Impact of Graft-versus-Host Disease on Allogeneic Hematopoietic Cell Transplantation for Adult T Cell Leukemia-Lymphoma Focusing on Preconditioning Regimens: Nationwide Retrospective Study

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INTRODUCTION

Adult T cell leukemia-lymphoma (ATL) is an aggressive peripheral T cell neoplasm caused by human T cell lymphotropic/leukemia virus type 1 (HTLV-1). It has a very poor prognosis, and it has been generally accepted that conventional chemotherapeutic agents alone, even including zidovudine/IFN-α, yield few or no long-term remissions or potential cures in patients with ATL [1-6]. Although early experience in myeloablative chemoradiotherapy together with autologous hematopoietic cell rescue for ATL has been associated with high incidences of relapse and fatal toxicities [7], allogeneic hematopoietic cell transplantation (HCT) has been explored as a promising alternative treatment that can provide long-term remission in a proportion of patients with ATL [8-10].

We previously performed a nationwide retrospective study of patients with ATL who underwent allogeneic HCT in Japan, with special emphasis on the effect of the graft source. We concluded that allogeneic HCT using currently available sources is an effective treatment in selected patients with ATL, but that the use of unrelated cord blood as a stem cell source is associated with lower survival [11]. Our results suggest that allogeneic bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) could be considered the more standard transplantation forms compared with unrelated cord blood transplantation (CBT) for ATL.

A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT), but not autologous HCT, can provide long-term remission in some patients with adult T cell leukemia-lymphoma (ATL). We retrospectively analyzed the effects of acute graft-versus-host disease (GVHD) among the 616 patients with ATL who survived at least 30 days after allogeneic HCT with other than cord blood grafts. Multivariate analyses treating the occurrence of GVHD as a time-varying covariate demonstrated an association between grade I-II acute GVHD and favorable overall survival (OS) (hazard ratio [HR], 0.634; 95% confidence interval [CI], 0.477 to 0.843), whereas grade III-IV acute GVHD showed a trend toward unfavorable OS (HR, 1.380; 95% CI, 0.988 to 1.927) compared with nonacute GVHD. In subsequent multivariate analyses of patients who survived at least 100 days after HCT (n = 431), the presence of limited chronic GVHD showed a trend toward favorable OS (HR, 0.597; 95% CI, 0.354 to 1.007), and extensive chronic GVHD had a significant effect on OS (HR, 0.585; 95% CI, 0.389 to 0.880). There were no significant interactions between myeloablative conditioning or reduced-intensity conditioning with OS even when acute GVHD was absent or present at grade I-II or grade III-IV or when chronic GVHD was absent, limited, or extensive. This study demonstrates the actual existence of graft-versus-ATL effects in patients with ATL regardless of whether myeloablative conditioning or reduced-intensity conditioning is used.

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As the next step, we conducted a nationwide retrospective study of patients with ATL who underwent allogeneic HCT other than CBT, with special emphasis on the effects of the preconditioning regimen, whether conventional myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC). No significant difference in overall survival (OS) was observed between patients receiving MAC and those receiving RIC, but a trend toward RIC contributing to better OS in older patients was noted. Thus, we conclude that allogeneic HCT not only with MAC, but also with RIC, is an effective treatment resulting in long-term survival in selected patients with ATL [12].

ATL has a long latency and occurs in older individuals at a median age of nearly 66 years. The median age at diagnosis of ATL has been increasing over the last few decades [13]. Accordingly, the proportion of patients with ATL undergoing HCT with RIC is currently increasing in relation to HCT with MAC. It is thought that compared with HCT with MAC, allogeneic HCT with RIC depends more on donor cellular immune effects after transplantation and less on the cytotoxic effects of the conditioning regimen to eradicate residual tumor cells. In this context, RIC might be suitable for ATL, given that several reports have indicated the high immunogenicity of ATL cells [14-18] and even the existence of graft-versus-HTLV-1 and/or graft-versus-ATL effects [19-21].

Although we previously reported the impact of post-transplantation immune reactions, graft-versus-host disease (GVHD), on outcomes in patients with ATL [21], our cohort included CBT recipients whose OS curve had a quite different trajectory from that of BMT and PBSCT recipients [12]. Thus, in the present study, we evaluated whether acute and chronic GVHD affect outcomes in patients with ATL undergoing allogeneic HCT other than unrelated CBT, with special emphasis on the effects of the preconditioning regimen. Our present analysis included the previous cohort (1996 to 2005) [21] with updated clinical information, as well as data on 1 patient who underwent allogeneic HCT in 1995 and patients who underwent allogeneic HCT between 2006 and 2010.

