBMTR) criteria.[21] Grades II-IV and III-IV aGVHD were defined by the Glucksberg scale,[22] and chronic GVHD was defined as limited or extensive chronic GVHD according to the Seattle criteria.[23]

Statistical analysis

For univariate analysis, probabilities for OS and DFS were calculated using the Kaplan-Meier estimator with variance estimated by Greenwood's formula. Values for other outcomes were calculated according to cumulative incidence. Death was considered a competing risk for all endpoints except OS and DFS. Relapse and TRM were considered competing risks for each other.

The association between number and type of HLA mismatches were evaluated by Cox proportional hazards models adjusting for significant clinical covariates. Stepwise selection procedures were fit to determine which risk factors were related to a given outcome. All variables were tested for the affirmation of the proportional hazards assumption. Factors violating the proportional hazards assumption were adjusted for using time-varying covariates. Engraftment was reported as the cumulative incidence by day 100, with death as a competing risk. Interactions were checked between each selected variable and the main effect. Covariates tested include disease, disease status (early vs. intermediate vs. advanced), performance status, patient age, donor age, donor/recipient sex match (F/M vs. other), donor/recipient CMV match, graft source (PB vs. BM), T-cell depletion (anti-thymocyte globulin/alemtuzumab vs. none), GVHD regimen (calcineurin inhibitor-based (CNI) vs. other), and year of transplantation. Variables were categorized after examination of the data or based on current evidence for relevant breakpoints. The main analysis compares subgroups of HLA-mismatched pairs with 8/8 HLA-matched pairs. Given the multiple comparisons, p values <0.01 were be considered significant.

Results

Patient Characteristics

From 1999-2011, 2,588 patients underwent RIC URD HCT from 144 centers and 12 countries and were reported to the CIBMTR. 2,025 patients received transplantation from an HLA-matched unrelated donor (8/8 URD; HLA-A, -B, -C, -DRB1) and 563 patients were transplanted with a 7/8 allele or antigen matched unrelated donor (7/8 URD). Patient and transplant characteristics are shown in table 1. Briefly, the 8/8 URD recipients were older (p<0.003), more likely Caucasian (p<0.001), and were transplanted with younger donors (34 vs. 36 years, p=0.04). The two groups did not differ in disease status (p=0.09), conditioning (p=0.92), graft type (p=0.42), donor parity (p=0.07), use of TBI (p=0.33), *in vivo* T-cell depletion (p=0.10), or GVHD prophylaxis (p=0.74). Considering the whole group (both 8/8 and 7/8 URD patients), the conditioning intensity was more likely RIC compared to NMA (79% vs. 21%), and GVHD prophylaxis was mainly CNI-based, with either tacrolimus (70%) or cyclosporine A (27%). The median follow-up for the 8/8 URD group was 38 months and for 7/8 URD recipients it was 48 months, thus 7/8 transplants were performed earlier (p<0.001).

Outcomes of URD 7/8 vs. 8/8 URD RIC Transplants

Table 2 shows the univariate analysis comparing outcomes between HLA 7/8 and HLA 8/8 RIC URD transplants. As shown, 7/8 RIC URD recipients had more frequent grade II-IV (43% vs. 35%, p=0.0018) and III-IV aGVHD (21% vs. 13%, p<0.001) and TRM (29% vs. 20%, p<0.001). There was no association with relapse at 1, 3 or 5 years (p=0.73, p=0.78, p=0.84) or chronic GVHD at 1, 3 or 5 years (p=0.3, p=0.06, p=0.06, respectively). OS was worse in 7/8 matched recipients at 1 year (48% vs. 55, p=0.003), 3 years (30% vs. 38%, p<0.001) and 5 years (22% vs. 30%, p=0.004).

