

Table 2. Multivariate analysis of OS

Variable	Total (n = 779)		Standard-risk (n = 492)		High-risk (n = 262)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Donor type						
8/8 MUD	1.00		1.00		1.00	
RD/1AG-MM-GVH	1.49 (1.19-1.86)	< .001	1.72 (1.24-2.39)	.001	1.30 (0.96-1.76)	.095
Age, y						
≤ 50	1.00		1.00			
> 50	1.44 (1.16-1.79)	.001	1.55 (1.13-2.15)	.007		
Performance status						
0/1	1.00				1.00	
2/3/4	1.79 (1.30-2.48)	< .001			1.76 (1.24-2.52)	.002
Disease risk						
Standard	1.00					
High	2.41 (1.92-3.03)	< .001				
Unknown	1.38 (0.82-2.33)	.227				

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

was superimposed on that from an MUD in both standard- and high-risk patients (MRD vs MUD: standard-risk group, $P = .895$, and high-risk group, $P = .581$). Multivariate analysis confirmed that OS in the MRD group was comparable to the MUD group (MRD vs MUD: standard-risk group, HR, 1.02; 95% CI, 0.79-1.32; $P = .878$; high-risk group, HR, 0.98; 95% CI, 0.76-1.26; $P = .865$).

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 with those in the 8/8-MUD group, we evaluated the impact of each HLA-A, HLA-B, or HLA-DR Ag mismatch in the GVH direction and the number of Ag 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 Ag mismatch in the GVH direction and that from a donor with 2 or 3 Ag mismatches in the HVG direction were significantly lower than those in other groups (log-rank test for HLA-A Ag mismatch vs HLA-B Ag mismatch vs HLA-DR Ag mismatch in the GVH direction, $P < .001$, and 0-1 mismatches vs 2-3 mismatches in the HVG direction, $P = .003$; Figure 2). However, multivariate analysis revealed that only the presence of an HLA-B Ag mismatch in the GVH direction (HR, 1.57; 95% CI, 1.13-2.18; $P = .007$) 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 (Figure 2). Although the interaction between the presence of an HLA-B Ag mismatch and disease risk did not reach statistical difference ($P = .232$), the adverse impact of an HLA-B Ag mismatch in the GVH direction was observed in the standard-risk group (HR, 1.86 95% CI, 1.14-3.01; $P = .012$), but not in the high-risk group (Table 3). Conversely, the survival curve for the HLA-A Ag or HLA-DR Ag-mismatched group was almost superimposed on that for 8/8-MUDs (Figure 2; standard-risk group: for the HLA-A Ag-mismatched group vs the 8/8-MUD group, HR, 1.26; 95% CI, 0.73-2.19; $P = .411$; for the HLA-DR Ag-mismatched group vs the 8/8-MUD group, HR, 1.37; 95% CI, 0.89-2.11; $P = .154$; high-risk group: for the HLA-A Ag-mismatched group vs the 8/8-MUD group, HR, 1.26; 95% CI, 0.80-2.00; $P = .320$; and for the HLA-DR Ag-mismatched group vs the 8/8-MUD group, HR, 1.03; 95% CI, 0.67-1.59; $P = .880$). The impact of 2 or 3 Ag 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

Our findings showed that an HLA-B Ag 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 with the 8/8-MUD group. Therefore, we evaluated the impact of an HLA-B Ag 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 Ag mismatch in the GVH direction (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Two or 3 Ag mismatches in the HVG direction were observed more frequently in the HLA-B Ag-mismatched group (28%) than in the HLA-A Ag-mismatched group (2%) or the HLA-DR Ag-mismatched group (17%). Although there was no information available on allelic mismatch or HLA-C Ag mismatch in more than half of the patients, an HLA-C Ag mismatch in either the GVH or HVG direction was observed more frequently in the HLA-B Ag-mismatched group (61% among the available data) than in the HLA-A Ag-mismatched group (25%) or the HLA-DR Ag-mismatched group (17%).

The incidence of TRM was higher in the HLA-B Ag-mismatched group (3-year mortality rate: HR, 0.47; 95% CI, 0.32-0.60) than in the HLA-A Ag-mismatched group (HR, 0.28; 95% CI, 0.14-0.44) or the HLA-DR Ag-mismatched group (HR, 0.27; 95% CI, 0.17-0.38; Figure 3A; log-rank test, $P = .030$). The presence of an HLA-B Ag mismatch in the GVH direction was an independent significant adverse factor that affected TRM in the RD/1AG-MM-GVH group (Table 4). Conversely, the incidence of relapse did not significantly differ among the 3 groups (Figure 3B and Table 4).