PATIENTS AND METHODS

Data Collection

Data on patients with ATL who had undergone a first allogeneic BMT, PBSCT, or BMT + PBSCT were collected from nationwide survey data of the Japan Society for Hematopoietic Cell Transplantation (JSJHCT). Cases with missing preconditioning information, acute GVHD, or survival data were excluded, leaving 679 patients. 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 or were censored within 29 days of transplantation (n = 63) were excluded; thus, 616 patients who underwent HCT between March 1995 and December 2010 were included in our analysis.

Data collected for analysis included clinical characteristics, such as age at HCT, sex, disease status at HCT, date of diagnosis from ATL to HCT, performance status (PS) according to the Eastern Cooperative Oncology Group criteria at transplantation, stem cell source, donor–recipient relationship, ATL clinical subtype [22], preconditioning regimen, type of GVHD prophylaxis, date alive at last follow-up, and date of occurrence of acute GVHD and maximum grade of acute GVHD, and grade and date of occurrence of chronic GVHD. The study was approved by the Data Management Committees of the JSJHCT, as well as by the Institutional Ethics Committee of Nagoya City University Graduate School of Medical Sciences.

Definitions

OS was defined as the time from HCT until death, and patients who remained alive at the time of the last follow-up were censored. Reported causes of death were reviewed and categorized into ATL-related mortality or treatment-related mortality (TRM). ATL-related mortality was defined as death caused by relapse or progression of ATL based on the judgment of each institution. TRM was defined as any death other than ATL-related mortality.

Acute GVHD was diagnosed and graded using traditional criteria [23] by the physicians who performed HCT at each institution, as was chronic GVHD [24]. Among the 487 patients who survived at least 100 days after HCT, 431 patients with complete information on the grade and the day of occurrence of chronic GVHD were included in the analysis for chronic GVHD.

Patients undergoing allogeneic BMT or PBSCT were divided into 2 groups, MAC and RIC, based on the preconditioning regimen. MAC and RIC were defined according to Giralt et al. [25] and Bacigalupo et al. [26] with slight modifications. In the present study, MAC was defined as any regimen that includes (1) >5 Gy of total body irradiation (TBI) as a single fraction or ≥8 Gy fractionated, (2) busulfan >8 mg/kg orally or the i.v. equivalent, or (3) melphalan >140 mg/m². All other regimens were classified as RIC.

Statistical Analysis

Comparisons among the groups were performed using Fisher’s exact test as appropriate for categorical variables. The probability of survival was

Table 1: Patient and Transplantation Characteristics by Type of Conditioning Regimen

