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Histocompatibility

Comparison of HLA Allele Mismatch and Antigen Mismatch in Unrelated Bone Marrow Transplantation in Patients with Leukemia

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A B S T R A C T

We compared the effect of HLA single-antigen and single-allele mismatched unrelated bone marrow transplantation (UBMT) without in vivo/ex vivo T cell depletion. Becasue a single DRB1 mismatch is preferred among 1-allele or 1-antigen mismatched donors, we performed mismatched allele- or antigen-specific analyses with a single DRB1 mismatch as the reference. In adjusted comparison by multivariate analyses, an HLA-DRB1 single-allele mismatch resulted in a decreased risk of nonrelapse mortality (NRM; relative risk [RR], 1.33; 95% confidence interval [CI], 1.08 to 1.63, $P = .006$) compared with an HLA-DR single-antigen mismatch and conferred a decreased risk of NRM (RR, 1.25; 95% CI, 1.01 to 1.57; $P = .025$) and overall mortality (RR, 1.16; 95% CI, 1.00 to 1.37; $P = .046$) compared with an HLA-C single-antigen mismatch. Relative to an HLA-DRB1 single-allele mismatch, 2-mismatch transplants, including those with 1 or more antigen mismatches, resulted in a significantly increased risk of NRM (1-antigen/1-allele mismatch: RR, 1.68; 95% CI, 1.03 to 2.05; $P < .001$; 2-antigen mismatch: RR, 1.58; 95% CI, 1.04 to 2.02; $P = .001$) and overall mortality (1-antigen/1-allele mismatch: RR, 1.27; 95% CI, 1.09 to 1.47; $P = .002$; 2-antigen mismatch: RR, 1.27; 95% CI, 1.03 to 1.57; $P = .02$). NRM correlated with the combined number of mismatches and allele or antigen mismatches, with rates of 22%, 27%, 32%, 31%, and 38% at 4 years for full match, single-allele mismatch, single-antigen mismatch, 2-allele mismatch, and 2 mismatches that included an antigen mismatch, respectively. Our results support the preference for an allele mismatch rather than an antigen mismatch in unrelated bone marrow donors with 1 DR mismatch or 2 mismatches for T cell–replete UBMT.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HCT) is the curative treatment of choice for many hematologic malignancies [1]. An HLA-identical sibling is the donor of choice if available, but fewer than 30% of candidates who are eligible for allogeneic HCT have such a donor. High-resolution, donor–recipient HLA matching has contributed to the success

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of unrelated donor marrow transplantation, and studies have shown that the survival results after unrelated bone marrow transplantation (UBMT) from HLA-A, -B, -C, and -DRB1 8/8-allele matched unrelated donors are similar to those after HCT from HLA-identical sibling donors [2–4].

A single mismatch, identified by low-resolution (antigen-level) or high-resolution (allele-level) DNA testing, at HLA-A, -B, -C, or -DRB1 loci was shown to be associated with higher mortality and decreased 1-year survival of 5% to 10% [3,5]. However, this reduced survival may be acceptable given the even lower survival rates with currently available alternative treatments. Early reports from the Japan Marrow Donor Program showed favorable survival outcomes after transplants from HLA-DRB1 single-allele mismatched donors compared with transplants from HLA-A, -B, or -C (class I) single-allele mismatched donors; therefore, HLA-DRB1 single-allele mismatched donors are preferentially selected among HLA single-mismatched donors in Japan [2,6].

The effect of single antigen-level mismatch compared with single allele-level mismatch remains controversial. Comparisons of the impact of single-allele and single-antigen mismatches on overall mortality did not reveal significant differences [3,7,8], except for the HLA-C locus, which is more important in peripheral blood stem cell transplantation where allele mismatches have been reported to be less detrimental than antigen mismatches [9,10]. The aim of this study was to compare the effect of single-antigen versus single-allele mismatched UBMT. Because single-DRB1 allele mismatch is preferred among donors with 1-allele or 1-antigen mismatch, as described above, we performed mismatched allele- or antigen-specific analyses, with a single DRB1 allele mismatch as the reference.

METHODS

Data Collection and Sources

HCT recipient clinical data were collected by the Japan Society for Hematopoietic Cell Transplantation and the Japanese Data Center for Hematopoietic Cell Transplantation using the Transplant Registry Unified Management Program, as described previously [11,12]. Information on survival, underlying disease status, and long-term complications, including chronic graft-versus-host disease (GVHD) and second malignancies, is renewed annually.

