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One-Antigen Mismatched Related versus HLA-Matched Unrelated Donor Hematopoietic Stem Cell Transplantation in Adults with Acute Leukemia: Center for International Blood and Marrow Transplant Research Results in the Era of Molecular HLA Typing

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Approximately 13% of patients lacking an HLA-identical sibling have a one-antigen–mismatched related donor (MMRD). Historically, outcomes from the use of a one-antigen MMRD were considered equivalent to those from the use of a matched unrelated donor (UD). Recent improvements in UD stem cell transplantation (SCT) resulting from better molecular HLA matching justifies investigating whether UD should be preferred over MMRD in adult patients with acute leukemia. Here, we compared the outcomes of MMRD (n = 89) and HLA-A, -B, -C, and -DRB1 allele–matched UD (n = 700) SCT reported to the Center for International Blood and Marrow Transplant Research between 1995 and 2005. The patients underwent transplantation for acute myelogenous leukemia or acute lymphoblastic leukemia in first or second complete remission. Donor type was not associated with hematologic recovery. Univariate and multivariate comparisons of MMRD versus HLA-matched UD transplants showed no statistically significant differences in overall survival, disease-free survival, treatment-related mortality, relapse, or 100-day grade III-IV acute graft-versus-host disease (GVHD). MMRD SCT was associated with a lower rate of chronic GVHD at 1 year (35% vs 47%; $P = .03$), which was confirmed by multivariate analysis (relative risk, 0.58; 95% confidence interval, 0.39-0.85; $P < .01$). According to our data, HLA-matched UD and MMRD SCT are associated with comparable survival. Given that less chronic GVHD was observed in the MMRD transplantations, this option, when available, remains the first choice in patients with acute leukemia without an HLA-identical sibling in need of allogeneic SCT.

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INTRODUCTION

Although HLA-identical siblings are considered the optimal donors, they are available for only one-third or fewer of patients with acute leukemia for whom allogeneic stem cell transplantation (allo-SCT) is recommended. The probability of finding an HLA-A, -B, or -DR antigen–mismatched related donor (MMRD) is approximately 3% between siblings and 10% among other

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relatives [1]. Another option for these patients is to undergo a search for an unrelated donor (UD). The overall probability of identifying an HLA-compatible unrelated volunteer in the international registries is approximately 10%-75%, depending on the race and ethnicity of the patient (http://www.marrow.org).

In recent years, survival after UD allo-SCT has improved, mainly because of better matching of donor–recipient pairs based on molecular typing of HLA class I and II loci [2-5]. Moreover, recent reports show similar outcomes of allo-SCT in patients with an HLA-matched UD and those with an HLA-identical sibling donor [6-10].

The progress in the UD allo-SCT setting provides the rationale for reexamining whether this option should be recommended to patients with an available MMRD. This question warrants investigation because it is well recognized that HLA mismatch increases graft failure and graft-versus-host disease (GVHD) after transplantation. Given that previous comparisons between UD and MMRD transplants were published before the introduction of HLA typing at the allele level [11-16], we reevaluated this question in recent transplantations for patients with acute leukemia included in the Center for International Blood and Marrow Transplant Research (CIBMTR) database.

PATIENTS AND METHODS

Data Collection

The data used in this study were obtained from the CIBMTR's Statistical Center. A research affiliate of the International Bone Marrow Transplant Registry, the Autologous Blood and Marrow Transplant Registry, and the National Marrow Donor Program (NMDP), the CIBMTR comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic SCTs to the Statistical Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all transplantations consecutively; compliance is monitored by onsite audits. Patients are followed longitudinally with yearly follow-up. Computerized checks for errors, physicians' reviews of submitted data, and onsite audits of participating centers ensure data quality. Observational studies are conducted by the CIBMTR with a waiver of informed consent and in compliance with HIPAA regulations as determined by the Medical College of Wisconsin's Institutional Review Board and Privacy Officer.