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MAC</th>
<th>RIC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients, n (%)</td>
<td>284 (46.1)</td>
<td>332 (53.9)</td>
<td></td>
</tr>
<tr>
<td>Age at HCT, y, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>178 (62.7)</td>
<td>43 (13.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>51-55</td>
<td>79 (27.8)</td>
<td>91 (27.4)</td>
<td></td>
</tr>
<tr>
<td>56-60</td>
<td>20 (7.0)</td>
<td>125 (37.7)</td>
<td></td>
</tr>
<tr>
<td>61+</td>
<td>7 (2.5)</td>
<td>73 (22.0)</td>
<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>159 (56.0)</td>
<td>160 (48.2)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Female</td>
<td>125 (44.0)</td>
<td>172 (51.8)</td>
<td></td>
</tr>
<tr>
<td>Disease status at HCT, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>104 (36.6)</td>
<td>128 (38.6)</td>
<td>0.1013</td>
</tr>
<tr>
<td>Not in CR</td>
<td>161 (56.7)</td>
<td>194 (58.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>19 (6.7)</td>
<td>10 (3.0)</td>
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</tr>
<tr>
<td>GVHD prophylaxis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA + MTX</td>
<td>129 (45.4)</td>
<td>112 (33.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FK506 + MTX</td>
<td>142 (50.0)</td>
<td>147 (44.3)</td>
<td></td>
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<tr>
<td>CyA</td>
<td>6 (2.1)</td>
<td>58 (17.5)</td>
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<tr>
<td>FK506</td>
<td>5 (1.8)</td>
<td>13 (3.9)</td>
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<tr>
<td>Unknown</td>
<td>2 (0.7)</td>
<td>2 (0.6)</td>
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<tr>
<td>Stem cell source, n (%)</td>
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<td></td>
</tr>
<tr>
<td>BM</td>
<td>216 (76.1)</td>
<td>213 (64.2)</td>
<td>0.0015</td>
</tr>
<tr>
<td>PBSCs</td>
<td>68 (23.9)</td>
<td>117 (35.2)</td>
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<tr>
<td>BM + PBSCs</td>
<td>0 (0.0)</td>
<td>2 (0.6)</td>
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<tr>
<td>Donor−recipient relationship, n (%)</td>
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<tr>
<td>HLA-matched related</td>
<td>98 (34.5)</td>
<td>120 (36.1)</td>
<td>0.3649</td>
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<tr>
<td>HLA-mismatched related</td>
<td>24 (8.5)</td>
<td>40 (12.0)</td>
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<tr>
<td>Unrelated</td>
<td>160 (56.3)</td>
<td>171 (51.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.7)</td>
<td>1 (0.3)</td>
<td></td>
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<tr>
<td>PS at HCT, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>111 (39.1)</td>
<td>144 (43.4)</td>
<td>0.0012</td>
</tr>
<tr>
<td>1</td>
<td>127 (44.7)</td>
<td>154 (46.4)</td>
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<tr>
<td>2</td>
<td>26 (9.2)</td>
<td>27 (8.1)</td>
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<tr>
<td>3</td>
<td>3 (1.1)</td>
<td>5 (1.5)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (0.4)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>16 (5.6)</td>
<td>1 (0.3)</td>
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</tr>
<tr>
<td>ATL clinical subtype, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chronic/smoldering</td>
<td>11 (3.9)</td>
<td>10 (3.0)</td>
<td>0.5278</td>
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<tr>
<td>Acute</td>
<td>171 (60.2)</td>
<td>189 (56.9)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>80 (28.2)</td>
<td>97 (29.2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>22 (7.7)</td>
<td>36 (10.8)</td>
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</tr>
<tr>
<td>Time from diagnosis to HCT, d, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>16-153</td>
<td>82 (28.9)</td>
<td>72 (21.7)</td>
<td>0.0632</td>
</tr>
<tr>
<td>154-204</td>
<td>64 (22.5)</td>
<td>88 (26.5)</td>
<td></td>
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<tr>
<td>205-307</td>
<td>75 (26.4)</td>
<td>78 (23.5)</td>
<td></td>
</tr>
<tr>
<td>308-4355</td>
<td>63 (22.2)</td>
<td>91 (27.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td>3 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Time of HCT, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>March 1995 to March 2005</td>
<td>75 (26.4)</td>
<td>79 (23.8)</td>
<td>0.3119</td>
</tr>
<tr>
<td>April 2005 to May 2007</td>
<td>75 (26.4)</td>
<td>79 (23.8)</td>
<td></td>
</tr>
<tr>
<td>June 2007 to February 2009</td>
<td>73 (25.7)</td>
<td>81 (24.4)</td>
<td></td>
</tr>
<tr>
<td>March 2009 to December 2010</td>
<td>61 (21.2)</td>
<td>93 (28.0)</td>
<td></td>
</tr>
<tr>
<td>Grade of acute GVHD, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No acute GVHD</td>
<td>80 (28.2)</td>
<td>128 (38.6)</td>
<td>0.0111</td>
</tr>
<tr>
<td>Grade I-II</td>
<td>148 (52.1)</td>
<td>159 (47.9)</td>
<td></td>
</tr>
<tr>
<td>Grade III-IV</td>
<td>56 (18.7)</td>
<td>45 (13.6)</td>
<td></td>
</tr>
</tbody>
</table>
estimated by the Kaplan-Meier method. TRM and ATL-related mortality were estimated using cumulative incidence curves to accommodate the competing events ATL-related mortality for TRM and TRM for ATL-related mortality [27]. Semilandmark plots were used to illustrate the effects of GVHD on survival and the cumulative incidence of ATL-related mortality and TRM. This landmark method was used to exclude bias that might have arisen from including patients who died too early to develop GVHD in the group without GVHD [28,29]. For patients with acute or chronic GVHD, the probability of survival and the cumulative incidences of ATL-related mortality and TRM were plotted as functions of time from the onset of acute or chronic GVHD. Day 25, the median day of onset for acute GVHD (range, 6 to 166 days), was designated the landmark day for acute GVHD. Day 126, the median day of onset for chronic GVHD (range, 52 to 1203 days), was designated the landmark day for chronic GVHD.