Subjects were patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and myelodysplastic syndromes (MDS) who received a first BMT from an HLA-matched or up to 2-allele/antigen mismatched unrelated donor between 2000 and 2014. We excluded patients with 3 or more mismatches (n = 290), those who received in vivo/ex vivo T cell depletion (n = 398 and n = 63, respectively), those who did not receive GVHD prophylaxis (n = 15), and those with missing information regarding age at transplant, survival status, or last follow-up day (n = 5).

A total of 7608 UBMT recipients met the inclusion criteria. Opt-out is permitted for observational studies using existing data according to the ethical guideline. Those who declined for registration were not included in the subjects for the study. The study was approved by the data management committees of the Japan Society for Hematopoietic Cell Transplantation and the Japanese Data Center for Hematopoietic Cell Transplantation and by the institutional review board of Saitama Medical Center, Jichi Medical University.

HLA Typing

Alleles at the HLA-A, -B, -C, and -DRB1 loci in unrelated bone marrow donor–recipient pairs were identified by the methods described previously [2,13]. Serologic or antigen-level typing was performed with low-resolution, DNA-based typing, usually by partially collapsing the second-field typing result back to its first field. Both host-versus-graft and graft-versus-host directions were accounted for in terms of HLA mismatch.

The main variables of interest were grouped as follows: HLA-DRB1 1-allele-level mismatched (HLA-DRB1 allele 1MM, as the reference), HLA 8/8-allele-level matched (8/8-matched), HLA-DR 1-antigen-level mismatched (HLA-DR antigen 1MM), HLA-A or -B 1-allele-level mismatched (HLA-AB allele 1MM), HLA-A or -B 1-antigen-level mismatched (HLA-AB antigen 1MM), HLA-C 1-allele-level mismatched (HLA-C allele 1MM), HLA-C 1-antigen-level mismatched (HLA-C antigen 1MM), HLA 2-allele-level-loci mismatched (6/8 matched allele 2MM), HLA 1-allele-level and 1-antigen-level mismatched (6/8 matched allele 1MM and antigen 1MM), and HLA 2-antigen-level mismatched (6/8 matched antigen 2MM). HLA-A and -B mismatches were grouped into a single group for both 1-allele-level and 1-antigen-level mismatch because of the small number of recipients who received BMT from HLA-A or -B single mismatched unrelated donor. HLA disparity groups according to the number of allele or antigen mismatches were then defined: HLA 8/8-allele-level matched (8/8-matched), 1-allele-level mismatched (1-allele-MM), 1-antigen-level mismatched (1-antigen-MM), 2-allele-level mismatched (2-allele-MM), and 1-allele-level and 1-antigen-level mismatched or 2-antigen-level mismatched (2-MM-including-antigen-MM).

Definitions

The primary outcome of the analyses was overall survival, defined as time from transplant to death from any cause. A number of secondary endpoints were also analyzed. Diagnosis and clinical grading of acute GVHD were performed according to the established criteria [14,15]. Relapse was defined as the recurrence of underlying hematologic malignant diseases. Nonrelapse death was defined as death during a continuous remission.

Statistical Analysis

Descriptive statistical analysis was performed to assess patient baseline characteristics, diagnosis, disease status at conditioning, donor–patient ABO mismatches, preparative regimens, and GVHD prophylaxis. Medians and ranges are provided for continuous variables, and percentages are given for categorical variables. Adjusted comparison of the groups on overall survival was performed with the use of the Cox proportional hazards regression model [16].

For other outcomes with competing risks, Fine and Gray's proportional hazards model for subdistribution of a competing risk was used [17]. For GVHD, death without GVHD and relapse were the competing events; for relapse, death without relapse was the competing event; and for nonrelapse mortality (NRM), relapse was the competing event. The variables considered were year of transplant (2000 to 2006 versus 2007 to 2014), patient age at transplant, patient sex, diagnosis (AML, ALL, CML, or MDS), disease status at conditioning (first or second complete remission of AML, first complete remission of ALL, first chronic phase of CML, and refractory anemia or refractory anemia with ringed sideroblasts as standard-risk diseases versus advanced for all others), conditioning regimen (reduced-intensity versus myeloablative conditioning), and type of prophylaxis against GVHD (tacrolimus versus cyclosporine based). Conditioning regimens were classified as myeloablative if total body irradiation > 8 Gy, oral busulfan ≥ 9 mg/kg, intravenous busulfan ≥ 7.2 mg/kg, or melphalan > 140 mg/m^2 were used based on the report from the Center for International Blood and Marrow Transplant Research [18,19].