Inclusion Criteria

The study population included 89 patients who received an MMRD transplant and 700 patients who received an 8/8 HLA-A, -B, -C, and -DRB1 allele–matched UD transplant between 1995 and 2005. This study was restricted to adult patients (18 years or older), with a diagnosis of acute myelogenous leukemia (AML) or acute lymphoblastic leukemia (ALL) in first or second complete remission (CR1, CR2), who underwent a first bone marrow or peripheral blood SCT with either myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC). T cell–depleted cases were excluded. Informed consent was obtained in accordance with the Declaration of Helsinki. All surviving UD recipients included in this analysis were retrospectively contacted and provided informed consent for participation in the NMDP research program. Informed consent was waived by the NMDP's Institutional Review Board for all deceased recipients. Approximately 10% of surviving patients would not provide consent for use of the research data. To adjust for the potential bias introduced by exclusion of nonconsenting surviving patients, a corrective action plan modeling process was used to randomly exclude approximately the same percentage of deceased patients using a biased coin randomization with exclusion probabilities based on characteristics associated with not providing consent for the use of data in survivors [17].

HLA Typing

In the UD group, HLA typing consisted of high-resolution typing of HLA-A, -B, -C, and -DRB1 alleles, verified through the NMDP retrospective typing program as described previously [18]. For the purpose of this study and in accordance with recent reports, mismatches affecting only the HLA-DQ locus were considered full matches [17,19]. In the MMRD group, HLA typing was verified by reviewing HLA typing reports and was restricted to low-resolution typing of HLA-A, -B, and -DRB1 loci.

Endpoints

The aim of the study was to compare the clinical outcomes among patients with acute leukemia who underwent a first SCT from a one-antigen MMRD or from an HLA-matched UD, to determine which donor type was associated with better outcomes. Analyzed outcomes were overall survival (OS), disease-free survival (DFS), hematologic engraftment, incidence of acute and chronic GVHD (aGVHD, cGVHD), incidence of relapse, and treatment-related mortality (TRM).

The date of engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L. Platelet engraftment was defined as the achievement of a platelet count $\geq 20 \times 10^9$/L without platelet transfusions in the previous 7 days. The aGVHD endpoint referred to the development of grades II-IV and grades III-IV according to

the Glucksberg criteria [20]. cGVHD was diagnosed using established definitions [21]. Relapse was defined as recurrence of leukemia, and TRM was defined as death resulting from any cause other than relapse. DFS was defined as survival in CR after SCT. For OS, death from any cause was considered an event. All living patients were censored at last follow-up. Disease was classified according to cytogenetic risk. For AML, the Medical Research Council (MRC) [22] and Southwest Oncology Group [23] classification systems were used; in cases where there was a discrepancy, the classification system that resulted in the higher risk status was applied. For ALL, the MRC/ Eastern Cooperative Oncology Group criteria were used [24].

Statistical Analysis

Patient-, disease-, and transplant-related variables were compared between the two groups using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Hematopoietic recovery and the occurrence of GVHD, TRM, and disease relapse were calculated using cumulative incidence estimates, taking into account the competing-risk structure [25,26]. Probabilities of DFS and OS were estimated from the time of transplantation using Kaplan-Meier curves [27]. Groups were compared using the two-sided log-rank test [25,26].

For the multivariate analysis, Cox proportional hazards regression models were applied. The proportional hazards assumption was assessed for each covariate using a time-dependent covariate approach. Covariates that violated the proportional hazard assumption were adjusted by stratification. Stepwise forward-backward selection was used to build the models from the prognostic factors under consideration. A threshold of .05 was used for the selection of covariates. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient, Disease, and Transplant Characteristics

Patient characteristics are compiled in Table 1. Compared with the HLA-matched UD group, the MMRD group differed in the following characteristics that have been associated with better outcome: younger age, more favorable cytogenetics in ALL cases, greater ABO matching between donor and patient, and more frequent use of methotrexate. Some differences suggested worse outcomes in the MMRD group, including more frequent transplantations from a female donor to a male recipient, older donor age, less common low-risk cytomegalovirus (CMV) donor–recipient serologic status, and lower percentage of patients undergoing transplantation during the later period (2001-2005). The median follow-up for survivors in the MMRD group was 54 months (range, 3-135 months), and that for survivors in the HLA-matched UD group was 38 months (range, 10-149 months).