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

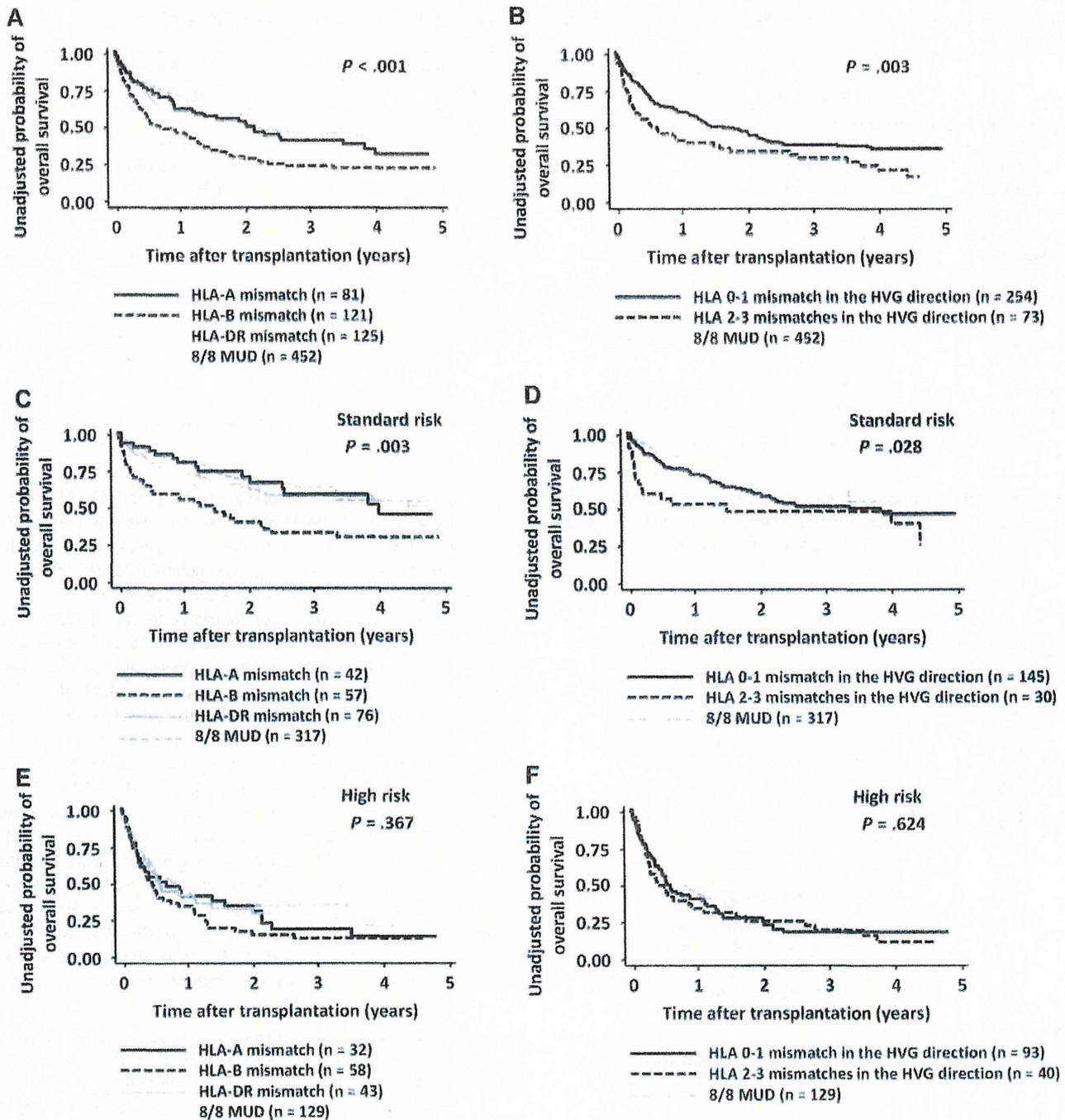


Figure 2. OS in patients with both-risk, standard-risk, or high-risk diseases according to the locus of HLA mismatch in the GVH direction and the number of mismatches in the HVG direction. Survival rates in patients with HLA-A, HLA-B, and HLA-DR Ag mismatches in the GVH direction were compared with the log-rank test (A,C,E). Survival rates in patients with 0-1 and 2-3 mismatches in the HVG direction were compared with the log-rank test (B,D,F). Survival rates of the 8/8-MUD group are shown for visual comparison.

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 reported previously that transplantation from a related donor with 1 Ag mismatch in the GVH or HVG direction gave a clinical outcome comparable to that of transplantation from a 6/6-Ag-MUD in patients with either standard-risk or high-risk diseases.¹ However, because HLA matching at the allelic level in unrelated transplantation significantly reduces the risk of GVHD, in the present study, 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.

Table 3. Multivariate analysis of OS 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)	
	HR (95% CI)	P	HR (95% CI)	P	HR (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)	.737	0.98 (0.54-1.81)	.966	1.11 (0.65-1.89)	.701
HLA-B mismatch	1.57 (1.13-2.18)	.007	1.86 (1.14-3.01)	.012	1.36 (0.86-2.17)	.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)	.154	1.67 (0.98-2.85)	.061	1.06 (0.69-1.61)	.799
Age, y						
≤ 50	1.00		1.00			
> 50	1.52 (1.14-2.03)	.004	1.87 (1.21-2.91)	.005		
Disease risk						
Standard	1.00					
High	2.06 (1.53-2.78)	< .001				
Unknown	1.00 (0.53-1.89)	.989				

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

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 donor and an 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 donor.^{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 with the presence of an HLA-DR Ag mismatch, the presence of an HLA-B Ag mismatch in the GVH direction was significantly associated with lower OS and higher TRM. Conversely, the rates of OS and TRM in the HLA-A Ag- or HLA-DR Ag-mismatched group were superimposed on those in the MUD group. However, HLA-A, HLA-B, and HLA-DR Ag mismatches had similar effects on the incidence of severe acute GVHD; consequently, the causal relationship between an HLA-B Ag mismatch in the GVH direction and higher TRM remains unknown. In contrast to our findings, Valcarcel et al reported that there was no significant difference in OS between the use of 1-Ag-mismatched related donors (n = 89) and 8/8-MUDs (n = 700) in transplantation for AML and ALL during the first or second complete remission.²³ This difference from our results can be partly