Patients with insufficient information regarding the doses of agents or radiation used in the conditioning regimen were categorized according to information on the conditioning intensity (whether or not the conditioning regimen was intended to be myeloablative) as reported by the treating clinicians. The HLA disparity group variable was maintained in the model. Other variables were selected in a backward stepwise manner with a variable retention criterion of $P < .05$. Adjusted probabilities of overall survival and adjusted cumulative incidences of NRM and grades III to IV acute GVHD were estimated using the Cox proportional hazards regression model or the Fine and Gray's proportional hazards model, with consideration of other significant clinical variables in the final multivariate models. No significant interactions were identified between any of the variables and HLA disparity groups. All P values were 2-sided, and $P < .05$ was considered significant.

RESULTS

Patient Characteristics

Characteristics of patients, diseases, and transplant regimens are shown in Table 1. The median patient age at transplant showed a narrow range from 39 to 48 years. Recipient sex, recipient–donor sex and ABO matching, diagnosis, and disease status were similar among the HLA disparity groups. More than 70% of recipients in all groups underwent myeloablative conditioning regimens, and most recipients in all groups received tacrolimus-based GVHD prophylaxis. In the more recent 2007 to 2014 period the number of patients who underwent HCT was higher in the HLA-DR antigen 1MM and HLA-C allele 1MM groups. The median follow-up periods for survivors in the HLA disparity groups were 4.7, 4.7, 3.7, 5.9, 6.4, 4.8, 5.4, 5.7, 6.3, and 4.9 years in the HLA-DRB1 allele 1MM, 8/8-matched, HLA-DR antigen 1MM, HLA-AB allele

Table 1
Patient, Disease, and Transplant Characteristics According to HLA Mismatches