Engraftment

The data for hematologic engraftment are given in Table 2. The incidence of neutrophil engraftment at 28 days was 89% (95% confidence interval [CI], 81%-95%) for the MMRD group and 93% (95% CI, 91%-95%) for the HLA-matched UD group ($P = .21$). Among those who engrafted, the median time to neutrophil engraftment (0.5×10^9/L) was 16 days after MMRD allo-SCT and 15 days after HLA-matched UD allo-SCT, and the median time to platelet engraftment (20×10^9/L) was 18 days and 20 days, respectively.

GVHD

The probability of grade II-IV aGVHD at 100 days was 49% (95% CI, 38%-60%) in the MMRD group and 47% (95% CI, 43%-51%) in the HLA-matched UD group (Table 2). In multivariate analysis, donor type was not associated with grade II-IV aGVHD (relative risk [RR], 1.11; 95% CI, 0.80-1.55; $P = .53$) or with grade III-IV aGVHD (RR, 1.53; 95% CI, 0.91-2.57; $P = .11$) (Table 3). The 1-year probability of cGVHD after MMRD allo-SCT was 35% (95% CI, 25%-46%), compared with 47% (95% CI, 44%-51%), after HLA-matched UD allo-SCT. The 1-year probability of extensive cGVHD after MMRD allo-SCT was 24% (95% CI, 15%-34%), compared with 36% (95% CI, 33%-40%) after HLA-matched UD allo-SCT ($P = .01$). Multivariate analysis also showed a significantly lower rate of cGVHD in the MMRD group compared with the HLA-matched UD group (RR, 0.58; 95% CI, 0.39-0.85; $P < .01$) (Figure 1). Unadjusted cumulative incidence curves of cGVHD are shown in Figure 2.

Relapse

The cumulative incidence of relapse was 15% (95% CI, 8%-23%) at 1 year, 19% (95% CI, 11%-28%) at 2 years, and 20% (95% CI, 12%-29%) at 3 years after MMRD allo-SCT, and 23% (95% CI, 20%-26%) at 1 year, 27% (95% CI, 24%-31%) at 2 years, and 28% (95 CI, 25%-32%) at 3 years after HLA-matched UD allo-SCT ($P = .06$, .07, and .09, respectively). Table 4 shows the results of the multivariate analysis for relapse; of note, the type of donor was not significant (RR, 0.81; 95% CI, 0.50-1.30; $P = .38$), whereas the variables associated with higher relapse were CR2 at time of transplantation (RR, 1.78; 95% CI, 1.13-2.81; $P = .01$), RIC/nonmyeloablative conditioning (RR, 1.50; 95% CI, 1.12-2.01; $P < .01$), and <12 months from diagnosis to transplantation (RR, 0.56; 95% CI, 0.35-0.90;