The consequences of a 7/8 URD RIC transplant were also considered relative to an 8/8 URD RIC transplants in multivariable analysis (Table 3). When adjusting for other significant covariates, the 7/8 URD RIC recipients were more likely to develop grade II-IV aGVHD (RR=1.29; p=0.003) (Figure 1A). Grade III-IV aGVHD (RR=1.69; p=0.05) did not meet the criteria for significance. Higher TRM (RR=1.52; p<0.0001) (Figure 1B), inferior DFS (RR=1.20; p=0.0015), and lower OS (RR=1.25; p=0.0001, Figure 1C) were seen in 7/8 compared to 8/8 URD RIC recipients. The impact of allele vs. antigen level mismatches in aggregate was also assessed. Comparing single allele mismatches to single antigen mismatches showed no differences in TRM (RR=1.37; p=0.27) or OS (RR=0.74; p=0.08). Whether ATG mitigated the negative impact of 7/8 donors was also investigated. However, there was no interaction between ATG and HLA matching, thus, while ATG may be improving outcomes in recipients 7/8 matched donors (compared to no ATG), it is not abrogating the negative effect of mismatch.

Potential differences in the association of HLA mismatching with disease status prior to transplantation were also considered, as described in myeloablative HLA-mismatched transplantation.[5] There was no interaction between disease status and HLA matching in the OS analysis (p=0.42). Survival differences at 3 years based on HLA mismatching were not

statistically different among early stage disease (43% HLA-matched vs. 38% HLA-mismatched), intermediate stage disease (40% vs. 31%), and advanced stage disease (27% vs. 19%).

Individual Locus Mismatch and Patient Outcomes

We investigated whether mismatching at specific HLA loci impacted RIC URD transplant outcomes. Mismatching at HLA-DQ and –DP were not associated with TRM, aGVHD, relapse, DFS and OS (not shown). Recently, certain HLA-DP mismatches have been identified as being permissive (or non-permissive) on the basis of T cell-epitope matching.[20] Patients with available HLA-DP typing (n=1,056) were categorized as either matched (n=160), mismatched permissive (n=498) or mismatched non-permissive (n=398). In multivariable analysis, non-permissive mismatches were not associated with greater aGVHD II-IV (p=0.26) III-IV (p=0.57), chronic GVHD (p=0.79), TRM (p=0.3), relapse (p=0.47), DFS (p=0.8) or OS (p=0.45). Similarly, HLA C*03:03/C*03:04 mismatches have been reported to be permissive in MA transplantation.[19] Only a small numbers (n=50-59, depending on the outcome measure) were available to assess whether the HLA-C*03:03/C*03:04 mismatch was better tolerated than other HLA C mismatches or other allele mismatches (HLA-A, -B or –DRB1). No differences were seen in TRM, GVHD, DFS or OS (not shown).

Adjusted multivariable outcomes for single allele mismatched recipients are shown in table 5. The number of patients in each HLA locus mismatch group became relatively small, ranging from 52-219 patients depending on the group and the transplant outcome analyzed. Mismatches at HLA-A and –C were more common than HLA-B or –DRB1 (33% vs. 39% vs. 14% vs. 13%, respectively, table 4). No differential impact of mismatching at a particular locus (HLA-A, -B, -C or –DRB1) was detected for either relapse or chronic GVHD. Mismatching at HLA-A was not associated with grade II-IV aGVHD, but did significantly increase grade III-IV aGVHD (RR=1.75; p=0.005) and TRM (RR=1.62; p=0.0002), and lower DFS (RR=1.26; p=0.009) and OS (RR=1.43; p<0.0001). Single allele mismatches at HLA-B showed no association with aGVHD grades II-IV or III-IV, but were strongly associated with higher TRM (RR=2.26; p<0.0001), and lower DFS (RR=1.51, p=0.001) and OS (RR=1.57; p=0.0005). HLA-C mismatched pairs had increased grade II-IV aGVHD (RR=1.4; p=0.005), but not grade III-IV aGVHD, TRM, DFS or OS. Lastly, HLA-DRB1 mismatches were associated with increased grade III-IV aGVHD (RR=2.49; p=0.001), but not grade II-IV aGVHD, TRM, DFS or OS. Collectively, these results show that mismatching at any loci (HLA-A, -B, and –C, or -DRB1) was associated with at least one inferior transplant outcome following RIC URD.