	HLA-DRB1 Allele 1MM	8/8 Matched	HLA-DR1 Antigen 1MM	HLA-A or -B Allele 1MM	HLA-Aor -B Antigen 1MM	HLA-C Allele 1MM	HLA-C Antigen 1MM	6/8 Matched Allele 2MM	6/8 Matched Allele 1MM and Antigen 1MM	6/8 Matched Antigen 2MM
No. of transplants	647	4090	717	263	27	106	778	184	568	228
Year of transplant										
2000-2006	262 (40)	1454 (36)	137 (19)	156 (59)	7 (26)	18 (17)	357 (46)	96 (52)	323 (57)	70 (31)
2007-2014	385 (60)	2636 (64)	580 (81)	107 (41)	20 (74)	88 (83)	421 (54)	88 (48)	245 (43)	158 (69)
Patient age at transplant, yr										
Median (Range)	43 (0-70)	44 (0-77)	44 (1-71)	39 (1-71)	40 (15-65)	48 (2-68)	40.5 (0-74)	41.5 (1-68)	40 (1-68)	43 (2-72)
Patient sex										
Female	235 (36)	1660 (41)	294 (41)	109 (41)	12 (44)	43 (41)	337 (43)	74 (40)	211 (37)	77 (34)
Male	412 (64)	2430 (59)	423 (59)	154 (59)	15 (56)	63 (59)	441 (57)	110 (60)	357 (63)	151 (66)
Sex matching										
Matched	387 (60)	2441 (60)	417 (58)	159 (60)	11 (41)	67 (63)	449 (58)	98 (53)	336 (59)	140 (61)
Male to Female	128 (20)	992 (24)	184 (26)	56 (21)	10 (37)	13 (12)	169 (22)	44 (24)	122 (21)	38 (17)
Female to Male	132 (20)	650 (16)	114 (16)	47 (18)	6 (22)	26 (25)	156 (20)	42 (23)	109 (19)	50 (22)
Unknown	0 (<1)	7 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)	4 (<1)	0 (0)	1 (<1)	0 (0)
Diagnosis										
AML	317 (49)	2029 (50)	339 (47)	129 (49)	13 (48)	50 (47)	370 (48)	82 (45)	277 (49)	130 (57)
ALL	194 (30)	1137 (28)	205 (29)	77 (29)	6 (22)	26 (25)	214 (28)	69 (38)	161 (28)	57 (25)
CML	57 (9)	287 (7)	53 (7)	22 (8)	2 (7)	4 (4)	75 (10)	11 (6)	53 (9)	8 (4)
MDS	79 (12)	637 (16)	120 (17)	35 (13)	6 (22)	26 (25)	119 (15)	22 (12)	77 (14)	33 (14)
Disease status										
Standard	349 (54)	2427 (59)	383 (53)	128 (49)	14 (52)	62 (58)	461 (59)	98 (53)	292 (51)	122 (54)
Advanced	283 (44)	1588 (39)	324 (45)	131 (50)	12 (44)	43 (41)	302 (39)	81 (44)	257 (45)	101 (44)
Unknown	15 (2)	75 (2)	10 (1)	4 (2)	1 (4)	1 (1)	15 (2)	5 (3)	19 (3)	5 (2)
ABO matching										
Matched	289 (45)	2406 (59)	331 (46)	116 (44)	15 (56)	41 (39)	338 (43)	91 (49)	258 (45)	96 (42)
Minor mismatch	154 (24)	759 (19)	166 (23)	70 (27)	4 (15)	24 (23)	191 (25)	40 (22)	121 (21)	55 (24)
Major mismatch	128 (20)	596 (15)	138 (19)	49 (19)	5 (19)	28 (26)	146 (19)	36 (20)	115 (20)	49 (21)
Bidirectional	75 (12)	324 (8)	82 (11)	28 (11)	3 (11)	13 (12)	102 (13)	17 (9)	66 (12)	28 (12)
Unknown	1 (<1)	5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	8 (1)	0 (<1)
Preparative regimen										
Myeloablative										
CY+TBI±other	302 (47)	1956 (48)	349 (49)	142 (54)	11 (41)	41 (39)	406 (52)	93 (51)	306 (54)	108 (47)
Other TBI regimen	47 (7)	228 (6)	24 (3)	26 (10)	2 (7)	11 (10)	44 (6)	17 (9)	47 (8)	15 (7)
BU+CY±other	94 (15)	511 (12)	84 (12)	31 (12)	4 (15)	8 (8)	125 (16)	22 (12)	57 (10)	27 (12)
Other nonTBI regimen	75 (12)	557 (14)	89 (12)	23 (9)	4 (15)	16 (15)	70 (9)	14 (8)	53 (9)	21 (9)
Reduced intensity										
FL±TBI±other	114 (18)	764 (19)	155 (22)	37 (14)	6 (22)	25 (24)	118 (15)	31 (17)	96 (17)	53 (23)
Other RIST	15 (2)	66 (2)	14 (2)	4 (2)	0 (0)	5 (5)	14 (2)	6 (3)	7 (1)	4 (2)
Missing	0 (0)	8 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (1)	2 ()	0 (0)
GVHD prophylaxis										
Cycrosporine A + sMTX	127 (20)	954 (23)	64 (9)	61 (23)	2 (7)	20 (19)	201 (26)	32 (17)	96 (17)	16 (7)
Cyclosporine A ± other	1 (<1)	20 (<1)	0 (0)	3 (1)	0 (0)	0 (0)	5 (1)	1 (1)	3 (1)	0 (<1)
Tacrolimus + sMTX	492 (76)	2891 (71)	618 (86)	187 (71)	25 (93)	80 (75)	526 (68)	136 (74)	439 (77)	204 (89)
Tacrolimus ± other	19 (3)	166 (4)	23 (3)	6 (2)	0 (0)	3 (3)	32 (4)	10 (5)	13 (2)	5 (2)
Others/data missing	8 (1)	59 (1)	12 (2)	6 (2)	0 (0)	3 (3)	14 (2)	5 (3)	17 (3)	3 (1)

Values are n (%) unless otherwise defined. CY indicates cyclophosphamide; BU, oral busulfan; TBI, total body irradiation; FL, fludarabine; RIST, reduced-intensity conditioning stem cell transplantation; xMTX, short-term methotrexate.

1MM, HLA-AB antigen 1MM, HLA-C allele 1MM, HLA-C antigen 1MM, 6/8 matched allele 2MM, 6/8 matched allele 1MM and antigen 1MM, and 6/8 matched antigen 2MM groups, respectively.

Outcomes

Overall survival

When compared with the HLA-DRB1 allele 1MM group, the risk of overall mortality was higher in the HLA-C antigen 1MM, 6/8 matched allele 1MM and antigen 1MM, and 6/8 matched antigen 2MM groups (relative risk [RR], 1.16; 95% confidence interval [CI], 1.00 to 1.37; $P = .046$; RR, 1.27; 95% CI, 1.09 to 1.47; $P = .002$; and RR, 1.27; 95% CI, 1.04 to 1.57; $P = .02$, respectively) and lower in the 8/8-matched group (RR, .87; 95% CI, .77 to .97; $P = .017$). No significant differences were observed between the HLA-DR antigen 1MM, HLA-AB allele 1MM, HLA-AB antigen 1MM, HLA-C allele 1MM, and 6/8 matched allele 2MM groups (Table 2). The effect of 1-allele or antigen mismatch for each locus was compared with fully matched HLA, and a locus-specific comparison of allele versus antigen was also performed (Supplemental Table 1). In general, a single-allele or -antigen mismatch in HLA-A, -B, -C, or -DR loci was associated with an increased risk of mortality compared with 8/8 HLA-matched pairs. Locus-specific allele versus antigen comparison did not reveal a significant difference in overall mortality.