Table 1. Patient, Disease, and Transplant Characteristics

Characteristic	MMRD		HLA-Matched UD		*P* Value
	Number Evaluated	n (%)	Number Evaluated	n (%)	
Number of patients		89		700	
Age, median (range), years	89	35 (18-64)	700	43 (18-74)	<.01
Sex	89		700		.50
Male		50 (56)		367 (52)	
Female		39 (44)		333 (48)	
Donor/recipient race match		—	700		NA
Mismatched				42 (6)	
Matched				616 (88)	
Unknown				42 (6)	
Karnofsky score before transplantation	89		700		.29
<90		24 (27)		158 (23)	
≥90		60 (67)		469 (67)	
Unknown		5 (6)		73 (10)	
Disease	89		700		.66
AML		59 (66)		480 (69)	
ALL		30 (34)		220 (31)	
Disease status	89		700		.26
CR1		61 (69)		437 (62)	
CR2		28 (31)		263 (38)	
AML cytogenetics	59		480		.63
Low		5 (8)		46 (10)	
Intermediate/high		40 (68)		345 (72)	
Unknown		14 (24)		89 (19)	
ALL cytogenetics	30		220		<.01
Low		13 (43)		40 (18)	
Intermediate/high		8 (27)		102 (46)	
Unknown		9 (30)		78 (36)	
Graft type	89		700		.35
Bone marrow		35 (39)		312 (45)	
Peripheral blood		54 (61)		388 (55)	
Conditioning regimen	89		700		.24
Ablative		73 (82)		535 (76)	
RIC/nonmyeloablative		16 (18)		165 (24)	
Use of ATG in conditioning	87		700		.16
No		72 (83)		616 (88)	
Yes		15 (17)		84 (12)	
GVHD prophylaxis	89		700		.01
CsA/tacrolimus ± others (no MTX)		10 (11)		158 (23)	
CsA/tacromlimus + MTX		79 (89)		542 (77)	
Time from diagnosis to transplantation, months, median (range)	89	7 (2-183)	699	7 (1-171)	.12
Donor relationship	89		700		NA
Sibling		54 (61)		—	
Parent		15 (17)		—	
Child		13 (15)		—	
Other relative		7 (8)		—	
Unrelated		—		700 (100)	
HLA difference	88		700		
HLA-A		39 (44)		—	
HLA-B		25 (28)		—	
HLA-DRB1		25 (28)		—	
ABO match	89		700		<.01
Matched		51 (57)		300 (43)	
Minor mismatch		13 (15)		183 (26)	
Major mismatch/bidirectional		19 (21)		217 (31)	
Unknown		6 (7)		0	
Donor/recipient sex match	89		700		.02
Male/male		26 (29)		266 (38)	
Male/female		22 (25)		198 (28)	
Female/male		24 (27)		101 (14)	
Female/female		17 (19)		135 (19)	
CMV match	89		700		<.01
D^-/R^-		20 (22)		217 (31)	
D^-/R^+		14 (16)		230 (33)	
D^+/R^-		14 (16)		96 (14)	
D^+/R^+		41 (46)		141 (20)	
Unknown		0		16 (2)	
Donor age, year, median (range)	88	38 (9-71)	700	34 (18-60)	.05
Year of transplantation	89		700		<.01
1995-2000		55 (62)		169 (24)	

(*Continued*)

Table 1. (*Continued*)

Characteristic	MMRD		HLA-Matched UD		*P* Value
	Number Evaluated	n (%)	Number Evaluated	n (%)	
2001-2005		34 (38)		531 (76)	
Follow-up of survivors, months, median (range)	37	54 (3-135)	299	38 (10-149)	
Deaths, n	52		401		NA
Primary disease		12 (23)		145 (36)	
New malignancy		0		3 (1)	
GVHD		9 (17)		48 (12)	
IPN		7 (13)		18 (4)	
Infection		9 (17)		78 (19)	
Organ failure		8 (15)		84 (21)	
Graft failure		1 (2)		1 (<1)	
Hemorrhage		1 (2)		14 (3)	
Accidental death		0		2 (<1)	
Unknown		5 (10)		8 (2)	

MMRD indicates mismatched related donor; UD, unrelated donor; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CR1, first complete remission; CR2, second complete remission; CsA, cyclosporine; MTX, methotrexate; CMV, cytomegalovirus; GVHD, graft-versus-host disease.

$P = .02$). Relapse was the primary cause of death in both groups (Table 1).

