and 6 of them subsequently achieved 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 two prospective studies including a total of 29 ATL patients 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 confirmed that a substantial proportion of patients with ATL can enjoy long-term disease-free survival after transplantation; the overall survival rates at 3 years among patients who received transplants in complete remission and not in complete remission were 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

three largest HCT registries in our country; their roles were detailed elsewhere.[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 one 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 $x10^9$/L for three consecutive days following 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. Since 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) were also excluded from the study. Among these 53 patients, 22 were evaluable for acute GVHD: grade 0 in 17, grade 1-2 in 3, and grade 3-4 in 2 patients. Two physicians

(J.K. and T.I.) independently reviewed the quality of collected data, and a total of 294 patients (158 males and 136 females), with a median age of 51 years (range, 18-79), were found to meet these criteria and included in the study: 163 patients from JSHCT, 82 from JMDP, and 49 from JCBBN. No overlapping cases were identified. Of these 294 patients, the effects of chronic GVHD, which was reported and graded according to 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.

Endpoints

The primary endpoint of the study was the effect of acute GVHD on overall survival, which was defined as the period from the date of transplantation until the date of death from any cause or the last follow-up. The secondary endpoints 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, while 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 events[26]: 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, which was 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, which was the median day of onset for chronic GVHD, was termed as the landmark day.

Univariable and multivariable Cox proportional–hazards regression models were used to evaluate variables potentially affecting overall survival, while 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 or 2 acute GVHD group" or to the "grade 3 or 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 younger or greater than 50 years at transplantation); sex of the recipient (female or male); disease status prior to 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 others); 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, longer than 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 to 4 acute GVHD was also added to the multivariable models. We also assessed the interaction between acute GVHD and the intensity of conditioning regimen in the

multivariable models. Only factors with a p value of less than 0.10 in univariable analysis were included in the multivariable models. Additionally, 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 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 were expressed as hazard ratios and their 95% confidence intervals (CI). All tests were two-sided, and a p value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with STATA version 11 (Stata Corp., College Station, TX) software.

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 41–60 years (median, 51 years). The disease status at transplantation 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,

busulfan plus cyclophosphamide in 15, busulfan plus melphalan in 1, purine analogue-containing regimen in 6, and other TBI-based regimens in 26, although the intensity of these regimens was considered unclassifiable due to 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 (45%), HLA-mismatched related donor in 31 (11%), unrelated bone marrow donor in 82 (28%), and unrelated cord blood unit in 49 (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).

The effect 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 (69%), 150 (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 three 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 was also 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, while 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. Multivariable 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=0.018), and adverse impact of grade 3–4 acute GVHD on overall survival (HR, 1.64; 95% CI, 1.10–2.42; p=0.014) (Table 2). Patients who received reduced-intensity conditioning and myeloablative conditioning had similar rates of overall survival by both univariable (HR of reduced-intensity versus myeloablative transplant 1.19; 95% CI, 0.85-1.68; p=0.318) and multivariable analysis (HR 0.95; 95% CI, 0.61-1.47; p=0.814). There was no interaction effect between conditioning intensity and grade 1-2 (p=0.704) or grade 3-4 acute GVHD (p=0.891) 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, while only grade 4 acute GVHD was associated with inferior survival (Supplemental Table 1). 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).

The 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, 1C). Disease-associated mortality was defined as cumulative incidence of death directly attributable to relapse or progression of ATL, while treatment-related mortality was calculated as cumulative incidence of any death not included in disease-associated deaths. Multivariable 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 0.023; and grade 3–4 acute GVHD: HR, 0.44; 95% CI, 0.22–0.90; p 0.024) (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 0.001) (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=0.975) and treatment-related death (HR, 0.98; 95% CI, 0.60-1.59; p=0.928) by multivariable 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 succumbed to infectious complications: bacterial in 13, viral in 7 (including 3 cases of CMV disease), viral and bacterial in 1, fungal in 5, and no specific organism reported in 1. 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 multivariable 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=0.008), while 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=0.169).

The 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). 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 multivariable 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, while treatment-related mortality was higher in the presence of extensive chronic GVHD (HR, 2.75; 95% CI, 1.34–5.63; p 0.006) 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 multivariable analysis, no statistically significant association was found between infection-related death and the occurrence of either limited (p=0.289) or extensive GVHD (p=0.836).

