transplantation.[9-12] Therefore, we conducted a nationwide retrospective study to compare the clinical outcomes of transplantation from a related donor with 1-antigen mismatch in the GVH direction (RD/1AG-MM-GVH) to those from an 8/8 MUD.

Methods

Data collection

Data for patients (age: 16–70 years) with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), and chronic myelogenous leukemia (CML) who received a first allogeneic transplantation from a related donor or HLA-6/6-antigen-MUD between January 1, 2001 and December 31, 2008 were obtained from the Transplant Registry Unified Management Program (TRUMP),[13] which includes data from the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and Japan Marrow Donor Program (JMDP). Our analysis included 344 patients who received a graft from an RD/1AG-MM-GVH (RD/1AG-MM-GVH group) and 453 patients who received a graft from an 8/8 MUD (8/8 MUD group). The following patients were excluded: 11 patients who lacked data on survival status, survival date, sex of recipient and donor, stem cell source, GVHD prophylaxis, or performance status; 2 patients who received both bone marrow and peripheral blood in related transplantation; and 5 patients who received stem cells manipulated by *ex vivo* T-cell depletion or CD34 selection. Finally, 327 patients who received a graft from an RD/1AG-MM-GVH and 452 from an 8/8 MUD fulfilled the criteria. The data on 2318 patients who received transplantation from an MRD were also collected on the basis of similar inclusion and exclusion criteria to compare the overall survival (OS) rate. The study was approved by the data management committees of TRUMP and by the institutional review board of Saitama Medical Center, Jichi Medical University, where this study was organized.

Histocompatibility

Histocompatibility data for serological and genomic typing for the HLA-A, HLA-B, HLA-C, and HLA-DR loci were obtained from reports obtained from the institution at which the transplantation was performed. To reflect current practice in Japan, HLA matching in RD/1AG-MM-GVHs was assessed by serological data for HLA-A, HLA-B, and HLA-DR loci, while that in 8/8-MUD was assessed by genomic data for HLA-A, HLA-B, HLA-C, and HLA-DR loci. An HLA mismatch in the GVH direction was defined as when the recipient's antigens or alleles were not shared by the donor; on the other hand, a mismatch in the HVG direction was defined as when the donor's antigens or alleles were not shared by the recipient. SCT from a related donor with a 1-antigen mismatch in the GVH direction has been performed by accepting multiple antigen mismatches in the HVG direction,[1,2] and therefore was included in this study.

Endpoints and statistical analyses

The primary endpoint of the study was to compare OS rates between the RD/1AG-MM-GVH and 8/8 MUD groups. For exploratory purposes, OS, treatment-related mortality (TRM), relapse, acute and chronic GVHD, and cumulative incidences of neutrophil engraftment were analyzed in a subset of cohorts. The physicians who performed transplantation at each center diagnosed and graded acute and chronic GVHD according to the traditional criteria.[14,15] The incidence of chronic GVHD was evaluated in patients who survived for at least 100 days. Neutrophil recovery was considered to have occurred when the absolute neutrophil count exceeded 0.5×10^9/L for 3 consecutive days following transplantation.

Descriptive statistics were used to summarize variables related to the patient characteristics. Comparisons between groups were performed with the chi-square statistic

or extended Fisher's exact test as appropriate for categorical variables and the Mann-Whitney *U*-test or Kruskal-Wallis test as appropriate for continuous variables. The probability of OS was estimated according to the Kaplan–Meier method, and the groups were compared with the log-rank test. The probabilities of TRM, relapse, acute and chronic GVHD, and neutrophil engraftment were estimated on the basis of cumulative incidence curves to accommodate the following competing events:[16] death for relapse, relapse for TRM, death without GVHD for acute and chronic GVHD, and death without engraftment for neutrophil engraftment; the groups were compared with Gray's test.[17] Cox proportional-hazards regression was used to evaluate variables that may affect OS, while Fine and Gray's proportional-hazard model was used to evaluate variables that may affect TRM, relapse, acute and chronic GVHD, and neutrophil engraftment.[18] For patients for whom conditioning intensity (myeloablative or reduced-intensity) was not reported, we re-classified the conditioning regimen as either myeloablative or reduced-intensity according to the NMDP/CIBMTR operational definitions.[19] To be consistent with our previous study, acute leukemia in the first or second remission, CML in the first or second chronic phase, and MDS without leukemic transformation were defined as standard-risk diseases, and others were defined as high-risk diseases.[1] The following variables were considered: the recipient's age group ($\leq$50 years or >50 years at transplantation), recipient's sex, presence of female (donor) to male (recipient) sex mismatch, performance status (PS) (0–1 or 2–4), disease (AML, ALL, CML, or MDS), disease status prior to transplantation (standard- or high-risk), type of conditioning regimen (myeloablative or reduced-intensity), type of GVHD prophylaxis (cyclosporine- or tacrolimus-based, or other), use of antithymocyte globulin (ATG) or alemtuzumab, and the time from diagnosis to transplantation (<6 months or $\geq$6 months). In addition, a variable of graft source (bone marrow or peripheral blood) was also considered in the analysis specific to related donors. Factors with $P < 0.10$ in the univariate analysis were