TRM

The cumulative incidence of TRM was 34% (95% CI, 24%-44%) at 1 year, 38% (95% CI, 28%-48%) at 2 years, and 39% (95% CI, 29%-50%) at 3 years after MMRD allo-SCT and 24% (95% CI, 21%-27%) at 1 year, 27% (95% CI, 24%-31%) at 2 years, and 31% (95% CI, 27%-34%) at 3 years after HLA-matched UD allo-SCT ($P = .07$, .06, and .14, respectively). Table 4 presents the results of the multivariate analysis for TRM. There was no significant difference in TRM in the two groups (RR, 1.14; 95% CI, 0.77-1.69: $P = .52$). The only variables associated with increased TRM were older patient age (31-50 years vs 18-30 years; RR, 1.47; 95% CI, 1.08-2.01; $P = .02$) and transplantation before 2001 (RR, 1.64; 95% CI, 1.19-2.27: $P < .01$).

DFS

The DFS was 51% (95% CI, 41%-62%) at 1 year, 44% (95% CI, 33%-55%) at 2 years, and 41% (95%

Table 2. Univariate Analysis

Outcome Event	MMRD		HLA-Matched UD		*P*
	n	Probability (95% CI)	n	Probability (95% CI)	
ANC >0.5 × 10^9/L	89		700		
@28 days		89% (81%-95%)		93% (91%-95%)	.21
@100 days		93% (87%-97%)		95% (94%-97%)	.43
Platelets >20 × 10^9/L	89		700		
@60 days		71% (61%-80%)		81% (78%-84%)	.05
@100 days		75% (65%-83%)		85% (82%-87%)	.04
Acute GVHD II-IV	86		695		
@ 100 days		49% (38%-60%)		47% (43%-51%)	.71
Acute GVHD III-IV	86		698		
@ 100 days		22% (14%-32%)		15% (13%-18%)	.15
Chronic GVHD	85		690		
@ 1 year		35% (25%-46%)		47% (44%-51%)	.03
TRM	86		698		
@ 1 year		34% (24%-44%)		24% (21%-27%)	.07
@ 2 year		38% (28%-48%)		27% (24%-31%)	.06
@ 3 year		39% (29%-50%)		31% (27%-34%)	.14
Relapse	86		698		
@ 1 year		15% (8%-23%)		23% (20%-26%)	.06
@ 2 year		19% (11%-28%)		27% (24%-31%)	.07
@ 3 year		20% (12%-29%)		28% (25%-32%)	.09
DFS	86		698		
@ 1 year		51% (41%-62%)		53% (50%-57%)	.74
@ 2 year		44% (33%-55%)		46% (42%-49%)	.74
@ 3 year		41% (30%-52%)		41% (37%-45%)	.93
OS	89		700		
@ 1 year		57% (46%-67%)		61% (57%-64%)	.51
@ 2 year		46% (35%-56%)		50% (46%-54%)	.49
@ 3 year		42% (31%-52%)		44% (40%-48%)	.65

MMRD indicates mismatched related donor; UD, unrelated donor; ANC, absolute neutrophil count; GVHD, graft-versus-host disease; TRM, treatment-related mortality; DFS, disease-free survival; OS, overall survival.

Table 3. Multivariate Analysis for Acute and Chronic GVHD

	Acute GVHD II-IV*		Acute GVHD III-IV†		Chronic GVHD‡	
Main Effect	RR (95%CI)	*P*	RR (95%CI)	*P*	RR (95%CI)	*P*
HLA-matched UD	1.00		1.00		1.00	
MMRD	1.11 (0.80-1.55)	.53	1.53 (0.91-2.57)	.11	0.58 (0.39-0.85)	<.01

GVHD indicates graft-versus-host disease; UD, unrelated donor; MMRD, mismatched related donor.
*The acute GVHD II-IV model was stratified on conditioning regimen and adjusted for CMV match ($P = .02$) and graft type ($P < .01$).
†Acute GVHD III-IV was adjusted for CMV match ($P < .01$), Karnofsky score ($P < .01$), ABO match ($P = .04$), and time from diagnosis to transplantation ($P = .03$).
‡Chronic GVHD was adjusted for ATG use in conditioning ($P < .01$), graft type ($P < .01$), and patient sex ($P = .04$).