Relapse and NRM

The risk of relapse was lower in HLA-DR antigen 1MM and 6/8 matched allele 1MM and antigen 1MM when compared with HLA-DRB1 allele 1MM (RR, .77; 95% CI, .62 to .96; $P = .018$; and RR, .68; 95% CI, .54 to .86; $P = .001$, respectively). No significant difference was observed for HLA-AB allele 1MM, HLA-AB antigen 1MM, HLA-C allele 1MM, HLA-C antigen 1MM, 6/8 matched allele 2MM, or 6/8 matched antigen 2MM (Table 2). When compared with HLA-DRB1 allele 1MM, the risk of NRM was higher in HLA-DR antigen 1MM (RR, 1.33; 95% CI, 1.08 to 1.63; $P = .006$), HLA-C antigen 1MM (RR, 1.25; 95% CI, 1.01 to 1.57; $P = .025$), 6/8 matched allele 1MM and antigen 1MM (RR, 1.68; 95% CI, 1.03 to 2.05; $P < .001$), and 6/8 matched antigen 2MM (RR, 1.58; 95% CI, 1.04 to 2.02; $P = .001$) (Table 2). HLA-A allele 1MM, HLA-C antigen 1MM, HLA-DRB1 allele 1MM, and HLA-DR antigen 1MM were associated with increased risk of NRM compared with HLA 8/8 matched (RR, 1.50; 95% CI, 1.19 to 1.90; $P = .001$; RR, 1.51; 95% CI, 1.31 to 1.74; $P < .001$; RR, 1.20; 95% CI, 1.02 to 1.41; $P = .032$; and RR, 1.58; 95% CI, 1.36 to 1.84; $P < .001$, respectively). HLA-DR antigen 1MM showed increased risk of NRM and decreased risk of relapse compared with HLA-DRB1 allele 1MM (RR, 1.32; 95% CI, 1.08 to 1.62; $P = .007$; RR, .77; 95% CI, .62 to .96; $P = .019$) (Supplemental Table 1).

Acute GVHD

When compared with HLA-DRB1 allele 1MM, the risk of grades II to IV acute GVHD was higher in 6/8 matched allele 1MM and antigen 1MM (RR, 1.25, 95% CI, 1.07 to 1.47; $P = .007$) and lower in 8/8 matched (RR, .70; 95% CI, .62 to .79; $P < .001$). No significant difference was observed for other groups. The risk of severe (grades III to IV) acute GVHD was higher in 6/8 matched allele 2MM (RR, 1.86; 95% CI, 1.32 to 2.62; $P < .001$), 6/8 matched allele 1MM and antigen 1MM (RR, 1.79; 95% CI, 1.38 to 2.32; $P < .001$), and 6/8 matched antigen 2MM (RR, 1.58; 95% CI, 1.12 to 2.22; $P = .009$) and was lower in 8/8 matched (RR, .80; 95% CI, .64 to 1.00; $P = .045$) when compared with HLA-DRB1 allele 1MM (Table 3). HLA-A allele 1MM, HLA-C antigen 1MM, and HLA-DR allele or antigen 1MM showed an increased risk of grades II to IV acute GVHD and HLA-A allele 1MM, HLA-C antigen 1MM, and HLA-DR antigen 1MM showed an increased risk of grades III to IV acute GVHD compared with HLA 8/8 matched (Supplemental Table 2).

Number of allele or antigen mismatches and HCT outcomes

The number of allele or antigen mismatches correlated with increased rates of overall mortality and NRM as well as severe acute GVHD. The RRs of overall mortality according to the numbers of allele or antigen mismatches in the HLA disparity