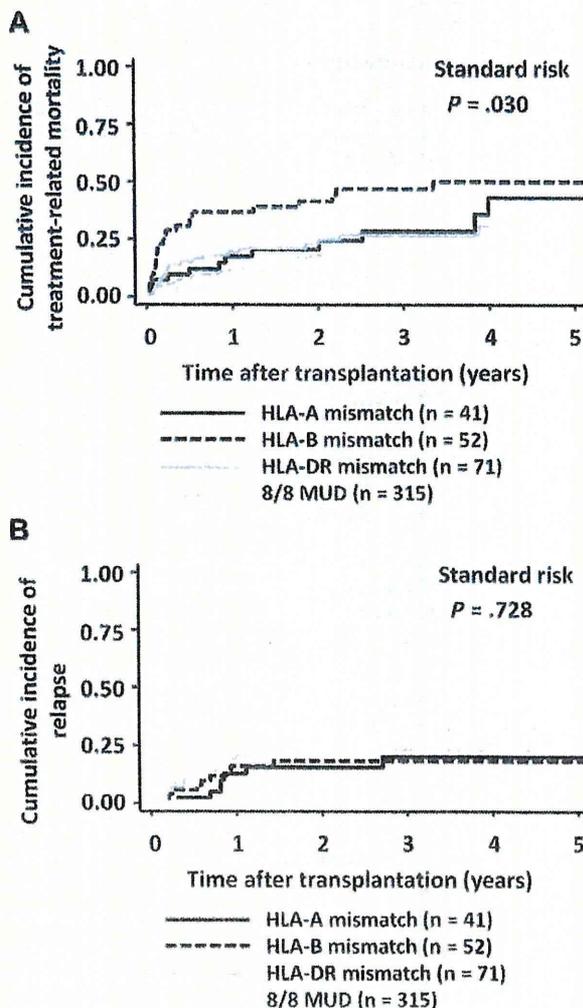


Figure 3. Cumulative incidence according to the locus of HLA mismatch in the GVH direction in patients with standard-risk diseases. Cumulative incidences in the related transplantation groups were compared with the Gray test. (A) TRM. (B) Relapse.

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

Variable	TRM (n = 164)		Relapse (n = 164)	
	HR (95% CI)	P	HR (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)	.587	0.70 (0.29-1.67)	.418
HLA-B mismatch	2.00 (1.09-3.65)	.025	0.80 (0.34-1.87)	.605
HLA mismatch in the HVG direction				
0-1 mismatches	1.00		1.00	
2-3 mismatches	2.21 (1.14-4.28)	.019	0.67 (0.23-1.98)	.467
Age, y				
≤ 50	1.00			
> 50	2.08 (1.18-3.65)	.011		
Duration from diagnosis to transplantation				
< 6 mo	1.00			
≥ 6 mo	2.40 (1.19-4.82)	.014		
Unknown	2.23 (0.77-6.48)	.140		

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

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, in our study, genetic homogeneity in the Japanese population might affect the lower incidence of severe acute GVHD in MUD transplantation because of the less frequent mismatches in minor histocompatibility Ags.^{24,25}

The frequency of an HLA-C Ag mismatch was substantially higher in the HLA-B Ag-mismatched group than in the HLA-A or HLA-DR Ag-mismatched groups. This finding may represent linkage disequilibrium between the HLA-B and HLA-C genes, which are located at a very close physical proximity within the major histocompatibility complex.^{26,27} Therefore, the impact of HLA-B-Ag might be affected by the co-presence of HLA-C Ag mismatch. We could not evaluate the impact of HLA-C Ag mismatch on OS rates because of the limited information on HLA-C Ag mismatch; therefore, an analysis with larger cohorts with complete HLA-C Ag information will be needed to evaluate the impact of HLA-C and/or HLA-B mismatch in transplantation from an RD/1AG-MM-GVH donor. 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 OS.^{12,28,29} The analysis of KIR matching would be helpful in elucidating the mechanism underlying the adverse effect of HLA-B mismatch in T cell-replete transplantation from an RD/1AG-MM-GVH donor.

Whether the presence of allelic mismatches in addition to the 1-Ag mismatch (2 or more allelic mismatches in total) affects transplantation outcome is also an important clinical question in transplantation from an RD/1AG-MM-GVH donor. A high frequency of 2-allele mismatches in the GVH direction was seen in the HLA-B Ag-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 donor, possibly because of the small sample size.

Our study has several limitations. First, because several months are required to arrange unrelated transplantations, patients at low risk for relapse may more often be selected for these procedures. 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. In particular, the stem-cell source in unrelated transplantation was exclusively BM. However, the analysis of OS in the subgroup of patients who received a BM graft from an RD/1AG-MM-GVH donor or an 8/8-MUD showed similar results. Third, because we have incomplete Ag and allele information on the HLA-C and -DQB1 loci, we may have underestimated the degree of mismatch-

ing in transplantation from an RD/1AG-MM-GVH donor. 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 because of 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 donor for patients without an MRD if an immediate transplantation is not necessary. In particular, the presence of an HLA-B Ag mismatch in the GVH direction has an adverse effect on OS because of treatment-related complications. This may be because of the high frequencies of additional mismatches of HLA-C Ag or allele in the HLA-B Ag-mismatched group. To elucidate the mechanism of the adverse outcomes in RD/1AG-MM-GVH donors with an HLA-B Ag mismatch, HLA Ag/allele matching including HLA-C should be performed in transplantations from an RD/1AG-MM-GVH donor.

Acknowledgments

The authors are indebted to all of the physicians and data managers at the centers who contributed valuable data on transplantation to the Japan Society for Hematopoietic Cell Transplantation and the Japan Marrow Donor Program. They also thank all of the members of the data management committees of the Japan Society for Hematopoietic Cell Transplantation and the Japan Marrow Donor Program for their management of data.

J.K. is a Research Fellow of the Japan Society for the Promotion of Science. This work was supported in part by a grant-in-aid for Japan Society for the Promotion of Science (to J.K.).