CI, 30%-52%) at 3 years after MMRD allo-SCT and 53% (95% CI, 50%-57%) at 1 year, 46% (95% CI, 42%-49%) at 2 years, and 41% (95% CI, 37%-45%) at 3 years after HLA-matched UD allo-SCT ($P = .74$, .74, and .93, respectively). Multivariate analysis revealed no significant difference in DFS between the two groups (Table 4). The only factor associated with decreased DFS was a Karnofsky score <90% (RR, 1.37; 95% CI, 1.10-1.69; $P < .01$).

OS

OS curves are shown in Figure 3. OS probability was 57% (95% CI, 46%-67%) at 1 year, 46% (95% CI, 35%-56%) at 2 years, and 42% (95% CI, 31%-52%) at 3 years after MMRD allo-SCT and 61% (95% CI, 57%-64%) at 1 year, 50% (95% CI, 46%-54%) at 2 years, and 44% (95% CI, 40%-48%) at 3 years after HLA-matched UD allo-SCT ($P = .51$, .49, and .65, respectively). As shown in Table 4, there was no significant association between OS and donor type. Variables associated with decreased OS were older patient age (31-50 years vs 18-30 years; RR, 1.34; 95% CI, 1.06-1.69; $P = .01$) and transplantation before 2001 (RR, 1.35; 95% CI, 1.05-1.72; $P = .02$).

Subset Analyses

Inclusion of cell dose (total nucleated cells in BM allo-SCT and mononuclear cells in PB allo-SCT) was limited by missing data, but an analysis of available data did not change our conclusions (data not shown). No significant differences were identified between class I mismatches and class II mismatches within the one-antigen–MMRD group for all endpoints (data not shown). Finally, no significant differences in outcomes were identified when the comparison of the HLA-matched UD and one-antigen–MMRD groups were limited to the nonmyeloablative/RIC conditioning subset (data not shown).

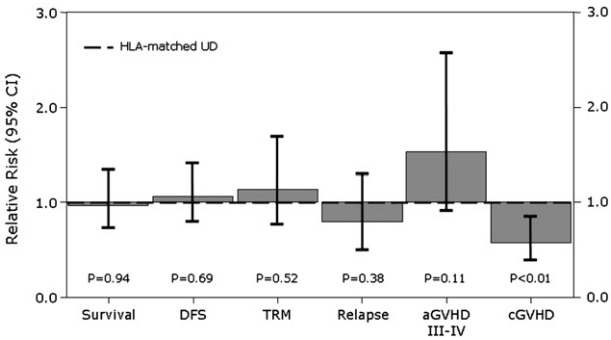

Figure 1. Relative risks of MMRD SCT versus HLA-matched UD SCT (RR, 1.0) from multivariate analysis. Whiskers represent 95% CIs.

DISCUSSION

Because HLA matching is the most important variable in allo-SCT [12,15,17], and current HLA typing methods using high-resolution molecular techniques have improved the results after UD allo-SCT over the last 10 years [2], previously reported comparisons between related and unrelated transplants may be outdated [19]. Some patients may have both an MMRD and a high likelihood of having an 8/8 HLA-matched UD, and for this group of patients, it is of interest to determine whether a search for a UD should be initiated.

A key finding from the present study is that the main outcomes of TRM, relapse, DFS, and OS were similar in the HLA-matched UD and MMRD groups, suggesting that the two alternatives are indeed comparable. Although more patients in the MMRD group received methotrexate as GVHD prophylaxis (89% vs 77%), GVHD prophylaxis was not statistically significant in the univariate or multivariate analysis, and thus it likely did not contribute to the difference in cGVHD incidence. This finding is in agreement with previous studies comparing the two donor sources [14,15]. The only observed difference was an increased