Table 2
Multivariate Analyses of Overall Mortality and NRM and Relapse

		Overall Mortality			Relapse			NRM		
	No. of Cases	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
HLA-DRB1 1MM										
Allele-level mismatch	647	1.00			1.00			1.00		
8/8 matched	4090	.87	.77-.97	.017	1.00	.85-1.17	.993	.83	.71-.98	.028
HLA-DR1 1MM										
Antigen-level mismatch	717	1.11	.95-1.29	.180	.77	.62-.96	.018	1.33	1.08-1.63	.006
HLA-A or B 1MM										
Allele-level mismatch	263	1.13	.93-1.37	.215	.88	.66-1.17	.377	1.25	.97-1.62	.086
Antigen-level mismatch	27	.76	.41-1.37	.368	.47	.17-1.34	.16	1.18	.47-2.42	.674
HLA-C 1MM										
Allele-level mismatch	106	1.15	.86-1.57	.334	.97	.64-1.17	.873	1.11	.86-1.61	.603
Antigen-level mismatch	778	1.16	1.00-1.37	.046	.91	.74-1.12	.372	1.25	1.01-1.57	.025
6/8 matched										
2 allele-level mismatch	184	1.13	.90-1.47	.293	.81	.59-1.12	.204	1.23	.92-1.61	.186
1 allele-, 1 antigen-level mismatch	568	1.27	1.09-1.47	.002	.68	.54-.86	.001	1.68	1.03-2.05	<.001
2 antigen-level mismatch	228	1.27	1.03-1.57	.02	.81	.60-1.10	.176	1.58	1.04-2.02	.001

For overall mortality other predictive variables were transplant year before 2007, older age at transplant (continuous variable), male sex, CML, and MDS lower risk of mortality compared with AML, advanced disease status at transplant, and cyclosporine-based GVHD prophylaxis compared with tacrolimus-based GVHD prophylaxis. For relapse other predictive variables were ALL, CML, and MDS lower risk of relapse compared with AML and advanced disease status at transplant. For transplant-related mortality other predictive variables were transplant year before 2007, older age at transplant (continuous variable), male sex, ALL, CML, and MDS higher risk of mortality compared with AML and advanced disease status at transplant.

Table 3
Multivariate Analyses of Grades II-IV and III-IV Acute GVHD

		Grades II-IV Acute GVHD			Grades III-IV Acute GVHD		
	No. of Cases	RR	95% CI	*P*	RR	95% CI	*P*
HLA-DRB1 1MM							
Allele-level mismatch	647	1.00			1.00		
8/8 matched	4090	.70	.62-.79	<.001	.80	.64-1.00	.045
HLA-DR1 1MM							
Antigen-level mismatch	717	1.09	.93-1.28	.283	1.21	.92-1.59	.172
HLA-A,or B1MM							
Allele-level mismatch	263	.89	.72-1.11	.305	1.24	.88-1.74	.227
Antigen-level mismatch	27	.79	.44-1.39	.409	1.04	.39-2.76	.940
HLA-C 1MM							
Allele-level mismatch	106	.73	.52-1.01	.06	.88	.49-1.59	.674
Antigen-level mismatch	778	.88	.75-1.03	.124	1.27	.98-1.65	.074
6/8 matched							
2 allele-level mismatch	184	1.22	.96-1.54	.108	1.86	1.32-2.62	<.001
1 allele-, 1 antigen-level mismatch	568	1.25	1.07-1.47	.007	1.79	1.38-2.32	<.001
2 antigen-level mismatch	228	1.21	.98-1.49	.078	1.58	1.12-2.22	.009

For grades II-IV acute GVHD other predictive variables were younger age at transplant (continuous variable), ALL, and CML higher risk compared with AML and cyclosporine-based GVHD prophylaxis compared with tacrolimus-based GVHD prophylaxis. For grades III-IV acute GVHD other predictive variables were transplant year before 2007, younger age at transplant (continuous variable), male sex, advanced disease status at transplant, and cyclosporine-based GVHD prophylaxis compared with tacrolimus-based GVHD prophylaxis.

groups of 1-allele-MM, 1-antigen-MM, 2-allele-MM, and 2-MM-including-antigen-MM groups compared with 8/8-matched group were 1.21 ($P < .001$), 1.30 ($P < .001$), 1.30 ($P = .011$), and 1.46 ($P < .001$), respectively (P for trend $< .001$). The RRs of the groups compared with the 8/8 matched group were 1.29 ($P < .001$), 1.54 ($P < .001$), 1.48 ($P = .006$), and 1.99 ($P < .001$; P for trend $< .001$) for NRM and 1.32 ($P = .003$), 1.55 ($P < .001$), 2.32 ($P < .001$), and 2.17 ($P < .001$; P for trend $< .001$) for grades III to IV acute GVHD (Supplemental Table 3). The unadjusted probabilities of overall survival for the whole group (n = 7608) were 57%, 51%, and 48% at 2, 4, and 6 years post-transplant, respectively. The unadjusted cumulative incidences of NRM and of grades III to IV acute GVHD for the whole group were 27% at 4 years and 15% at 120 days post-transplant. The adjusted probabilities of survival, the adjusted cumulative incidences of NRM, and the adjusted cumulative incidences of grades III to IV acute GVHD according to the numbers of allele/antigen mismatches in the HLA disparity groups are described in Figure 1.