used in the first multivariate model without donor type and deleted in a stepwise manner from the model by backward selection. Then, we added donor type to the final model. All tests were 2-sided, and $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed with STATA version 11 (Stata Corp., College Station, TX) and R, Version 2.12.0 (The R Foundation for Statistical Computing, Vienna, Austria) software.

Results

Patient characteristics

Compared to recipients of an 8/8 MUD, recipients of an RD/1AG-MM-GVH were more likely to be younger, be male receiving a transplant from a female donor, have a shorter duration from diagnosis to transplantation, have a high-risk disease, receive cyclosporine for GVHD prophylaxis, use ATG or alemtuzumab, and have a longer follow-up period (Table 1). Approximately half of the recipients in the RD/1AG-MM-GVH group received peripheral blood stem cells, whereas, during this period in Japan, the source of transplantation from an MUD was restricted to bone marrow. In the RD/1AG-MM-GVH group, the number of antigen mismatches in the HVG direction was 0 in 11%, 1 in 67%, 2 in 20%, and 3 in 2%. HLA-A, -B and -DRB1 allelic information in both recipients and donors was available in 148 of 327 transplantations from an RD/1AG-MM-GVH, and information on HLA-C antigen mismatch in either the GVH or HVG direction was available in 123 of 327 transplantations from an RD/1AG-MM-GVH.

OS

The 2-year OS rates in the 8/8 MUD and RD/1AG-MM-GVH groups were 0.59 (95% confidence interval [CI], 0.53–0.64) and 0.44 (95% CI, 0.38–0.49), respectively (log-rank test; $P < 0.001$) (Fig. 1A). Multivariate analysis revealed that, compared to the use of an

8/8 MUD, the use of an RD/1AG-MM-GVH was a significant adverse factor for OS (hazard ratio (HR) [95% CI], 1.49 [1.19–1.86], $P < 0.001$) (Table 2). Age > 50 years, PS $\geq$ 2, and high-risk disease were also found to be significant adverse factors, while other variables, such as the time from diagnosis to transplantation, were not.

Since our previous study showed that the impact of an HLA 1-antigen mismatch in a related transplantation on OS differed according to whether patients had either standard-risk or high-risk disease,[1] the survival rates were compared separately in each disease-risk group. The OS rates of patients with standard-risk diseases in the 8/8 MUD group were significantly higher than those in the RD/1AG-MM-GVH group ($P = 0.003$), while there was no significant difference in high-risk patients ($P = 0.090$) (Fig. 1B and 1C). Although the interaction between the donor type and disease risk did not reach statistical significance ($P = 0.140$), multivariate analyses in each disease-risk group showed that the adverse impact of the use of an RD/1AG-MM-GVH was significant in standard-risk patients (HR [95% CI], 1.72 [1.24–2.39], $P = 0.001$), but not in high-risk patients (Table 2).

To visually compare MRDs and other stem cell sources, the OS rate for MRDs was layered on those for MUDs and RD/1AG-MM-GVHs (Fig. 1). The OS curve of transplantation from an MRD was superimposed on that from an MUD in both standard- and high-risk patients (MRD vs. MUD; standard-risk group, $P = 0.895$, and high-risk group, $P = 0.581$). Multivariate analysis confirmed that overall survival in the MRD group was comparable to the MUD group (MRD vs. MUD; standard-risk group, HR [95% CI], 1.02 [0.79–1.32], $P = 0.878$, and high-risk group, HR [95% CI], 0.98 [0.76–1.26], $P = 0.865$).

Effect of HLA mismatches on OS

To identify factors that may contribute to the inferior OS in standard-risk patients in the

RD/1AG-MM-GVH group compared to those in the 8/8 MUD group, we evaluated the impact of each HLA-A, HLA-B, or HLA-DR-antigen mismatch in the GVH direction and the number of antigen mismatches in the HVG direction on OS rates in the RD/1AG-MM-GVH group.