Discussion

A significant proportion of patients lack a fully HLA-matched URD for transplantation and one option is to use HLA partially-matched URDs. Over the past 10-15 years a number of large studies have shown that MA conditioning and HLA mismatched URD RIC transplantation results in inferior transplant outcomes.[3-9] However, over the past two decades utilization of RIC conditioning has steadily increased worldwide. With this change,

it is important to identify the risks and benefits of partially HLA-matched URD transplantation. There are a number of fundamental differences between RIC and MA transplants including the degree of tissue injury induced by the conditioning regimen, the kinetics of donor engraftment, and immunological reconstitution. As well, patients undergoing RIC conditioning tend to be older, have worse performance status and are more likely to have chronic or indolent malignancies relative to MA treated patients. In this large international registry study we demonstrate that single allele mismatched (7/8) RIC URD transplantation resulted in significantly inferior outcomes when compared to a cohort of HLA 8/8 matched donors. In particular, 7/8 mismatched RIC URD recipients experienced greater rates of aGVHD (grade II-IV) and TRM and inferior DFS and OS. RIC URD 7/8 recipients had an approximately 6.5 % reduction in OS at 3 years compared to RIC URD 8/8 recipients. These decrements are similar to, but perhaps lower than those observed in the MA setting where mismatched donors yielded a 9-14% reduction in OS.[5, 6, 11] Thus, despite inherent differences between RIC and MA conditioning the overall impact of single locus mismatch appears to be similar.

The other goal of this analysis was to determine the impact of mismatching at individual HLA loci on RIC transplant outcomes to help identify better mismatched donors. Despite being a registry study of >2,500 patients, when the groups were analyzed based on individual locus mismatch (at HLA-A, -B, -C and –DRB1), patient numbers were reduced and thus, caution should be used in interpreting negative results since power may be limited. Importantly, all mismatch groups had at least one transplant outcome which was inferior to fully matched recipients. These findings contrast with Woolfrey who in a CIBMTR RIC URD subgroup analysis (n=673) reported that only HLA-C antigen mismatches had worse outcomes.[11] In the current study, we had greater power to address this question and found that mismatching at any locus resulted in inferior transplant outcomes compared to fully matched donors. Of note, there was only 19% overlap between these two CIBMTR studies.

A number of interesting findings differed when compared to prior MA studies. First, we were surprised to observe that mismatches in HLA-DRB1 (n=75) were as well tolerated as HLA class I mismatches. In fact, in multivariable analysis HLA-DRB1 mismatches were not associated with reductions in DFS or OS, contrasting with prior data in the MA data.[6, 7] Also interesting was that HLA-B mismatches were not associated with aGVHD grade II-IV or III-IV, but were strongly associated with TRM. In contrast, we found that mismatches at HLA-C were associated with aGVHD grade II-IV and TRM, but not severe grade III-IV aGVHD. Acknowledging the caveat of small patient numbers, the current results suggest the use of HLA-C or –DRB1 mismatched donors may be preferable over mismatches at HLA-A and or –B for RIC URD transplantation.

While MHC-disparity may drive allogeneic reactions that may protect against relapse, there was no reduction in relapse for the HLA-mismatched RIC cohort. Prior studies showed that disease status modified outcomes of HLA mismatched MA transplants, with advanced disease patients not experiencing as large an absolute decrement in survival with HLA mismatching as low risk patients.[24] In this analysis there was no interaction between disease status and HLA-matching status. While on the one hand, relapse rates are generally higher in the RIC setting and this might have allowed us to more readily detect an association of HLA

mismatching with relapse, this study was not specifically designed to address this question. Thus, the disease groups were heterogeneous, making it difficult to identify any protective effect of HLA mismatching. As well, HLA mismatching was strongly associated with the development of aGVHD. Therefore any benefit of HLA mismatching (i.e., increased GVL) might have been blunted by GVHD therapy. These findings are consistent with other studies that fail to show differences in relapse when comparing sibling to URD stem cell sources, where the latter might be expected to have more alloreactivity, but also increased aGVHD.[25, 26]

In summary, in the largest study to examine the association of HLA mismatching with RIC URD transplant outcomes, we found that compared to HLA 8/8 matched recipients, a single locus mismatch (i.e., 7/8 match) was associated with a considerable reduction in survival, mainly due to increased rates of aGVHD and TRM, with no change in relapse rates. We also found that mismatching at individual HLA loci had differential negative impacts on transplant outcomes, but caution is needed in interpreting these findings since the sample size of each subgroup is relatively small. Nonetheless, recipients of mismatched RIC URD donors showed inferior outcomes compared to fully matched donor transplants. Overall these findings show that while mismatched RIC URD transplantation is feasible, it comes at a significant cost in the form of toxicity and reduction in survival. Novel regimens to improve 7/8 URD RIC HCT outcomes are needed.