Multivariate Cox proportional hazards regression models were used to evaluate variables potentially affecting OS, and Fine and Gray proportional subdistribution hazards models [30] were used to evaluate variables potentially affecting ATL-related mortality and TRM. In these regression models, the occurrence of acute and chronic GVHD was treated as a time-varying covariate [31]. In the analysis of acute GVHD, patients were assigned to the no acute GVHD group at the time of HCT and then transferred to the grade I-II acute GVHD group or to the grade III-IV acute GVHD group at the onset of acute GVHD. In the analysis of chronic GVHD, patients were assigned to the no chronic GVHD group at the time of HCT and then transferred to the limited chronic GVHD group or to the extensive chronic GVHD group at the onset of chronic GVHD. We also assessed the interaction between acute and chronic GVHD and the preconditioning regimen in the multivariate models.

The heterogeneities of the effects of grade I-II or III-IV acute GVHD on OS according to background transplantation characteristics were evaluated by forest plots stratified by variables included in the regression analyses. Results are expressed as hazard ratio (HR) with 95% confidence interval (CI). All tests were 2-sided, and a P value <.05 was considered to indicate statistical significance. All statistical analyses were performed by Kureha Special Laboratory (Tokyo, Japan) using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Among the 616 patients in the study cohort, 284 received MAC and the remaining 332 received RIC. Characteristics of these patients are summarized in Table 1. Compared with MAC recipients, significantly fewer RIC recipients belonged to the youngest age group (<50 years), and significantly more were in the 2 oldest age groups (56 to 60 and 61+ years). In addition, significantly fewer RIC recipients received cyclosporin A (CyA) + methotrexate (MTX), but significantly more received CyA without MTX. PBSCT was significantly more frequent in RIC recipients compared with MAC recipients. There was no significant difference between MAC and RIC recipients regarding PS distribution from 0 to 4, but an unknown PS was observed significantly more frequently in the MAC recipients. A significantly greater number of RIC recipients did not have acute GVHD, and significantly fewer had grade III-IV acute GVHD.

Effects of Acute GVHD on Survival

In the 208 patients with ATL and no acute GVHD, the unadjusted 1-year and 3-year probabilities of survival from the landmark day for acute GVHD were 45.4% (95% CI, 38.3 to 52.2%) and 37.3% (95% CI, 30.3 to 44.4%), respectively. The unadjusted 1-year and 3-year probabilities of survival from the onset of acute GVHD were 60.1% (54.2 to 65.5%) and 49.1% (43.0 to 55.0%), respectively, in the 307 patients with grade I-II acute GVHD and 36.4% (26.9 to 46.0%) and 21.7% (13.9 to 30.6%), respectively, in the 101 patients with grade III-IV acute GVHD (Figure 1A).

Forest plots revealed that the development of grade I-II acute GVHD was associated with longer OS compared with the absence of acute GVHD in patients with the following characteristics: age <56 years, either male or female, not in complete remission (CR), receiving FK506 + MTX, undergoing either BMT or PBSCT, having an unrelated donor, PS 1 at transplantation, acute type of ATL, interval between ATL diagnosis and HCT of 308 to 4355 days, and date of HCT between June 2007 and February 2009. The development of grade I-II acute GVHD was also significantly associated with longer OS compared with the absence of acute GVHD regardless of whether the patient received MAC or RIC. On the other hand, this comparison revealed a shorter OS in the patients with lymphoma type ATL (Figure 2). These plots also revealed that the development of grade III-IV acute GVHD...
was significantly associated with shorter OS compared with the absence of acute GVHD in patients with PS 0 and who underwent HCT between March 2009 and December 2010. However, this comparison revealed no significant findings for OS according to whether the patient received MAC or RIC (Figure 2).

Multivariate analysis of the 616 study patients was performed to examine whether acute GVHD affects OS using the following variables: age (15 to 55 or 56 to 72 years), sex, disease status at HCT (CR, not CR, or unknown), pre-conditioning regimen (MAC or RIC), GVHD prophylaxis (CyA + MTX, FK506 + MTX, or other/unknown), relationship between recipient and donor (HLA-matched related, HLA-mismatched related unrelated), PS (0, 1, 2 to 4, or unknown), ATL clinical subtype (chronic/smoldering, acute, lymphoma, or unknown), time from diagnosis to HCT (16 to 153, 154 to 204, 205 to 307, or 308 to 4355 days or unknown), date of HCT (March 1995 to March 2005, April 2005 to May 2007, June 2007 to February 2009, or March 2009 to December 2010), and source of stem cells (bone marrow [BM], peripheral blood stem cells [PBSCs], or BM + PBSCs), as well as acute GVHD as a time-dependent covariate (no, grade I-II, grade III-IV). There was a significant positive impact of grade I-II acute GVHD on OS (HR, 0.634; 95% CI, 0.477 to 0.843) compared with no acute GVHD (Table 2).