Authorship

Contribution: Y.K. designed the research and organized the project; J.K., H. Saji, and Y.K. reviewed and analyzed the data and wrote the manuscript; J.K. and Y.K. performed the statistical analysis; H. Sakamaki, J.T., R.S., and Y.A. collected data from Japan Society for Hematopoietic Cell Transplantation; K.K. and Y.M. collected data from Japan Marrow Donor Program; and all authors interpreted the data and reviewed and approved the final manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Impact of graft-versus-host disease on outcomes after allogeneic hematopoietic cell transplantation for adult T-cell leukemia: a retrospective cohort study

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Allogeneic hematopoietic cell transplantation (HCT) is an effective treatment for adult T-cell leukemia (ATL), raising the question about the role of graft-versus-leukemia effect against ATL. In this study, we retrospectively analyzed the effects of acute and chronic graft-versus-host disease (GVHD) on overall survival, disease-associated mortality, and treatment-related mortality among 294 ATL patients who received allogeneic HCT and survived at least 30 days posttransplant with sustained engraftment. Multivariate anal-

yses treating the occurrence of GVHD as a time-varying covariate demonstrated that the development of grade 1-2 acute GVHD was significantly associated with higher overall survival (hazard ratio [HR] for death, 0.65; $P = .018$) compared with the absence of acute GVHD. Occurrence of either grade 1-2 or grade 3-4 acute GVHD was associated with lower disease-associated mortality compared with the absence of acute GVHD, whereas grade 3-4 acute GVHD was associated with a higher risk for treatment-related mortality

(HR, 3.50; $P < .001$). The development of extensive chronic GVHD was associated with higher treatment-related mortality (HR, 2.75; $P = .006$) compared with the absence of chronic GVHD. Collectively, these results indicate that the development of mild-to-moderate acute GVHD confers a lower risk of disease progression and a beneficial influence on survival of allografted patients with ATL. (*Blood*. 2012;119(9):2141-2148)

Introduction

Adult T-cell leukemia (ATL) is a mature T-cell neoplasm that is causally associated with a retrovirus designated human T-cell leukemia virus type I (HTLV-I).¹⁻⁴ HTLV-I is endemic in southwestern Japan, sub-Saharan Africa, the Caribbean Basin, and South America.^{3,4} In Japan, more than 1 million people were estimated to be infected with HTLV-I. Although the majority of HTLV-I-infected individuals remain asymptomatic throughout their lives, ~ 5% develop ATL at a median age of 40 to 60 years.^{4,5}

ATL is categorized into 4 clinical variants according to its clinical features: smoldering, chronic, acute, and lymphoma types.⁶ The acute and lymphoma variants of ATL have an extremely poor prognosis, mainly because of resistance to a variety of cytotoxic agents and susceptibility to opportunistic infections; the median

survival time is ~ 13 months with conventional chemotherapy,^{7,8} although encouraging results have been recently reported with the use of novel agents such as mogamulizumab.⁹⁻¹¹

Over the past decade, allogeneic hematopoietic cell transplantation (HCT) has been increasingly performed with the aim of improving dismal prognosis of patients who developed ATL.¹²⁻¹⁸ Notably, some patients with ATL who relapsed after allogeneic HCT were shown to achieve remission only with the cessation of immunosuppressive agents, raising the question of whether the graft-versus-leukemia effect against ATL can be induced as part of graft-versus-host reaction.^{19,20} In 1 study, among 10 patients who experienced relapse of ATL after transplantation and were withdrawn from immunosuppressive therapy, 8 developed graft-versus-host disease (GVHD), and 6 of them subsequently achieved

Submitted July 17, 2011; accepted January 3, 2012. Prepublished online as *Blood* First Edition paper, January 10, 2012; DOI 10.1182/blood-2011-07-368233.

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The online version of the article contains a data supplement.

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complete remission of ATL.¹⁹ Similar observations have been rarely reported in other aggressive mature lymphoid neoplasms,²¹ suggesting the unique susceptibility of ATL to graft-versus-host reactions. Recently, a combined analysis of 2 prospective studies including 29 ATL patients in total undergoing allogeneic HCT suggested that development of mild acute GVHD favorably affected overall survival and progression-free survival.²² However, the impact of GVHD on the outcome of allogeneic HCT in ATL needs to be verified in a much larger cohort. We previously conducted a nationwide retrospective study to evaluate the current results of allogeneic HCT for ATL, and we confirmed that a substantial proportion of patients with ATL can enjoy long-term, disease-free survival after transplantation: the overall survival rate at 3 years among patients who received transplants in complete remission and not in complete remission was 51% and 26%, respectively.²³ Using the same cohort, we further evaluated the effects of acute and chronic GVHD on long-term outcomes of allografted patients with ATL.

Methods

Collection of data

Data on 417 patients with acute or lymphoma type ATL who had undergone allogeneic bone marrow, peripheral blood, or cord blood transplantation between January 1, 1996, and December 31, 2005, were collected through the Japan Society for Hematopoietic Cell Transplantation (JSHCT), the Japan Marrow Donor Program (JMDP), and the Japan Cord Blood Bank Network (JCBBN), the 3 largest HCT registries in our country; their roles were detailed previously.²³ The patients were included from 102 transplant centers; the data were updated as of December 2008. The study was approved by the data management committees of JSHCT, JMDP, and JCBBN, as well as by the institutional review boards of Kyoto University Graduate School of Medicine, where this study was organized.

Inclusion and exclusion criteria

Patients were included in the analysis if the following data were available: age at transplantation, sex of the recipient, donor type, stem cell source, agents used in the conditioning regimen and GVHD prophylaxis, the maximum grade and day of occurrence of acute GVHD, and the day of neutrophil recovery. Acute GVHD was reported according to the traditional criteria,²⁴ except that 1 patient was considered to have late-onset acute GVHD at day 133; neutrophil recovery was considered to have occurred when an absolute neutrophil count exceeded $0.5 \times 10^9/L$ for 3 consecutive days after transplantation. Patients who missed any of these data ($n = 37$), who had a history of prior autologous or allogeneic HCT ($n = 8$), who had received an *ex vivo* T cell–depleted graft ($n = 1$), who experienced primary or secondary graft failure ($n = 24$) were excluded from the analysis. Because the association between the occurrence of acute GVHD and disease-associated mortality was difficult to evaluate in the event of early toxic death, patients who died within 30 days of transplantation ($n = 53$) also were excluded from the study. Among these 53 patients, 22 were evaluable for acute GVHD: grade 0 in 17 patients, grade 1-2 in 3 patients, and grade 3-4 in 2 patients. Two physicians (J.K. and T.I.) independently reviewed the quality of collected data, and 294 patients in total (158 males and 136 females), with a median age of 51 years (range, 18-79 years), were found to meet these criteria and included in the study: 163 patients from JSHCT, 82 patients from JMDP, and 49 patients from JCBBN. No overlapping cases were identified. Of these 294 patients, the effects of chronic GVHD, reported and graded according to using traditional criteria,²⁵ were considered evaluable for the 183 patients who survived at least 100 days after transplantation with complete information on the type and the day of occurrence of chronic GVHD.