In the RD/1AG-MM-GVH group, the OS rate for patients who received a transplantation from a related donor with an HLA-B-antigen mismatch in the GVH direction and that from a donor with 2- or 3-antigen mismatches in the HVG direction were significantly lower than those in other groups (log-rank test for HLA-A-antigen mismatch vs. HLA-B-antigen mismatch vs. HLA-DR-antigen mismatch in the GVH direction; $P < 0.001$ and 0-1 mismatch vs. 2-3 mismatches in the HVG direction; $P = 0.003$) (Fig. 2). However, a multivariate analysis revealed that only the presence of an HLA-B-antigen mismatch in the GVH direction (HR [95% CI], 1.57 (1.13–2.18), $P = 0.007$) was significantly associated with a lower OS (Table 3).

The OS rates were also compared separately in the standard-risk and high-risk disease groups (Fig. 2). Although the interaction between the presence of HLA-B-antigen mismatch and disease risk did not reach statistical difference ($P = 0.232$), the adverse impact of an HLA-B-antigen mismatch in the GVH direction was observed in the standard-risk group (HR [95% CI], 1.86 (1.14–3.01), $P = 0.012$), but not in the high-risk group (Table 3). On the other hand, the survival curve for HLA-A- or HLA-DR-antigen-mismatched group was almost superimposed on that for 8/8 MUDs (Fig. 2) (standard-risk group; HR [95% CI] for HLA-A-antigen mismatched group vs. 8/8 MUD, 1.26 [0.73–2.19], $P = 0.411$ and HR [95% CI] for HLA-DR-antigen mismatched group vs. 8/8 MUD, 1.37 [0.89–2.11], $P = 0.154$, high-risk group; HR [95% CI] for HLA-A-antigen mismatched group vs. 8/8 MUD, 1.26 [0.80–2.00], $P = 0.320$ and HR [95% CI] for HLA-DR-antigen mismatched group vs. 8/8 MUD, 1.03 [0.67–1.59], $P = 0.880$). The impact of 2- or 3-antigen mismatches in the HVG direction was not

significant in either the standard-risk or high-risk group (Table 3).

Effect of an HLA-B mismatch on TRM, relapse, GVHD, and neutrophil engraftment in patients with standard-risk diseases

These findings showed that an HLA-B-antigen mismatch in the GVH direction strongly contributed to the low survival rate in standard-risk patients, which can explain the inferior survival rates in the RD/1AG-MM-GVH group compared to the 8/8 MUD group. Therefore, we evaluated the impact of an HLA-B-antigen mismatch in the GVH direction on other outcomes in patients with standard-risk diseases in the RD/1AG-MM-GVH group.

First, we compared the characteristics of patients with standard-risk diseases who received transplantation from a related donor with an HLA-A, HLA-B, and HLA-DR-antigen mismatch in the GVH direction (Supplemental Table 1). Two- or three-antigen mismatches in the HVG direction were observed more frequently in the HLA-B-antigen-mismatched group (28%) than in the HLA-A-antigen- (2%) or HLA-DR-antigen-mismatched group (17%). Although there was no information available on allelic mismatch or HLA-C-antigen mismatch in more than half of the patients, an HLA-C-antigen mismatch in either the GVH or HVG direction was observed more frequently in the HLA-B-antigen-mismatched group (61% among the available data) than in the HLA-A-antigen- (25%) or HLA-DR-antigen-mismatched group (17%).

The incidence of TRM was higher in the HLA-B-antigen-mismatched group (3-year mortality rate; 0.47 [95% CI, 0.32-0.60]) than in the HLA-A- (0.28 [95% CI, 0.14-0.44]) or HLA-DR-antigen-mismatched group (0.27 [95% CI, 0.17-0.38]) (Fig. 3A; log-rank test, $P = 0.030$). The presence of an HLA-B-antigen mismatch in the GVH direction was an independent significant adverse factor that affected TRM in the RD/1AG-MM-GVH group (Table 4). On the other hand, the incidence of relapse did not

significantly differ among the 3 groups (Fig. 3B, Table 4).