To further investigate the clinical significance of acute GVHD for OS, we divided acute GVHD into 5 categories (none or grade I, II, III, or IV) and then performed multivariate analysis in the same manner as described above. HRs for OS of patients with grade I, II, III, and IV acute GVHD compared with the absence of acute GVHD were 0.568 (95% CI, 0.402 to 0.801), 0.688 (95% CI, 0.501 to 0.946), 1.199 (95% CI, 0.831 to 1.730), and 2.245 (95% CI, 1.354 to 3.722), respectively.

### Interactions of the Preconditioning Regimen with Acute GVHD for OS
We tested statistical interactions between the preconditioning regimens and acute GVHD with regard to OS by adding an interaction term to the multivariate analysis. This analysis included the same variables as the multivariate Cox proportional hazards regression models for OS. Among the 616 patients, when the HR for death of MAC recipients with no acute GVHD was set as 1.000, the HRs in MAC recipients with grade I-II acute GVHD and in RIC recipients with no GVHD and with grade I-II acute GVHD were 0.659, 0.971, and 0.592, respectively (interaction = .7962), and the HRs in MAC and RIC recipients with grade III-IV acute GVHD were 1.343 and 1.387, respectively (interaction = .7603) (Figure 3A).

### Effects of Acute GVHD on ATL-Related Mortality and TRM
Among the 616 patients receiving allogeneic BMT or PBSC, 10 patients could not be assigned to either the ATL-related mortality or TRM category because of missing detailed information on the cause of death. The cumulative incidences of ATL-related mortality at 1 year and 3 years from the landmark day for acute GVHD were 35.0% (95% CI, 0.843).
model to the 606 patients. The analysis included the same
38.6% to 61.7%), respectively (Figure 1B and C).
TRM were 42.7% (95% CI, 31.8% to 53.3%) and 50.7% (95% CI,
and 27.0% (95% CI, 14.2% to 41.5%), respectively, and those of
the onset of acute GVHD were 21.2% (95% CI, 10.8% to 33.8%)
dences of ATL-related mortality at 1 year and 3 years from
patients with grade III-IV acute GVHD, the cumulative inci-
13.0% to 24.6%), respectively (Figure 1B and C). In the 99
TRM were 14.5% (95% CI, 10.1% to 19.6%) and 18.5% (95% CI,
304 patients with grade I-II acute GVHD, whereas those of
31.4%) and 33.0% (95% CI, 26.9% to 39.3%), respectively, in the
from the onset of acute GVHD were 25.8% (95% CI, 20.5% to
incidences of ATL-related mortality at 1 year and 3 years
were 20.0% (95% CI, 13.5% to 27.5%) and 22.0% (95% CI, 14.8%
to 30.1%), respectively (Figure 1B and C). The cumulative
incidences of ATL-related mortality at 1 year and 3 years from
the onset of acute GVHD were 25.8% (95% CI, 20.5% to
31.4%) and 33.0% (95% CI, 26.9% to 39.3%), respectively, in the
304 patients with grade I-II acute GVHD, whereas those of
TRM were 14.5% (95% CI, 10.1% to 19.6%) and 18.5% (95% CI,
13.0% to 24.6%), respectively (Figure 1B and C). In the 99
patients with grade III-IV acute GVHD, the cumulative inci-
cences of ATL-related mortality at 1 year and 3 years from
the onset of acute GVHD were 21.2% (95% CI, 10.8% to 33.8%)
and 270% (95% CI, 14.2% to 41.5%), respectively, and those of
TRM were 42.7% (95% CI, 31.8% to 53.3%) and 50.7% (95% CI,
38.6% to 61.7%), respectively (Figure 1B and C).
We next applied the Fine and Gray proportional hazards
model to the 606 patients. The analysis included the same
variables as in the multivariate Cox proportional hazards
regression models for OS. There were significant associations
between grade III-IV acute GVHD and lower ATL-related
mortality (HR, 0.599; 95% CI, 0.373 to 0.964) and higher
TRM (HR, 2.474; 95% CI, 1.495 to 0.964) compared with no
acute GVHD (Table 2).

In investigating the clinical significance of acute GVHD for
ATL-related mortality or TRM, we divided acute GVHD into 5
categories (none and grade I, II, III, and IV) and conducted the
analysis in the same manner as described above. HRs for ATL-
related mortality in patients with grade I, II, III, and IV acute
GVHD compared with the absence of acute GVHD were 0.809
(95% CI, 0.517 to 1.268), 0.857 (95% CI, 0.558 to 1.315), 0.585
(95% CI, 0.347 to 0.986), and 0.654 (95% CI, 0.298 to 1.435),
respectively. HRs for TRM in patients with grade I, II, III, and
IV acute GVHD compared with the absence of acute GVHD
were 0.519 (95% CI, 0.282 to 0.955), 0.747 (95% CI, 0.455 to
1.227), 2153 (95% CI, 1.267 to 3.659), and 4114 (95% CI, 2.033
to 8.326), respectively.