DISCUSSION

Our main objective was to compare single-antigen and single-allele mismatched UBMT in terms of overall mortality to provide useful data for selection of an appropriate donor for patients with hematologic malignancy. We sought to follow a practical selection process when selecting an HLA-mismatched unrelated donor, and we therefore defined the DRB1 1-allele mismatched transplant, which was the most common 1-allele mismatched transplant in our sample, as the reference. In our study HLA-DR single-antigen mismatched transplants showed an increased risk of NRM compared with HLA-DRB1 single-allele mismatched transplants, but the difference was not significant for overall mortality. HLA-C single-antigen mismatched transplants showed an increased risk of NRM and overall mortality compared with HLA-DRB1 single-allele mismatched transplants. When compared with HLA-DRB1 single-allele mismatched transplants, those with 2 mismatches that included 1 or more antigen mismatches showed significant increases in NRM and overall mortality. Our results support a preference for allele mismatch over antigen mismatch among HLA-DR single-locus or 2-loci mismatched unrelated bone marrow donors.

The importance of HLA matching for HLA-A, -B, -C, and -DRB1 at a high-resolution level has been repeatedly confirmed in studies worldwide [2,3,9,20–22]. More recent studies showed the effect of HLA-DPB1 mismatches on transplant outcomes [5,8]. An HLA single mismatch is considered to reduce survival probabilities by 5% to 10% [3,5]. Most studies comparing single-allele and single-antigen mismatches in unrelated donor stem cell transplantations showed no significant difference in clinical outcomes [3,7]. There were 2 exceptions: an increased risk of grades II to IV acute GVHD in HLA-B single-antigen mismatched transplants compared with single-allele mismatched transplants [8] and an increased risk of mortality in HLA-C single-antigen mismatched peripheral blood stem cell transplants compared with single-allele mismatched transplants [8,9]. The latter could possibly be explained by the high frequency of C*03:03/03:04 mismatches, whose incompatibility was previously reported to be more permissible in a National Marrow Donor Program study [10]. The above studies showing a difference in the clinical impact of single-allele and single-antigen mismatches included both bone marrow transplants and peripheral blood stem cell transplants as stem cell sources, which is also known to impact transplant outcomes [23,24].

An additional challenge when evaluating this clinical issue is the limited number of recipients available when making locus-specific comparisons of antigen versus allele mismatches. In Japan peripheral blood stem cell transplantation from unrelated donors was introduced in 2011 and has been performed at a slowly increasing rate since then. Assessing the effects of allele versus antigen mismatches in subjects limited to recipients of bone marrow without in vivo/ex vivo T cell depletion has been beneficial, because these patients constitute a more uniform population. Early reports from the Japan Marrow Donor Program showed favorable survival outcomes after transplants from HLA-DR single-mismatched donors compared with those from HLA-A, -B, or -C (class I) single-mismatched donors; therefore, HLA-DR single-mismatched donors were preferentially selected, which led to an accumulation of the number of BMTs from both HLA-DR single-antigen and HLA-DRB1 single-allele mismatched donors [2,6]. The impact of mismatched loci increases over time, and studies showed that survival outcomes were influenced by the total number of