The incidence of grade 2–4 acute GVHD in the HLA-B-antigen-mismatched group was higher than that in the HLA-A-antigen-mismatched group, but comparable to that in the HLA-DR-antigen-mismatched group (Supplemental Figure 1, Supplemental Table 2). There was no significant difference in the incidence of grade 3-4 acute GVHD among the 3 groups. Regarding neutrophil engraftment, a multivariate analysis showed that an HLA-B-antigen mismatch was significantly associated with inferior neutrophil engraftment, and 2- or 3-antigen mismatches in the HVG direction were associated with inferior neutrophil engraftment with marginal significance (Supplemental Table 2).

Discussion

In this nationwide retrospective study, we found that the survival rate of the RD/1AG-MM-GVH group was significantly inferior to that of the 8/8 MUD group, and this significant difference was observed only in patients with standard-risk diseases, although the interaction between donor type and disease risk did not reach statistical significance. We previously reported that transplantation from a related donor with a 1-antigen mismatch in the GVH or HVG direction gave a clinical outcome comparable to that of transplantation from a 6/6-antigen-MUD in patients with either standard-risk or high-risk diseases.[1] However, since HLA matching at the allelic level in unrelated transplantation significantly reduced the risk of GVHD, the survival curve of transplantation from an 8/8 MUD was substantially improved, and could be superimposed on a curve corresponding to that from an MRD in the current study. Consistent with our findings, several studies have shown that the clinical outcomes of transplantation from an 8/8–10/10 MUD are comparable to those from an MRD.[20,21] The significant difference in survival rates between transplantation from an RD/1AG-MM-GVH and 8/8 MUD disappeared in patients with high-risk diseases,

probably because the adverse impact of acute GVHD on survival might be offset by the potential GVL effect in transplantation from an RD/1AG-MM-GVH.[1,2,22]

We evaluated factors that may contribute to the inferior OS in patients with standard-risk diseases in the RD/1AG-MM-GVH group, and found that, compared to the presence of an HLA-DR-antigen mismatch, the presence of an HLA-B-antigen mismatch in the GVH direction was significantly associated with lower OS and higher TRM. On the other hand, the rates of OS and TRM in the HLA-A- or HLA-DR-mismatched group were superimposed on those in the MUD group. However, HLA-A, HLA-B, and HLA-DR-antigen mismatches had similar effects on the incidence of severe acute GVHD; consequently, the causal relationship between an HLA-B-antigen mismatch in the GVH direction and higher TRM remains unknown. In contrast to our findings, Valcarcel et al.[23] reported that there was no significant difference in OS between the use of 1-antigen-mismatched related donors (n = 89) and 8/8 MUDs (n = 700) in transplantation for AML and ALL during the first or second complete remission. The difference from our results can be partly explained by the fact that the MUD group in their study included a significantly smaller number of ALL patients with low-risk cytogenetics. In addition, genetic homogeneity in the Japanese population might affect the lower incidence of severe acute GVHD in MUD transplantation in our study, due to the less frequent mismatches in minor histocompatibility antigens.[24,25]

The frequency of an HLA-C-antigen mismatch was substantially higher in the HLA-B-antigen-mismatched group than in the HLA-A or HLA-DR-mismatched group. This finding may represent linkage disequilibrium between the HLA-B and HLA-C genes; they are located at a very close physical proximity within the major histocompatibility complex.[26,27] Therefore, the impact of HLA-B-antigen might be

affected by the co-presence of HLA-C-antigen mismatch. We could not evaluate the impact of HLA-C antigen mismatch on OS rates due to the limited information on HLA-C antigen mismatch; therefore, an analysis with larger cohorts with complete HLA-C antigen information will be needed to evaluate the impact of HLA-C and/or HLA-B mismatch in transplantation from an RD/1AG-MM-GVH. Accordingly, we could not evaluate the impact of the KIR ligand mismatch. Although the impact of KIR ligand mismatch is still controversial, several studies analyzing T-cell-replete transplantation showed that KIR ligand mismatch is associated with lower over survival.[12,28,29] The analysis of KIR matching would be helpful to elucidate the mechanism underlying the adverse effect of HLA-B mismatch in T-cell-replete transplantation from an RD/1AG-MM-GVH.

Whether the presence of allelic mismatches in addition to the 1-antigen mismatch (2 or more allelic mismatches in total) affects the transplantation outcome is also an important clinical question in transplantation from an RD/1AG-MM-GVH. A high frequency of 2-allele mismatches in the GVH direction was seen in the HLA-B-antigen-mismatched group, suggesting a possible association between 2-allele mismatches and low OS. However, we did not observe a significant effect of the number of allelic mismatches on OS after transplantation from an RD/1AG-MM-GVH, possibly due to the small sample size.