End points

The primary end point of the study was the effect of acute GVHD on overall survival, defined as the period from the date of transplantation until the date

of death from any cause or the last follow-up. The secondary end points of the study included the impact of acute GVHD on disease-associated and treatment-related mortality, and the impact of chronic GVHD on overall survival, disease-associated mortality, and treatment-related mortality. Reported causes of death were reviewed and categorized into disease-associated or treatment-associated deaths. Disease-associated deaths were defined as deaths from relapse or progression of ATL, whereas treatment-related deaths were defined as any death other than disease-associated deaths.

Statistical analysis

The probability of overall survival was estimated by the Kaplan-Meier method. Treatment-related and disease-associated mortality were estimated with the use of cumulative incidence curves to accommodate the following competing events²⁶: disease-associated death for treatment-related mortality and treatment-related deaths for disease-associated mortality. Data on patients who were alive at the time of last follow-up were censored. Semi-landmark plots were used to illustrate the effects of GVHD on overall survival and cumulative incidence of disease-associated and treatment-related deaths. For patients with acute or chronic GVHD, the probability of overall survival and the cumulative incidences of disease-associated and treatment-related deaths were plotted as a function of time from the onset of acute or chronic GVHD. Day 24.5, the median day of onset for acute GVHD, was termed as the landmark day in patients without acute GVHD. In the case of patients without chronic GVHD, day 116, the median day of onset for chronic GVHD, was termed as the landmark day.

Univariate and multivariate Cox proportional hazards regression models were used to evaluate variables potentially affecting overall survival, whereas the Fine and Gray proportional subdistribution hazards models were used to evaluate variables potentially affecting disease-associated and treatment-related mortality.²⁷ In these regression models, the occurrence of acute and chronic GVHD was treated as a time-varying covariate.²⁸ In the analysis of acute GVHD, patients were assigned to the “no acute GVHD group” at the time of transplantation and then transferred to the “grade 1-2 acute GVHD group” or to the “grade 3-4 acute GVHD group” at the onset of the maximum grade of acute GVHD. In the analysis of chronic GVHD, patients were assigned to the “no chronic GVHD group” at the time of transplantation and then transferred to the “limited chronic GVHD group” or to the “extensive chronic GVHD group” at the onset of the maximum grade of chronic GVHD. The variables considered were the age group of the recipient (≤ 50 years or > 50 years at transplantation), sex of the recipient (female or male), disease status before transplantation (complete remission, disease status other than complete remission, or unknown), intensity of conditioning regimen (myeloablative, reduced intensity, or unclassifiable), type of GVHD prophylaxis (cyclosporine-based, tacrolimus-based, or other), type of donor (HLA-matched related donor, HLA-mismatched related donor, unrelated donor for bone marrow, or unrelated cord blood), time from diagnosis to transplantation (within 6 months, > 6 months, or unknown), and year of transplantation (1995-2002 or 2003-2005). We classified the intensity of conditioning regimen as myeloablative or reduced intensity based on the working definition by Center for International Blood and Marrow Transplant Research if data on dosage of agents and total-body irradiation (TBI) used in the conditioning regimen were available.²⁹ For 110 patients for whom such information was not fully available, we used the information on conditioning intensity (myeloablative or reduced intensity) reported by treating clinicians. The cutoff points for year of transplantation were chosen such that we could make optimal use of the data with a proviso that the smaller group contained at least 30% of patients. In the analysis of the effect of chronic GVHD, the prior history of grade 2-4 acute GVHD also was added to the multivariate models. We also assessed the interaction between acute GVHD and the intensity of conditioning regimen in the multivariate models. Only factors with a *P* value of less than .10 in univariate analysis were included in the multivariate models. In addition, the heterogeneities of the effects of grade 1-2 or grade 3-4 acute GVHD on overall survival according to background transplant characteristics were evaluated by the forest plots stratified by variables included in the regression analyses. Furthermore, landmark analysis treating the development of acute GVHD as a time-fixed covariate was performed to confirm

Table 1. Characteristics of patients and transplants

Variable	No. of patients, n = 294 (%)
Age group at transplant, y	
≤ 30	7 (2)
> 30-40	30 (10)
> 40-50	109 (37)
> 50-60	123 (42)
> 60	25 (9)
Sex	
Male	158 (54)
Female	136 (46)
Disease status	
Complete remission	99 (34)
Not in complete remission	178 (61)
Unknown	17 (6)
Conditioning regimen	
Myeloablative	102 (34)
Reduced intensity	128 (44)
Unclassifiable	64 (22)
GVHD prophylaxis*	
Cyclosporine-based	195 (66)
Tacrolimus-based	94 (32)
Other	5 (2)
Source of stem cells	
Bone marrow	132 (45)
Peripheral blood	111 (38)
Bone marrow + peripheral blood	2 (1)
Cord blood	49 (17)
Type of donor†	
HLA-matched related	132 (45)
HLA-mismatched related	31 (11)
Unrelated, bone marrow	82 (28)
Unrelated, cord blood	49 (17)
Time from diagnosis to transplant	
≤ 6 mo	141 (48)
> 6 mo	141 (48)
Uncertain/missing	12 (4)
Year of transplant	
1995-1999	22 (7)
2000-2002	91 (31)
2003-2005	181 (62)
Follow-up of survivors	
Median time, mo (range)	42.8 (1.5-102.3)

Data are numbers (%) unless specified otherwise.

*Cyclosporine-based indicates cyclosporine with or without other agents; tacrolimus-based indicates tacrolimus with or without other agents.