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Manuscript Highlights

- Large registry cohort of RIC 8/8 vs. 7/8 matched URD donor transplantation

- HLA 7/8 mismatched donors were associated with significantly higher grade II-IV aGVHD (RR=1.29, p=0.0034), higher TRM (RR=1.52, p<0.0001) and lower DFS (RR=1.12, p=0.0015) and OS (RR=1.25, p=0.0001)

- HLA 7/8 mismatched donors were not associated with relapse protection

- HLA 7/8 mismatched donors were not associated with higher cGVHD
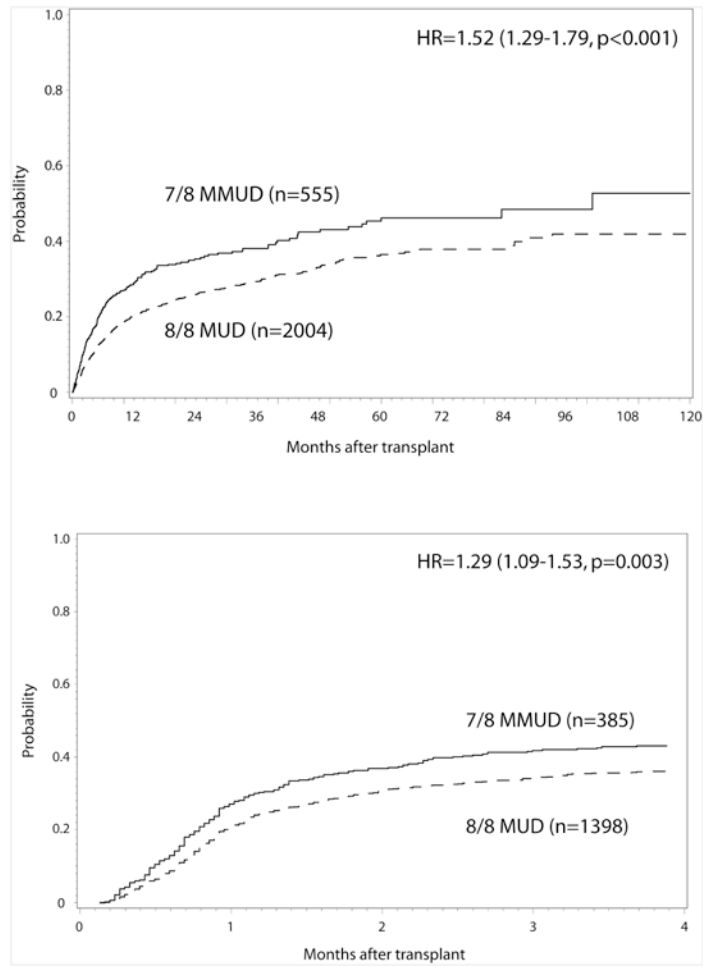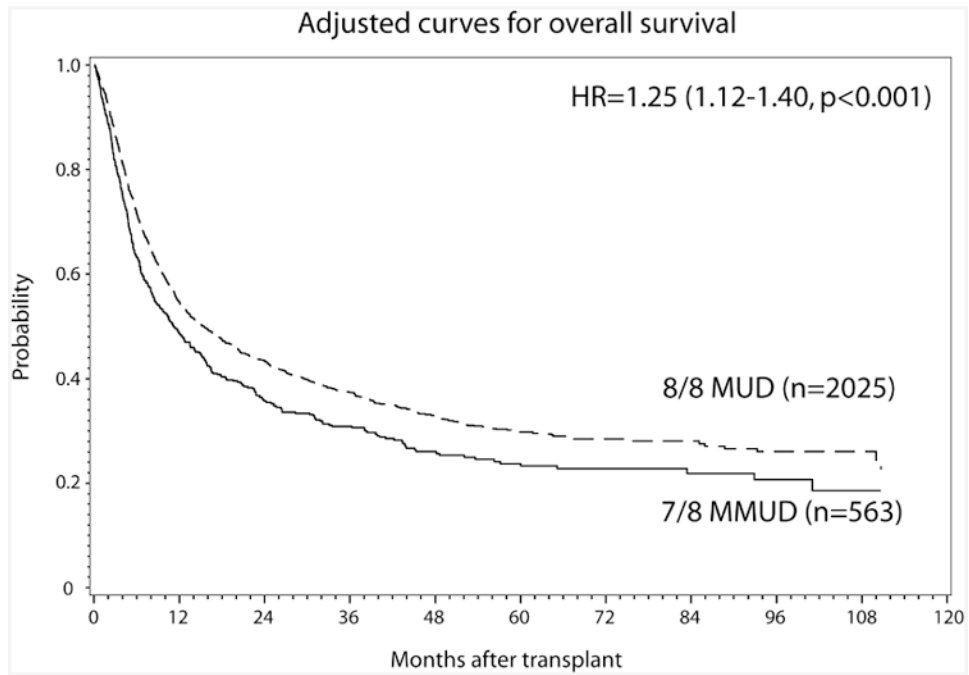
Figure 1. Impact of Single Allele Mismatch on (A) aGVHD II-IV, (B) cumulative incidence of TRM and (C) OS