This study has several limitations. First, since several months are required to arrange unrelated transplantation, patients at low risk for relapse may more often be selected for unrelated transplantation. To minimize this bias, we included the duration from diagnosis to transplantation in the multivariate analysis; however, this variable did not have a significant effect in the multivariate analysis. Second, heterogeneous

backgrounds may have resulted in a bias. Particularly, the stem cell source in unrelated transplantation was exclusively bone marrow. However, the analysis of OS in the subgroup of patients who received a bone marrow graft from an RD/1AG-MM-GVH or 8/8 MUD showed similar results. Third, because we have incomplete antigen information on HLA-C and -DQB1 loci as well as allelic information, we may have underestimated the degree of mismatching in transplantation from an RD/1AG-MM-GVH. Fourth, the difference in the impact of donor type between standard- and high-risk diseases should be cautiously interpreted, because the interaction between the donor type and disease risk did not reach statistical significance. This may be partly due to the lower statistical power to detect the interaction than the main effect.

In conclusion, our findings suggest that an 8/8 MUD, if available, should be prioritized over an RD/1AG-MM-GVH for patients without an MRD if an immediate transplantation is not necessary. In particular, the presence of an HLA-B-antigen mismatch in the GVH direction has an adverse effect on OS because of treatment-related complications. This may be due to the high frequencies of additional mismatches of HLA-C-antigen or allele in the HLA-B-antigen-mismatched group. To elucidate the mechanism of the adverse outcomes in RD/1AG-MM-GVHs with an HLA-B-antigen mismatch, HLA antigen/allele matching including HLA-C should be performed in transplantation from an RD/1AG-MM-GVH.

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Authorship

Contributions: Y.K. designed the research and organized the project; J.K., H.Saji., and Y.K. reviewed data, analyzed data, and wrote the paper; J.K. and Y.K. performed statistical analysis; H.Sakamaki., J.T., R.S., and Y.A. collected data from JSHCT; K.K. and Y.M. collected data from JMDP; all authors interpreted data, reviewed and approved final manuscript.

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Table 1. Patient characteristics

Variable		RD/1AG-MM-GVH (n = 327)	8/8 MUD (n = 452)	P
Age at transplant, median (range)		45 (16-69)	48 (16-68)	0.043
Recipient sex	Male	184 (56%)	267 (59%)	0.434
	Female	143 (44%)	185 (41%)	
Sex combination of donors and recipients	Female to male	91 (28%)	73 (16%)	<0.001
	Other combinations	236 (72%)	379 (84%)	
Performance status	0/1	298 (91%)	415 (92%)	0.736
	2/3/4	29 (9%)	37 (8%)	
Disease	AML	167 (51%)	249 (55%)	0.512
	ALL	90 (28%)	107 (24%)	
	CML	19 (6%)	21 (5%)	
	MDS	51 (16%)	75 (17%)	
Duration from diagnosis to transplant	<6 months	124 (38%)	102 (23%)	<0.001
	>=6 months	191 (58%)	350 (77%)	
	Unknown	12 (4%)	0 (0%)	
Disease risk	Standard	175 (54%)	317 (70%)	<0.001
	High	133 (41%)	129 (29%)	
	Unknown	19 (6%)	6 (1%)	
Source of stem cells	Bone marrow	142 (43%)	452 (100%)	<0.001
	Peripheral blood	185 (57%)	-	
HLA compatibility in the HVG direction*	Matched	36 (11%)	452 (100%)	<0.001
	One-antigen mismatch	218 (67%)	-	
	Two-antigen mismatch	65 (20%)	-	
	Three-antigen mismatch	8 (2%)	-	
HLA compatibility in the GVH direction*	Matched	0 (0%)	452 (100%)	<0.001
	One-allele mismatch	111 (34%)	-	
	Two-allele mismatch	36 (11%)	-	
	Three-allele mismatch	1 (0%)	-	
	Uncertain/missing	179 (55%)	-	

Conditioning regimen	Myeloablative	243 (74%)	338 (75%)	0.883
	Reduced-intensity	84 (26%)	114 (25%)	
GVHD prophylaxis	Cyclosporine-based	113 (35%)	108 (24%)	0.004
	Tacrolimus-based	209 (64%)	338 (75%)	
	Others	5 (2%)	6 (1%)	
Use of ATG/alemtuzumab	Yes	33 (10%)	13 (3%)	<0.001
	No	294 (90%)	439 (97%)	
Follow-up of survivors	Median time† (range)	36.2 (3.0-95.7)	13.5 (1.7-62.8)	<0.001

Data are numbers (%) unless specified otherwise.