†HLA compatibility was defined according to the results of serologic or low-resolution molecular typing for HLA-A, B, and DR antigens.

the results of analyses treating the occurrence of acute GVHD as a time-varying covariate; the landmark day was set at day 68 after transplantation, the date until when more than 95% of patients developed acute GVHD.

Results are expressed as hazard ratios (HRs) and their 95% confidence intervals (CI). All tests were 2-sided, and a *P* value of less than .05 was considered to indicate statistical significance. All statistical analyses were performed with STATA Version 11 software (StataCorp).

Results

Characteristics of patients and transplants

Characteristics of the patients and transplants are shown in Table 1. Most of the patients received transplants at the age of 41 to 60 years (median, 51 years). The disease status at transplan-

tation was mainly defined as other than complete remission. The intensity of conditioning regimen was classified as myeloablative in 102 (35%) patients and reduced intensity in 128 (44%) patients; the remaining 64 (22%) patients were reported to receive cyclophosphamide plus TBI in 16 patients; busulfan plus cyclophosphamide in 15 patients; busulfan plus melphalan in 1 patient; purine analog-containing regimen in 6 patients; and other TBI-based regimens in 26 patients, although the intensity of these regimens was considered unclassifiable because of lack of dosage information. Cyclosporine-based prophylaxis against GVHD was used in more than half of patients. Patients underwent transplantation using HLA-matched related donor in 132 patients (45%), HLA-mismatched related donor in 31 patients (11%), unrelated bone marrow donor in 82 patients (28%), and unrelated cord blood unit in 49 patients (17%). Half of the patients received transplants within 6 months of diagnosis. The median time of follow-up among the survivors was 42.8 months (range, 1.5-102.3 months).

Effects of acute GVHD on overall survival

The median onset day of acute GVHD of any grade after transplantation was 24.5 (range, 5-133). Acute GVHD of grades 1-4, 2-4, and 3-4 occurred in 202 patients (69%), 150 patients (51%), and 65 patients (22%), respectively. The effect of acute GVHD on overall survival was evaluated using semi-landmark plots with reference to the following 3 categories: no acute GVHD, grade 1-2 acute GVHD, and grade 3-4 acute GVHD (Figure 1A). The impact of grade 1-2 or grade 3-4 acute GVHD on overall survival also was evaluated by forest plots stratified by background characteristics of patients and transplants (Figure 2). These analyses revealed that development of grade 1-2 acute GVHD was consistently associated with higher overall survival compared with the absence of acute GVHD, whereas occurrence of grade 3-4 acute GVHD was consistently associated with lower overall survival, except that adverse impact of grade 3-4 acute GVHD was not observed in the subgroups of patients who received transplants from an HLA-matched related or HLA-mismatched related donor. Multivariate analysis treating an occurrence of acute GVHD as a time-dependent covariate also confirmed the positive impact of grade 1-2 acute GVHD (HR, 0.65; 95% CI, 0.45-0.93; *P* = .018) and the adverse impact of grade 3-4 acute GVHD on overall survival (HR, 1.64; 95% CI, 1.10-2.42; *P* = .014; Table 2). Patients who received reduced intensity conditioning and myeloablative conditioning had similar rates of overall survival by both univariate (HR of reduced intensity vs myeloablative transplant, 1.19; 95% CI, 0.85-1.68; *P* = .318) and multivariate analysis (HR, 0.95; 95% CI, 0.61-1.47; *P* = .814). There was no interaction effect between conditioning intensity and grade 1-2 (*P* = .704) or grade 3-4 acute GVHD (*P* = .891) on overall survival. The effect of each grade of acute GVHD on overall survival was additionally evaluated. It showed that only grade 2 acute GVHD was associated with superior overall survival, whereas only grade 4 acute GVHD was associated with inferior survival (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). In the landmark analysis treating an occurrence of acute GVHD as a time-fix covariate, consistent results were obtained for patients who survived at least 68 days (landmark day), although the adverse impact of grade 3-4 acute GVHD on overall survival became no longer significant (supplemental Table 2).

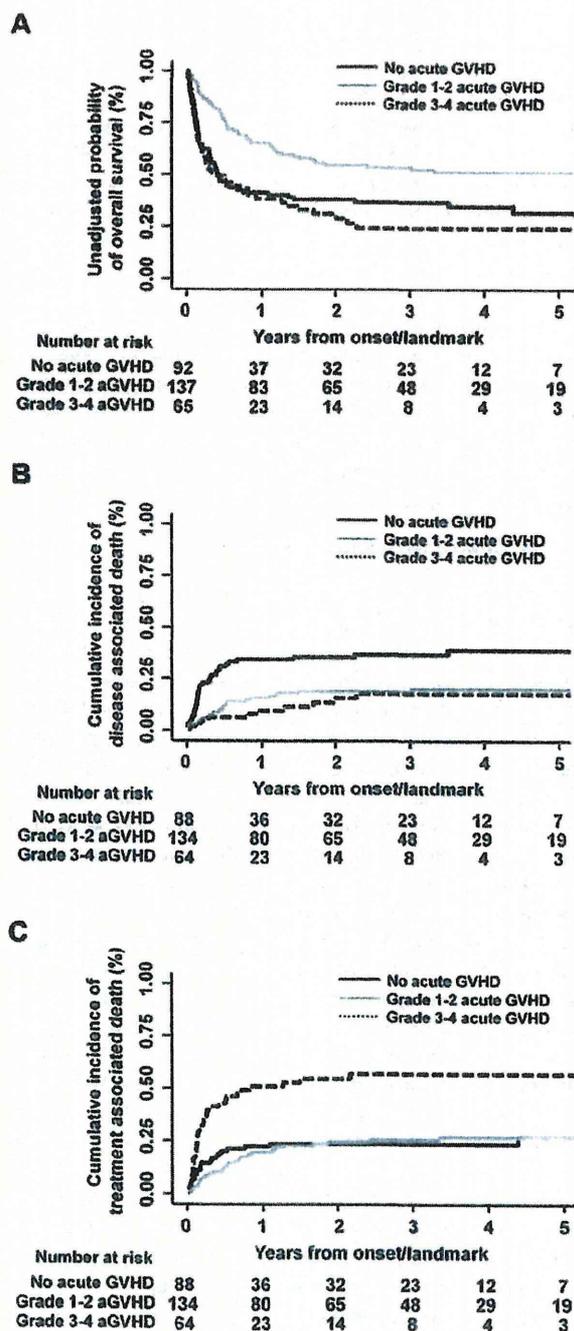


Figure 1. Semi-landmark plots for effects of acute GVHD. Semi-landmark plots illustrating the effects of acute GVHD on overall survival (A), disease-associated mortality (B), and treatment-related mortality (C).