Table 1

Patient Characteristics

Variable	8/8	7/8	p-value
Number of patients	2025	563	
Conditioning intensity			0.92
RIC	1601 (79)	444 (79)	
NMA	424 (21)	119 (21)	
Recipient age			0.03
Median (range)	59 (18-81)	58 (19-76)	0.003
18-39	215 (11)	67 (12)	
40-54	441 (22)	154 (27)	
55-59	397 (20)	107 (19)	
60-64	512 (25)	129 (23)	
>=65	460 (23)	106 (19)	
Recipient race			<0.001
Caucasian	1925 (95)	508 (90)	
African-American	44 (2)	30 (5)	
Asian	23 (1)	8 (1)	
Pacific islander	1 (<1)	0	
Native American	2 (<1)	3 (<1)	
Other	2 (<1)	0	
Unknown	28 (1)	14 (2)	
Recipient gender			0.20
Male	1162 (57)	306 (54)	
Female	863 (43)	257 (46)	
Karnofsky score			0.06
<90%	728 (36)	233 (41)	
>=90%	1190 (59)	303 (54)	
Missing	107 (5)	27 (5)	
Disease at HCT			0.11
AML	1318 (65)	372 (66)	
ALL	151 (7)	44 (8)	
CML	138 (7)	51 (9)	
MDS	418 (21)	96 (17)	
Disease status prior to HCT			0.09
Early	1038 (51)	268 (48)	
Intermediate	365 (18)	124 (22)	
Advanced	622 (31)	171 (30)	
Graft type			0.42
Bone marrow	296 (15)	90 (16)	
Peripheral blood	1729 (85)	473 (84)	
Total body irradiation			0.33

Variable	8/8	7/8	p-value
No	1575 (78)	427 (76)	
Yes	450 (22)	136 (24)	
GVHD prophylaxis			0.74
FK506 +- others	1431 (71)	392 (70)	
CSA +- others	540 (27)	158 (28)	
Others	54 (3)	13 (2)	
In vivo T-cell depletion			0.10
No	1194 (59)	310 (55)	
Yes	831 (41)	253 (45)	
Donor age			<0.001
Median (range)	34 (<1-221)	36 (19-221)	0.04
19-32	1017 (50)	231 (41)	
32-49	890 (44)	288 (51)	
>=50	114 (6)	40 (7)	
Not available	4 (<1)	4 (<1)	
Donor Parity			p=0.07
Male or not parous	1674 (83)	444 (79)	
Parous	307 (15)	100 (18)	
Not available	44 (2)	19 (3)	
Year of HSCT			<0.001
1999-2002	104 (5)	48 (9)	
2003-2006	578 (29)	190 (34)	
2007-2011	1343 (66)	325 (58)	
Median follow-up of survivors (range), months	38 (3-149)	48 (3-145)	