Effects of Chronic GVHD on Survival
Among the 431 patients evaluable for chronic GVHD, 199
received MAC and 232 received RIC. In the MAC group,
limited and extensive chronic GVHD occurred in 26 (13.1%) and
67 patients (33.7%), respectively, and in the RIC group,
limited and extensive chronic GVHD occurred in 35 (15.1%) and
65 patients (28.0%), respectively. Regarding the incidence
and grade of chronic GVHD, there were no significant
differences between MAC and RIC recipients. In the 214
patients with no chronic GVHD, the unadjusted 1-year and 3-
year probabilities of survival from the landmark day for
chronic GVHD were 58.7% (95% CI, 51.6 to 65.1%) and 51.0%
(95% CI, 43.6 to 57.9%), respectively. Those probabilities from
the onset of chronic GVHD were 77.4% (64.2 to 86.2%) and
61.7% (46.7 to 73.6%), respectively, in the 60 patients with
limited chronic GVHD and were 70.4% (61.7 to 77.5%) and
55.1% (45.5 to 63.7%), respectively, in the 132 patients with
extensive chronic GVHD. Twenty-five patients were
excluded from this semilandmark plot because they were
censored or died before the landmark day for chronic GVHD
(Figure 4A).

We performed a multivariate analysis of data on 431
patients to examine whether chronic GVHD affects OS using
the following variables: age, sex, disease status, pre-
conditioning regimen, GVHD prophylaxis, donor—recipient
relationship, PS, ATL clinical subtype, time from diagnosis to

Table 2
Effect of Acute GVHD on OS, ATL-related Mortality, and TRM after Allogeneic
HCT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No acute GVHD</td>
<td>1.000</td>
<td>Reference</td>
</tr>
<tr>
<td>Grade I-II acute GVHD</td>
<td>0.634 (0.477-0.843)</td>
<td>.0017</td>
</tr>
<tr>
<td>Grade III-IV acute GVHD</td>
<td>1.380 (0.988-1.927)</td>
<td>.0590</td>
</tr>
<tr>
<td>ATL-related mortality*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No acute GVHD</td>
<td>1.000</td>
<td>Reference</td>
</tr>
<tr>
<td>Grade I-II acute GVHD</td>
<td>0.833 (0.566-1.224)</td>
<td>.3511</td>
</tr>
<tr>
<td>Grade III-IV acute GVHD</td>
<td>0.599 (0.373-0.964)</td>
<td>.0347</td>
</tr>
<tr>
<td>TRM*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No acute GVHD</td>
<td>1.000</td>
<td>Reference</td>
</tr>
<tr>
<td>Grade I-II acute GVHD</td>
<td>0.645 (0.407-1.023)</td>
<td>.0624</td>
</tr>
<tr>
<td>Grade III-IV acute GVHD</td>
<td>2.474 (1.495-4.095)</td>
<td>.0004</td>
</tr>
</tbody>
</table>

* Other than acute GVHD, the following 4 variables significantly affected OS: older age (56 to 72 yr compared with 15 to 55 yr: HR, 1.356; 95% CI, 1.033 to 1.781), male sex (HR, 1.404; 95% CI, 1.127 to 1.750), not in CR compared with CR (HR, 1.877; 95% CI, 1.459 to 2.416), and worse PS (1 compared with 0: HR, 1.486; 85% CI, 1.168 to 1.889; 2 to 4 compared with 0: HR, 2.691; 95% CI, 1.918 to 3.777).

** Other than acute GVHD the following 2 variables significantly affected ATL-related mortality: not in CR compared with CR (HR, 1.666; 95% CI, 1.267 to 2.153) and chronic GVHD prophylaxis (HR, 1.227), 2.153 (95% CI, 1.267 to 3.659), and 4.114 (95% CI, 2.033 to 8.326), respectively.

** Other than acute GVHD, the following 3 variables significantly affected TRM: older age (56 to 72 yr compared with 15 to 55 yr: HR, 1.663; 95% CI, 1.025 to 2.697), male sex (HR, 1.545; 95% CI, 1.078 to 2.214), and transplantation from an unrelated donor compared with an HLA-matched related donor (HR, 2.988; 95% CI, 1.131 to 3.895).