Effects of acute GVHD on disease-associated and treatment-related mortality

We next evaluated the effects of acute GVHD on disease-associated and treatment-related mortality (Figure 1B-C). Disease-associated mortality was defined as cumulative incidence of death directly attributable to relapse or progression of ATL, whereas treatment-related mortality was calculated as cumulative incidence of any death not included in disease-associated deaths. Multivariate analysis revealed that disease-associated mortality was lower in the presence of grade 1-2 and grade 3-4 acute GVHD compared with

the absence of acute GVHD (grade 1-2 acute GVHD: HR, 0.54; 95% CI, 0.32-0.92; $P = .023$ and grade 3-4 acute GVHD: HR, 0.44; 95% CI, 0.22-0.90; $P = .024$; Table 2), and each grade of acute GVHD showed consistent inverse association with disease-associated mortality (supplemental Table 1). Although the risk of treatment-related mortality was not higher in the presence of grade 1-2 acute GVHD, development of grade 3-4 acute GVHD was significantly associated with higher treatment-related mortality compared with the absence of acute GVHD (HR, 3.50; 95% CI, 2.01-6.11; $P < .001$; Table 2). Patients undergoing reduced intensity transplantation and those undergoing myeloablative transplantation had similar risks of disease-associated death (HR, 0.99; 95% CI, 0.46-2.13; $P = .975$) and treatment-related death (HR, 0.98; 95% CI, 0.60-1.59; $P = .928$) by multivariate analysis. There was no interaction effect between conditioning intensity and grade 1-2 or grade 3-4 acute GVHD on disease-associated mortality and treatment-related mortality. Of 95 patients who experienced treatment-related deaths, 27 patients succumbed to infectious complications: bacterial in 13 patients, viral in 7 patients (including 3 cases of cytomegalovirus disease), viral and bacterial in 1 patient, fungal in 5 patients, and no specific organism reported in 1 patient. The proportions of patients who died of infectious complication among those without acute GVHD ($n = 92$), those with grade 1-2 ($n = 137$), and those with grade 3-4 acute GVHD ($n = 65$) were 4%, 9%, and 17%, respectively (supplemental Table 3). By multivariate analysis, development of grade 3-4 acute GVHD was significantly associated with higher risk of death related to infection (HR, 4.74; 95% CI, 1.51-14.8; $P = .008$), whereas the adverse influence on the infection-related deaths was less evident in the presence of grade 1-2 acute GVHD (HR, 2.17; 95% CI, 0.72-6.56; $P = .169$).

Effects of chronic GVHD on overall survival and mortality

Chronic GVHD was evaluated in 183 patients who survived at least 100 days after transplantation. The median day of chronic GVHD occurrence after transplantation was 116 (range, 100-146 days). Limited and extensive chronic GVHD occurred in 29 (16%) and 63 patients (34%), respectively. Semi-landmark plots were constructed to illustrate the effects of chronic GVHD on overall survival, disease-associated mortality, and treatment-related mortality with reference to the following subgroups: no chronic GVHD, limited chronic GVHD, and extensive chronic GVHD (Figure 3). In multivariate analysis treating an occurrence of chronic GVHD as a time-dependent covariate, neither overall survival nor disease-associated mortality was significantly associated with severity of chronic GVHD, whereas treatment-related mortality was higher in the presence of extensive chronic GVHD (HR, 2.75; 95% CI, 1.34-5.63; $P = .006$) compared with the absence of chronic GVHD (Table 3). The proportions of patients who died of infectious complication among those without chronic GVHD ($n = 91$), those with limited chronic GVHD ($n = 29$), and those with extensive chronic GVHD ($n = 63$) were 7%, 10%, and 8%, respectively. In multivariate analysis, no statistically significant association was found between infection-related death and the occurrence of either limited ($P = .289$) or extensive GVHD ($P = .836$).

Discussion

To our knowledge, this is the largest retrospective study to analyze the impact of acute and chronic GVHD on clinical