Abbreviations: AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; HVG, host-versus-graft; GVH, graft-versus-host; GVHD, graft-versus-host disease; cyclosporine-based, cyclosporine with or without other agents; tacrolimus-based, tacrolimus with or without other agents; ATG, antithymocyte globulin; RD/1AG-MM-GVH, related donor with 1-antigen mismatch in the GVH direction; 8/8 MUD, HLA-8/8-allele-matched unrelated donor.

*HLA compatibility was defined according to HLA-A, -B, and -DR loci.

†Data are expressed in months.

Table 2. Multivariate analysis of overall survival

Variable	Total (n = 779)		Standard risk (n = 492)		High risk (n = 262)	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Donor type						
8/8 MUD	1.00	-	1.00	-	1.00	-
RD/1AG-MM-GVH	1.49 (1.19-1.86)	<0.001	1.72 (1.24-2.39)	0.001	1.30 (0.96-1.76)	0.095
Age						
<=50	1.00	-	1.00	-		
>50	1.44 (1.16-1.79)	0.001	1.55 (1.13-2.15)	0.007		
Performance status						
0/1	1.00	-			1.00	-
2/3/4	1.79 (1.30-2.48)	<0.001			1.76 (1.24-2.52)	0.002
Disease risk						
Standard	1.00	-				
High	2.41 (1.92-3.03)	<0.001				
Unknown	1.38 (0.82-2.33)	0.227				

Only variables that remained after backward selection in the multivariate analysis are shown.

Abbreviations: 8/8 MUD, HLA-8/8-allele-matched unrelated donor; RD/1AG-MM-GVH, related donor with 1-antigen mismatch in the graft-versus-host direction; CI, confidence interval.

Table 3. Multivariate analysis of overall survival in patients receiving transplantation from a related donor with a 1-antigen mismatch in the GVH direction

Variable	Total (n = 327)		Standard risk (n = 175)		High risk (n = 133)	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
HLA mismatch in the GVH direction						
HLA-DR mismatch	1.00	-	1.00	-	1.00	-
HLA-A mismatch	1.07 (0.73-1.56)	0.737	0.98 (0.54-1.81)	0.966	1.11 (0.65-1.89)	0.701
HLA-B mismatch	1.57 (1.13-2.18)	0.007	1.86 (1.14-3.01)	0.012	1.36 (0.86-2.17)	0.193
HLA mismatch in the HVG direction						
0-1 mismatches	1.00	-	1.00	-	1.00	-
2-3 mismatches	1.27 (0.91-1.76)	0.154	1.67 (0.98-2.85)	0.061	1.06 (0.69-1.61)	0.799
Age						
<=50	1.00	-	1.00	-		
>50	1.52 (1.14-2.03)	0.004	1.87 (1.21-2.91)	0.005		
Disease risk						
Standard	1.00	-				
High	2.06 (1.53-2.78)	<0.001				
Unknown	1.00 (0.53-1.89)	0.989				
Source of stem cells						
Bone marrow						
Peripheral blood						

Only variables that remained after backward selection in the multivariate analysis are shown.

Abbreviations: GVH, graft-versus-host; HVG, host-versus-graft; CI, confidence interval.

Table 4. Multivariate analysis of treatment-related mortality and relapse in patients with standard-risk diseases receiving transplantations from a related donor with a 1-antigen mismatch in the GVH direction

Variable	Treatment-related mortality (n = 164)		Relapse (n = 164)	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
HLA mismatch in the GVH direction				
HLA-DR mismatch	1.00	-	1.00	-
HLA-A mismatch	1.22 (0.59-2.52)	0.587	0.70 (0.29-1.67)	0.418
HLA-B mismatch	2.00 (1.09-3.65)	0.025	0.80 (0.34-1.87)	0.605
HLA mismatch in the HVG direction				
0-1 mismatches	1.00	-	1.00	-
2-3 mismatches	2.21 (1.14-4.28)	0.019	0.67 (0.23-1.98)	0.467
Age				
<=50	1.00	-		
>50	2.08 (1.18-3.65)	0.011		
Duration from diagnosis to transplant				
<6 months	1.00	-		
>=6 months	2.40 (1.19-4.82)	0.014		
Unknown	2.23 (0.77-6.48)	0.140		

Only variables that remained after backward selection in the multivariate analysis are shown.

Abbreviations: GVH, graft-versus-host; HVG, host-versus-graft; CI, confidence interval.