Figure 3. Interactions of the preconditioning regimen with acute GVHD for overall survival. Statistical interactions between the preconditioning regimens (MAC or RIC) and acute GVHD (absent versus grade I-II or grade III-IV; A) and chronic GVHD (absent versus limited or extensive type; B) for overall survival were analyzed.
HCT, date of HCT, and stem cell source, as well as chronic GVHD as a time-dependent covariate. We found a significant positive impact of extensive chronic GVHD on OS compared with no chronic GVHD (HR, 0.585; 95% CI, 0.389 to 0.880) (Table 3).

**Interactions of the Preconditioning Regimen with Chronic GVHD for OS**

We tested the statistical interactions between the preconditioning regimens and chronic GVHD for OS by adding an interaction term into the multivariate analysis. The analysis included the same variables as the multivariate Cox proportional hazards regression models for OS with chronic GVHD. Among the 431 patients, when the HR for death of MAC recipients with no chronic GVHD was set as 1.000, the HRs in MAC recipients with limited chronic GVHD and RIC recipients with no GVHD and limited chronic GVHD were 0.845, 1.159, and 0.536, respectively (P interaction = .1502), and the HRs in MAC and RIC recipients with extensive chronic GVHD were 0.565 and 0.689, respectively (P interaction = .9413) (Figure 3B).

**Effects of Chronic GVHD on ATL-Related Mortality and TRM**

Among the 406 patients analyzed by a semilandmark plot for survival, 9 could not be assigned to either the ATL-related mortality or TRM category. The cumulative incidences of ATL-related mortality at 1 year and 3 years from the landmark day for chronic GVHD were 29.0% (95% CI, 22.4% to 35.8%) and 33.7% (95% CI, 26.4% to 41.1%), respectively, in the 208 patients with no chronic GVHD, whereas those of TRM were 12.0% (95% CI, 7.3% to 18.1%) and 13.9% (95% CI, 8.5% to 20.7%), respectively (Figure 4B and C). In the 59 patients with limited chronic GVHD, the cumulative incidences of ATL-related mortality at 1 year and 3 years from the onset of chronic GVHD were 7.0% (95% CI, 2.1% to 16.1%) and 18.3% (95% CI, 7.7% to 32.4%), respectively, and those of TRM were 16.0% (95% CI, 7.5% to 27.4%) and 20.8% (95% CI, 10.1% to 34.1%), respectively (Figure 4B and C). In the 130 patients with extensive chronic GVHD, the cumulative incidences of ATL-related mortalities at 1 year and 3 years from the onset of chronic GVHD were 15.1% (95% CI, 9.0% to 22.6%) and 23.1% (95% CI, 14.7% to 32.6%), respectively, and those of TRM were 15.0% (95% CI, 9.1% to 22.3%) and 21.6% (95% CI, 13.9% to 30.5%), respectively (Figure 4B and C).
We next applied the Fine and Gray proportional hazards model to the 422 patients evaluable for chronic GVHD who could be assigned to either the ATL-related mortality or the TRM category. The analysis included the same variables as the multivariate Cox proportional hazards regression models for OS. Chronic GVHD was significantly associated with reduced ATL-related mortality. HRs for recipients with limited and extensive chronic GVHD compared with the absence of chronic GVHD were 0.395 (95% CI, 0.184 to 0.847) and 0.421 (95% CI, 0.240 to 0.740), respectively (Table 3). On the other hand, chronic GVHD was not significantly associated with TRM.

**DISCUSSION**

To the best of our knowledge, this is the largest retrospective study reported to date analyzing the impact of acute and chronic GVHD on clinical outcomes in ATL. As shown in Table 1, the associations with no acute GVHD and without grade III-IV acute GVHD were significant in RIC recipients compared with MAC recipients. Those findings are consistent with reports of an association between dose-intensified conditioning, especially regimens including TBI, and acute GVHD [32,33]. Our results also show no significant difference in the occurrence of chronic GVHD between MAC and RIC recipients. This may be because the effects of older age and more frequent PBSCT, which increase the occurrence of chronic GVHD, were counterbalanced by the lower frequency of history of previous acute GVHD, which reduces the incidence of chronic GVHD, in the RIC recipients [32,34].

Forest plots revealed that the development of grade I-II acute GVHD was associated with favorable OS compared with the absence of acute GVHD in most categories, with the exception of lymphoma in the ATL clinical subtype category. The reason for this exception is unclear, however. Our forest plots also show that the occurrence of grade III-IV acute GVHD was associated with unfavorable OS in most categories.