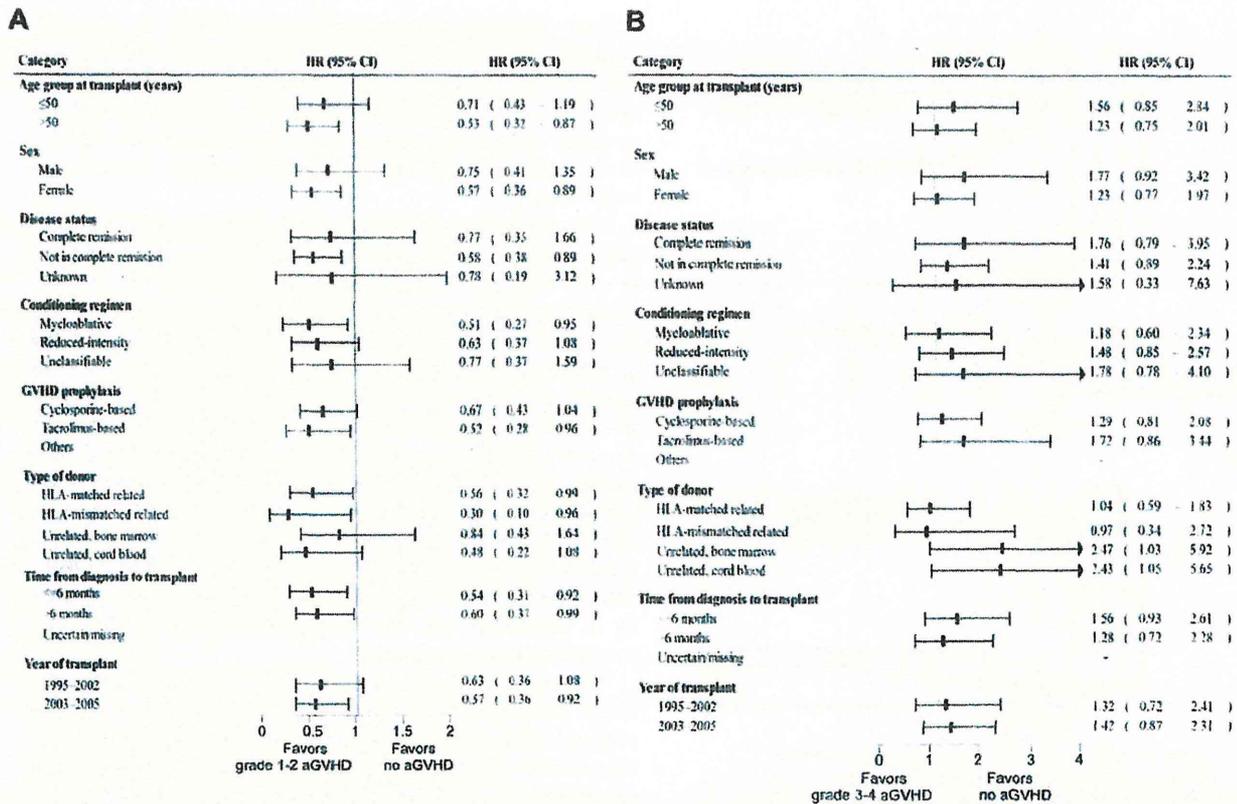


Figure 2. Impact of the grade of acute GVHD on overall survival in each stratified category. Effects of grade 1-2 (A) and grade 3-4 acute GVHD (B) on overall survival are shown as forest plots. Square boxes on lines indicate hazard ratios compared with “no acute GVHD group,” and horizontal lines represent the corresponding 95% CI. Abbreviations used are the same as described in the footnotes to Tables 1 and 2.

outcomes including overall survival, disease-associated mortality, and treatment-related mortality after allogeneic HCT for ATL. In the present study, the occurrence of both grade 1-2 and grade 3-4 acute GVHD was associated with lower disease-associated mortality compared with the absence of acute GVHD. However, positive effect of GVHD on reduced disease-associated mortality was counterbalanced by increased treatment-

related mortality among patients who developed severe acute GVHD, and an overall beneficial effect on survival was observed only with the development of mild-to-moderate acute GVHD. In contrast to acute GVHD, no beneficial effect was observed in association with the development of chronic GVHD, although the point estimate of the HR comparing limited chronic GVHD versus the absence of chronic GVHD

Table 2. Effect of acute GVHD on overall survival, disease-associated mortality, and treatment-related mortality after allogeneic hematopoietic cell transplantation for adult T-cell leukemia

Outcome	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Overall survival*				
Grade 1 or 2 acute GVHD vs no acute GVHD	0.60 (0.42-0.85)	.004	0.65 (0.45-0.93)	.018
Grade 3 or 4 acute GVHD vs no acute GVHD	1.38 (0.94-2.01)	.099	1.64 (1.10-2.42)	.014
Disease-associated mortality†				
Grade 1 or 2 acute GVHD vs no acute GVHD	0.47 (0.28-0.79)	.005	0.54 (0.32-0.92)	.023
Grade 3 or 4 acute GVHD vs no acute GVHD	0.41 (0.21-0.81)	.010	0.44 (0.22-0.90)	.024
Treatment-related mortality‡				
Grade 1 or 2 acute GVHD vs no acute GVHD	1.13 (0.67-1.89)	.649	1.22 (0.72-2.07)	.461
Grade 3 or 4 acute GVHD vs no acute GVHD	3.34 (1.94-5.74)	<.001	3.50 (2.01-6.11)	<.001

*Other significant variables were sex of recipient, female (reference, 1.00) and male (HR, 1.70; 95% CI, 1.24-2.32; $P = .001$); achievement of complete remission, complete remission (reference, 1.00), status other than complete remission (HR, 2.05; 95% CI, 1.44-2.92; $P < .001$), and status not known (HR, 2.21; 95% CI, 1.15-4.22; $P = .017$); type of donor, HLA-matched related donor (reference, 1.00), HLA-mismatched related donor (HR, 1.71; 95% CI, 1.04-2.84; $P = .036$), unrelated donor of bone marrow (HR, 1.39; 95% CI, 0.94-2.06; $P = .096$), and unrelated cord blood (HR, 1.86; 95% CI, 1.22-2.83; $P = .004$).

†Other significant variables were achievement of complete remission, complete remission (reference, 1.00), status other than complete remission (HR, 2.98; 95% CI, 1.62-5.47; $P < .001$), and status not known (HR, 0.96; 95% CI, 0.21-4.49; $P = .963$); type of donor, HLA-matched related donor (reference, 1.00), HLA-mismatched related donor (HR, 2.14; 95% CI, 1.00-4.55; $P = .049$), unrelated donor of bone marrow (HR, 1.45; 95% CI, 0.81-2.61; $P = .214$), and unrelated cord blood (HR, 1.25; 95% CI, 0.63-2.49; $P = .517$).

‡Another significant variable was achievement of complete remission, complete remission (reference, 1.00), status other than complete remission (HR, 1.17; 95% CI, 0.74-1.84; $P = .498$) and status not known (HR, 2.31; 95% CI, 1.04-5.15; $P = .040$).