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Table 2

Univariate Analysis Comparing Transplant Outcomes Between Fully Matched (HLA 8/8) Donors to Single Locus (HLA 7/8) Mismatched Donors

Outcomes	HLA 8/8 Donor		HLA 7/8 Donor		p value
	n	Prob (95% CI)	n	Prob (95% CI)	
Acute GVHD, grade II-IV	1398		385		
100-day		35 (33-38)%		43 (38-48)%	0.0018
Acute GVHD, grade III-IV	1403		387		
100-day		13 (11-15)%		21 (17-25)%	<0.001
Chronic GVHD	1989		516		
6 months		27 (25-29)%		30 (26-34)%	0.018
1-year		44 (42-47)%		44 (39-48)%	0.30
3-year		50 (48-52)%		50 (45-54)%	0.064
5-year		50 (48-53)%		50 (46-55)%	0.057
Extensive chronic GVHD	2000		518		
6 months		20 (18-22)%		24 (20-27)%	0.017
1-year		33 (31-35)%		33 (29-37)%	0.27
3-year		37 (35-39)%		38 (34-43)%	0.056
5-year		37 (35-40)%		38 (34-43)%	0.056
Engraftment	2061		510		
100-day		97 (96-98)%		94 (92-96)%	0.22
Relapse	2004		555		
1-year		36 (33-38)%		33 (29-37)%	0.78
3-year		42 (40-44)%		39 (35-43)%	0.73
5-year		44 (41-46)%		40 (36-45)%	0.84
TRM	2004		555		
1-year		20 (18-22)%		29 (25-33)%	<0.001
3-year		27 (25-29)%		36 (31-40)%	0.0011
5-year		31 (29-34)%		40 (35-44)%	0.0088
Disease free survival	2004		555		
1-year		44 (42-47)%		39 (35-43)%	0.02

Outcomes	HLA 8/8 Donor		HLA 7/8 Donor		
	n	Prob (95% CI)	n	Prob (95% CI)	p value
3-year		31 (29-33)%		25 (21-29)%	0.01
5-year		25 (23-27)%		20 (16-24)%	0.03
Overall survival	2025		563		
1-year		55 (53-57)%		48 (44-52)%	0.003
3-year		38 (35-40)%		30 (26-34)%	<0.001
5-year		30 (27-32)%		22 (19-27)%	0.004

Table 3

Multivariable Analysis Comparing outcomes between HLA 8/8 to HLA 7/8 Donors

Variable	RR	95% CI Lower Limit	95% CI Upper Limit	p value
aGVHD II-IV				
8/8 allele match	1			0.003
7/8 allele match	1.29	1.09	1.53	
aGVHD III-IV				
8/8 allele match	1			0.05
7/8 allele match	1.69	1.00	3.36	
CGVHD				
8/8 allele match	1			0.15
7/8 allele match	1.11	0.96	1.28	
TRM				
8/8 allele match	1			<.0001
7/8 allele match	1.52	1.29	1.79	
Relapse				
8/8 allele match	1			0.92
7/8 allele match	1.007	0.87	1.17	
DFS				
8/8 allele match	1			0.0015
7/8 allele match	1.20	1.07	1.34	
OS				
8/8 allele match	1			0.0001
7/8 allele match	1.25	1.12	1.40	

Multivariable models also included the following covariates: aGVHD II-IV: GVHD prophylaxis, graft type, in vivo T cell depletion, DPB1 matching; aGVHD III-IV: GVHD prophylaxis, TBI, in vivo T cell depletion; cGVHD: year of transplant, in vivo T cell depletion; TRM: graft type, recipient age, Karnofsky performance score, disease status, conditioning intensity, in vivo T cell depletion; Relapse: Karnofsky performance score, disease status, conditioning intensity, in vivo T cell depletion; DFS: Karnofsky performance score, disease status, conditioning intensity; OS: graft type, recipient age, Karnofsky performance score, donor age, and disease status.