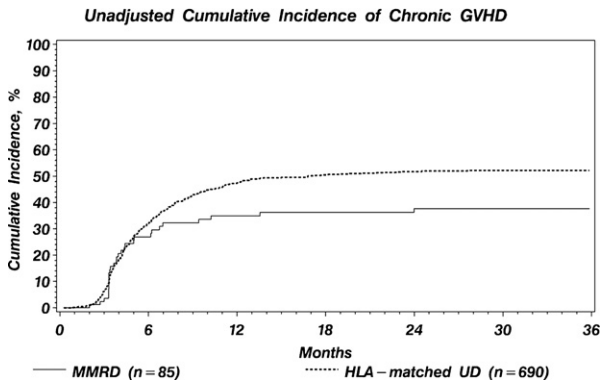

Figure 2. Unadjusted cumulative incidence of chronic GVHD by donor type.

Table 4. Multivariate Analysis for Relapse, TRM, DFS, and OS

	Relapse*		TRM†		DFS‡		OS§	
Main Effect	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
HLA-matched UD	1.00		1.00		1.00		1.00	
MMRD	0.81 (0.50-1.30)	.38	1.14 (0.77-1.69)	.52	1.06 (0.80-1.41)	.69	0.99 (0.73-1.34)	.94

TRM indicates treatment-related mortality; DFS, disease-free survival; OS, overall survival; UD, unrelated donor; MMRD, mismatched unrelated donor.
*The relapse model was adjusted for Karnofsky score at transplantation ($P = .03$), conditioning regimen ($P < .01$),disease status ($P = .01$), and time from diagnosis to transplantation ($P = .02$).
†The TRM model was stratified by graft type and donor/recipient sex match and adjusted for patient age ($P = .05$), and year of transplantation ($P < .01$).
‡The DFS model was adjusted for Karnofsky score at transplantation ($P < .01$).
§The OS model was stratified by graft type and adjusted for patient age at transplantation ($P < .01$) and year of transplantation ($P = .02$).

incidence of cGVHD after HLA-matched UD allo-SCT, a complication often leading to impaired quality of life [31]. Taking this into account, and given the lack of benefit in terms of DFS and OS, it is reasonable to use the MMRD when available, instead of initiating a UD search. Because this study was performed with patients with acute leukemia in CR1 or CR2, our findings are limited to these patients, and extension to patients with more advanced disease or other diseases requires further investigation.

HLA is inherited following Mendelian genetics, with two mechanisms explaining the availability of a one-antigen MMRD. The first is crossing-over in HLA genes, which occurs more frequently in class I, because HLA-A loci are far from those encoding HLA-B and HLA-C. The second is the presence of HLA alleles or at least one haplotype in the patient with high frequency in the overall population [28]. In this situation, the likelihood of finding a related donor sharing one HLA haplotype, with the other HLA haplotype being identical except for one gene in the extended family (eg, cousins, uncles, aunts), is increased, but the additional delay because of extended family typing must be balanced against the low likelihood of finding a suitable related donor. One study estimated that more than 30 individuals must be typed to identify a one-antigen MMRD [1]. Tools are available for calculating the probability of finding a related donor or a UD depending on HLA type, and consulting with an HLA expert may be helpful [28-30]. Given all of these considerations, and the fact that

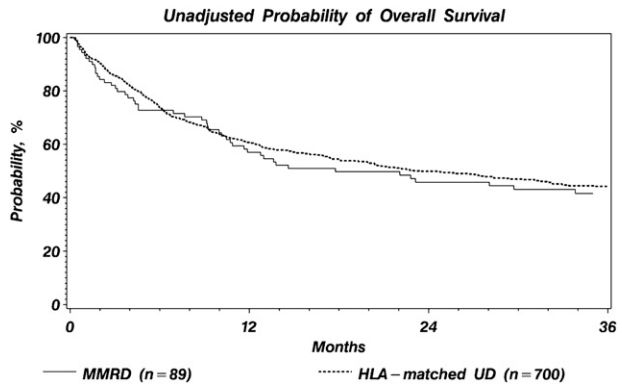

Figure 3. Unadjusted probability of OS by donor type.

one-antigen–MMRD allo-SCT was associated with similar clinical outcomes but with less cGVHD, one suggested approach would be to use a one-antigen–mismatched sibling if available but otherwise start a UD search. Because only 13% of patients will have an MMRD after extended family typing, with the aim of shortening the time to transplantation, a suitable strategy could be to perform a preliminary unrelated search while the familiar study is being performed.