The significant positive impact of grade I-II acute GVHD on OS identified by multivariate analysis confirmed the results presented in our previous report [21]. However, in the present study, we found that grade I-II acute GVHD had no significant association with ATL-related mortality, in disagreement with our previous report showing a significant association between grade I-II acute GVHD and decreased ATL-related mortality in ATL patients undergoing allogeneic HCT [21]. We surmise that the incompatibility might stem from 2 factors, the influence of unrelated CBT, which was included in the previous study [21], and the progress in transplantation-related medicine from 2006 onward. The clear trend of decreased TRM in patients with grade I-II acute GVHD observed here seems a bit puzzling, but we have no suitable explanation. With respect to preconditioning, there were no significant interactions between MAC and RIC for OS even when post-transplantation acute GVHD was absent or present at grade I-II or III-IV.

Our multivariate analysis revealed a clear trend toward a favorable OS with limited chronic GVHD and a significant association with lower ATL-related mortality. These findings are consistent with previous reports by our group [20] and others [35]. The latter report included a variety of hematologic diseases. Even though our univariate analyses revealed a trend toward better survival (but without significance) in patients with extensive chronic GVHD in the landmark plots (Figure 4A), our multivariate analysis demonstrated that a significant association between extensive chronic GVHD and a favorable OS. This finding is in disagreement with our previous report [21] and another study demonstrating a negative impact of extensive chronic GVHD on OS [35]. Extensive chronic GVHD had a significant association with lower ATL-related mortality, but not with TRM. The former finding was reasonable and expected, but the latter was not consistent with our previous report demonstrating significant associations between extensive chronic GVHD and greater TRM [21]. Although the present study found a significant association between extensive chronic GVHD and favorable OS in the patients with ATL, we also must pay special attention to the fact that quality of life after HCT is highly compromised by chronic GVHD [36]. With respect to preconditioning, there were also no significant interactions between MAC and RIC with OS even when chronic GVHD was absent, limited, or extensive.

Several promising new agents for treating ATL are currently under development [37-40]. These novel treatments should increase the number of patients with a sufficient disease control status and who have maintained a good PS who could become suitable candidates for HCT [12]. These agents will also contribute to the establishment of better rescue strategies for patients relapsing after HCT [41]. Among the novel agents, we should pay special attention to mogamulizumab (humanized anti-CCR4 monoclonal antibody) [42], which was approved for the treatment of ATL in Japan in 2012, because of its potent activity that depletes regulatory T (Treg) cells, leading to enhanced antitumor activity [38,43,44]. The occurrence and severity of GVHD are closely associated with low Treg frequency [45]; thus, a decrease in Treg cells caused by mogamulizumab not only may lead to enhanced GVHD, but also may provoke an anti-HTLV-1/ATL immune effect.

Although this study reports significant novel findings on GVHD in patients with ATL, it also has inherent limitations common to observational retrospective studies. First, eligibility for HCT as well as choice of transplantation protocol, including the selection of MAC or RIC, were determined by physicians at each institution. Second, regarding analysis of mortality, it was not always easy to determine whether death after allogeneic HCT was an ATL-related mortality or TRM, in part because patients with relapsed ATL sometimes achieve partial or complete remission after decreasing or discontinuing immunosuppressive agents, donor lymphocyte infusions, or chemotherapy, which can result in long-term remission and survival [20]. Third, acute GVHD is occasionally induced in some patients considered at high risk for relapse by treating clinicians. Finally, the evaluation of chronic GVHD according to the 2005 National Institutes of Health consensus criteria [46] is not possible in this study, which was based on nationwide survey data of the JSHT.

In conclusion, we found that the development of mild to moderate (grade I-II) acute GVHD was significantly associated with favorable OS, as was the development of both limited and extensive chronic GVHD. Regarding preconditioning, we found no difference in the clinical impact of acute GVHD and chronic GVHD on OS between patients receiving MAC and those receiving RIC. These findings confirm the actual existence of graft-versus-HTLV-1 and/or graft-versus-ATL effects in recipients of HCT for ATL regardless of whether MAC or RIC was used. New strategies that enhance the post-transplantation allogeneic anti-HTLV-1 effect targeting HTLV-1–associated antigens, such as Tax and/or HBZ [14-17], and/or the anti-ATL effect targeting tumor-specific antigens, such as cancer testis antigens [18],
which do not provoke GVHD, lead to improved outcomes in patients undergoing allogeneic HCT for ATL.

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Authorship statement: T.I., M.H., K.K., R.T., and A.U. designed the research, organized the project, and wrote the manuscript. T.I. helped with statistical analysis. H.S. and R.S. collected data from the JSHTC, and Y.M. collected data from the JMDP. All authors interpreted data and reviewed and approved the final manuscript.

REFERENCES