Table 4

Graft Matching Characteristics

Variable	8/8	7/8	P-value
High resolution matching for HLA-A,-B,-C and -DRB1			
Fully matched	2025	0	
Single MM at –A	0	188 (33)	
Single MM at –B	0	81 (14)	
Single MM at –C	0	219 (39)	
Single MM at -DRB1	0	75 (13)	
Low resolution matching for HLA-A,-B,-C and -DRB1			
Fully matched	2025	197 (35)	
Single MM at –A	0	143 (25)	
Single MM at –B	0	36 (6)	
Single MM at –C	0	170 (30)	
Single MM at -DRB1	0	17 (3)	
DQB1 match			<0.001
Allele matched	1804 (89)	488 (87)	
Single allele mismatch	70 (3)	36 (6)	
Double allele mismatch	0	1 (<1)	
Single antigen mismatch	71 (4)	27 (5)	
One allele and one antigen mismatch	2 (<1)	1 (<1)	
Double antigen mismatch	1 (<1)	1 (<1)	
Missing	77 (4)	9 (2)	
DPB1 match			0.06
Allele matched	160 (8)	41 (7)	
Single allele mismatch	559 (28)	175 (31)	
Double allele mismatch	337 (17)	110 (20)	
Missing	969 (48)	237 (42)	

Table 5

Transplant Outcomes Based On Allele Locus Mismatches

Matching	n	RR	p-value	95% CI Lower Limit	95% CI Upper Limit	Overall p-value
aGVHD II-IV						0.025
8/8 allele match	1366	1				
Single MM at -A	127	1.1	0.52	0.82	1.47	
Single MM at -B	63	1.27	0.24	0.85	1.90	
Single MM at -C	175	1.40	0.005	1.11	1.77	
Single MM at -DRB1	52	1.46	0.08	0.96	2.22	
aGVHD III-IV						0.0004
8/8 allele match	1371	1				
Single MM at -A	128	1.75	0.005	1.18	2.58	
Single MM at -B	63	1.72	0.06	0.98	3.01	
Single MM at -C	176	1.43	0.07	0.98	2.09	
Single MM at -DRB1	52	2.49	0.001	1.45	4.30	
TRM						<.0001
8/8 allele match	2004	1				
Single MM at -A	186	1.62	0.0002	1.25	2.09	
Single MM at -B	80	2.26	<.0001	1.63	3.14	
Single MM at -C	216	1.32	0.03	1.03	1.70	
Single MM at -DRB1	73	1.18	0.45	0.77	1.79	
DFS						0.0004
8/8 allele match	2004	1				
Single MM at -A	186	1.26	0.009	1.06	1.51	
Single MM at -B	80	1.51	0.001	1.18	1.93	
Single MM at -C	216	1.18	0.049	1.00	1.38	
Single MM at -DRB1	73	0.85	0.29	0.63	1.15	
OS						<.0001
8/8 allele match	2025	1				
Single MM at -A	188	1.43	<.0001	1.20	1.71	
Single MM at -B	81	1.57	0.0005	1.22	2.02	

Matching	n	RR	p-value	95% CI Lower Limit	95% CI Upper Limit	Overall p-value
Single MM at -C	219	1.13	0.16	0.96	1.34	
Single MM at -DRB1	75	0.97	0.82	0.71	1.31	

Multivariable models also included the following covariates: aGVHD II-IV: GVHD prophylaxis, graft type, in vivo T cell depletion; aGVHD III-IV: GVHD prophylaxis, TBI, in vivo T cell depletion; cGVHD: year of transplant, in vivo T cell depletion; TRM: graft type, recipient age, Karnofsky performance score, disease, GVHD prophylaxis; Relapse: Karnofsky performance score, disease status, conditioning intensity, in vivo T cell depletion; DFS: Karnofsky performance score, disease status, conditioning intensity; OS: graft type, recipient age, Karnofsky performance score, donor age, and disease status.