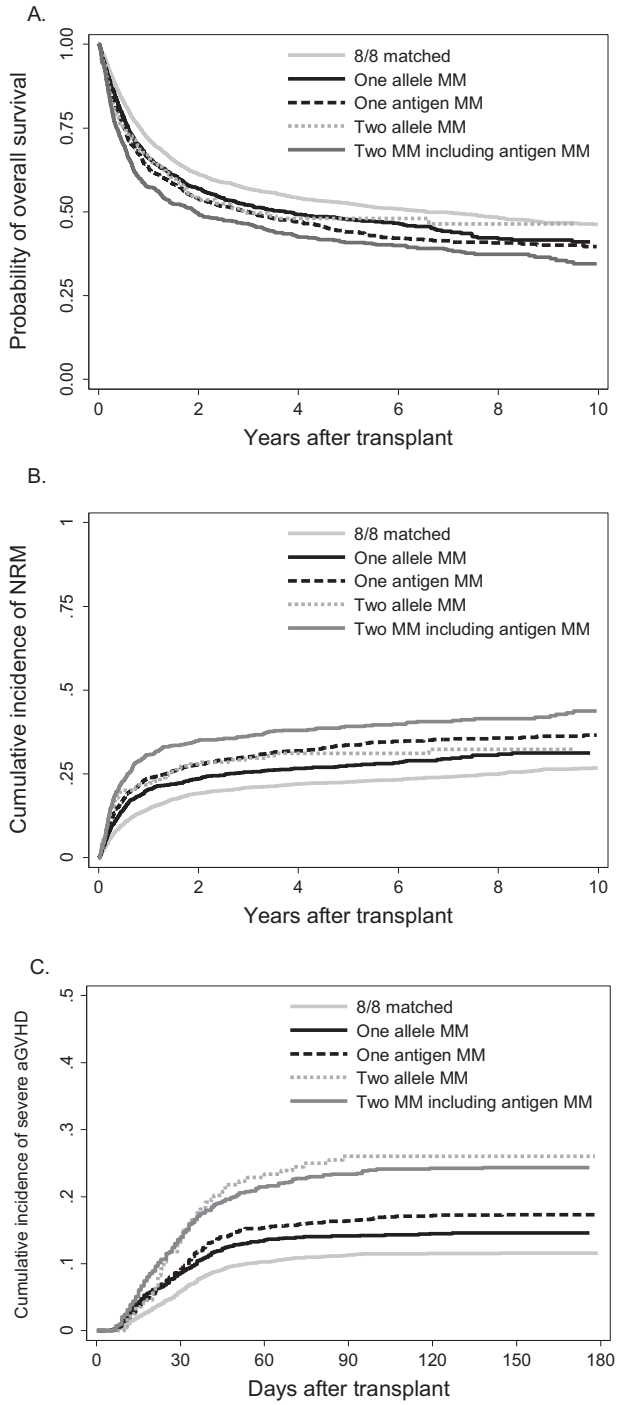

Figure 1. Adjusted probabilities of overall survival, NRM, and severe acute GVHD. The adjusted probabilities of survival among the HLA disparity groups according to the number of allele or antigen mismatches were as follows: 54%, 49%, 47%, 48%, and 42% for the 8/8-matched, 1-allele-MM, 1-antigen-MM, 2-allele-MM, and 2-MM-including-antigen-MM groups at 4 years post-transplant, respectively (1). The adjusted cumulative incidences of NRM and grades III to IV acute GVHD among the groups were 22%, 27%, 32%, 31%, and 38% at 4 years (1) and 12%, 14%, 17%, 26%, and 24% at 120 days post-transplant, respectively (1).

mismatches rather than the specific loci that were mismatched [5,25]. In our study the number of allele or antigen mismatches correlated with mortality and acute GHVD.

Our study analyzed a large number of recipients of HLA single-mismatched BMTs, but it had several limitations. Although we evaluated UBMTs that were performed during the past 15 years, the numbers of UBMTs from HLA-A single-antigen level mismatched donors, HLA-B allele-level mismatched donors, and HLA-B antigen-level mismatched donors were limited, resulting in insufficient statistical power to detect locus-specific differences for comparing allele versus antigen mismatches. In addition, the choice of unrelated donors was highly influenced by the availability of acceptable HLA disparity and also by many unmeasured factors that can affect outcomes. Although we performed adjusted comparisons between groups, we cannot rule out the influence of potential selection bias. We were not able to address the allele or antigen single-mismatch effect of HLA-DPB1 or -DQB1 in this study. Availability of HLA-DPB1 and -DQB1 information is limited to donor–recipient pairs whose samples were stored for research use to have their HLA retyped for HLA-DPB1 and -DQB1, because only HLA-A, -B, -C, and -DRB1 loci are typed for practice in Japan Marrow Donor Practice for donors and in transplant centers for recipients. In this study we compared HLA disparity groups that distinguished allele mismatch from antigen mismatch, where maximization of the number of samples for analyses among recipients registered to the database was necessary.

In conclusion, HLA-DRB1 single-allele mismatches resulted in a decreased risk of NRM compared with HLA-DR single-antigen mismatches and were associated with a decreased risk of NRM and overall mortality compared with HLA-C single-antigen mismatches. When compared with HLA-DRB1 single-allele mismatches, transplants with 2 mismatches that included 1 or more antigen mismatches showed a significant increase in NRM and overall mortality. Our results support the preference for allele rather than antigen mismatches in unrelated bone marrow donors with a mismatch at 1 DR mismatch or 2 mismatches for T cell–replete UBMT.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.10.002.

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