The significantly lower incidence of cGVHD in the MMRD group observed in this study was unexpected, given that HLA mismatch is known to predispose to aGVHD and less strongly to cGVHD [17]. Other characteristics also favoring this complication, such as female to male transplant, advanced age of the donor and/or patient, and positive CMV serologic status, were more frequent in the MMRD group. Previous studies found a similar incidence of cGVHD in MMRD allo-SCT and HLA-identical sibling allo-SCT [14]. Thus, the higher incidence of cGVHD in the HLA-matched UD group may be explained in part by undetected disparities between donor and recipient other than in HLA genes. Of note, most of these gene disparities may involve minor histocompatibility antigens (mHAs), which are increasingly associated with the development of GVHD in the setting of HLA-identical sibling SCT [32-34]. Because these antigens are frequently encoded in chromosomes other than chromosome 6, it is likely that UDs will differ in these mHAs more frequently than related donors, especially if they are siblings. Nevertheless, in a recent study from the CIBMTR, mismatching in known mHAs was not associated with a higher incidence of GVHD in patients who underwent allo-SCT from a matched UD [35]. Although that study is the largest to date evaluating the role of mHAs in the unrelated setting, the small subgroup size might have limited its power to detect differences. Moreover, a recent publication has emphasized the importance of haplotype matching in the setting of UD allo-SCT to avoid severe GVHD [36]. Because most of the MMRD transplants reported here were from one-antigen–mismatched siblings (and thus the HLA difference might result from crossing-over), the degree of extended haplotype matching is likely higher than in the UD group.

This study has some limitations. The first is the small number of patients in the MMRD group, which likely reflects the preference of initiating a UD search instead of an extended family search because it is time-consuming and expensive and has a low probability of success [1]. Nevertheless, this study included one of the largest numbers of one-antigen–MMRD patients analyzed in a single report. Another drawback of the findings reported here is that, as in other retrospective registry studies, there were differences between the MMRD and UD groups in certain aspects important to transplantation outcome, including age (younger in the MMRD group) and year of transplantation (earlier in the MMRD group) However, this latter limitation was partially corrected for by performing the multivariate analysis including these covariates and showing a practically identical RR of TRM and OS in the two groups. Of course, the only approach to definitively answering the question would be a randomized prospective comparison of the two transplantation alternatives, which is highly unlikely.

A third limitation of the study is that HLA-matching assessment of related donors was based on low-resolution typing and limited to HLA-A, -B, and -DRB1. This is the current practice in most institutions for related donor selection, however. Because information on HLA-C and HLA-DQ was not available, it is not possible to rule out additional mismatches in the related donor group. This is unlikely in most cases affecting HLA-A (n = 39; 44%), because linkage disequilibrium means that matching at HLA-B (n = 25; 28%) and -DR (n = 25; 28%) is generally associated with matching at HLA-C and -DQ. Nevertheless, it seems reasonable to recommend the study of at least HLA-C in patients with a mismatch in HLA-B. Although the numbers were small, the outcomes of class I mismatch versus class II mismatch within one-antigen–MMRD transplants were similar regarding all endpoints studied, which is in agreement with a previous Japanese study that included 112 MMRDs [11]. On the other hand, because of missing data, we were unable to analyze the possible impact of KIR ligand mismatches or noninherited maternal or paternal antigens, aspects that have been recently considered in donor selection.

In conclusion, our data support the conclusion that both MMRD and HLA-matched UD are acceptable for transplantation in patients who require allo-SCT and lack an HLA-identical sibling. The lower incidence of cGVHD after MMRD allo-SCT, the easy and rapid access to relatives, and the lower cost make the MMRD modality the first option to consider, if available.

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