Discussion

To our knowledge, this is the largest retrospective study to analyze the impact of acute and chronic GVHD on clinical 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 hazard ratio comparing limited chronic GVHD versus the absence of chronic GVHD suggested the trend toward a reduced risk of disease-associated deaths in the limited chronic GVHD group.

Our present findings are in contrast to the previous reports showing the beneficial effects of chronic GVHD rather than acute GVHD on the prevention of disease recurrence after allogeneic HCT. It is less likely that the particular characteristics of chronic GVHD in patients with ATL biased the results, because the incidence rate and median onset day of chronic GVHD in our cohort were

similar to those reported in previous studies evaluating the incidence of chronic GVHD among Japanese patients, most of whom had received allogeneic HCT for myeloid neoplasms or acute lymphoblastic leukemia.[30-32] Conceivably, the rapid tempo of disease recurrence of ATL might be such that chronic GVHD is less potent in terms of harnessing clinically relevant graft-versus-leukemia responses as compared with acute GVHD. However, the results of our analysis regarding the effect of chronic GVHD should be interpreted with caution because the number of patients evaluable for chronic GVHD were relatively small in our study for providing sufficient statistical power. The effect of chronic GVHD on outcomes after HCT for ATL should be further explored in a larger cohort.

The occurrence of GVHD has been shown to exert a potent graft-versus-leukemia effect in terms of reducing relapse incidence in acute leukemia or chronic myeloid leukemia.[33,34] On the other hand, multiple studies have documented a correlation between GVHD in its acute or chronic form and treatment-related mortality. In a study of patients undergoing HLA-identical sibling HCT for chronic myeloid leukemia, the overall beneficial effect on long-term survival was demonstrated only in a group of patients who developed grade 1 acute GVHD or limited chronic GVHD.[33] In another study of HLA-identical sibling HCT for leukemia using cyclosporine and methotrexate as GVHD prophylaxis, a benefit of mild GVHD was only seen in high-risk patients but not in standard-risk patients. Therefore, the therapeutic window between decreased relapse incidence and increased transplant-related mortality in association with the development of GVHD has been considered to be very narrow.[34]

With regard to the effectiveness of allogeneic HCT for ATL, it is also of note here that post-transplant eradication of ATL cells can be achieved without the use of high-dose chemoradiotherapy: patients who received a transplant with reduced-intensity conditioning had survival outcomes similar to those who received a transplant with myeloablative conditioning in our study. Intriguingly, several small cohort studies exhibited that abrupt discontinuation of immunosuppressive agents resulted in disappearance or reduction in the tumor burden in allografted patients with ATL. In some cases, remission of ATL was observed along with the development of GVHD.[19,20,22] Taken together with the findings of this study, it is suggested that ATL is particularly susceptible to immune modulation following allogeneic HCT. To clarify the presence of such "graft-versus-ATL" effect, further investigations are needed to assess the efficacy of donor lymphocyte infusion or withdrawal of immunosuppressive agents on relapse after transplantation.

Of the HTLV-I gene products, Tax is a dominant target of HTLV-I-specific cytotoxic T lymphocytes. The vigorous Tax-specific cytotoxic T-cell responses were demonstrated in recipients who obtained complete remission after allogeneic HCT for ATL, suggesting that "graft-versus-HTLV-I" responses might contribute to the eradication of ATL cells.[35,36] However, Tax is generally undetectable or present in very low levels in primary ATL cells.[37,38] In addition, small amounts of HTLV-I provirus can be detected in peripheral blood of recipients who attained long-term remission of ATL, even after HCT from HTLV-I-negative donors.[39,40] These findings suggest that "graft-versus-ATL" effect can be harnessed without complete elimination of HTLV-I. It is also

important to note that allogeneic HCT is emerging as an effective treatment option for other mature T-cell neoplasms not related to HTLV-I, such as mycosis fungoides/Sézary syndrome and various types of aggressive peripheral T-cell lymphomas.[41,42] These observations raised the possibility that the common targets for alloimmune responses might exist across a spectrum of malignant T-cell neoplasms including ATL. The minor histocompatibility antigens or tumor-specific antigens can be other targets of alloimmune anti-ATL effect.[43-45] Therefore, the elucidation of the mechanism underlying an immunologic eradication of primary ATL cells may lead to a new strategy for improving outcomes of allogeneic HCT not only for ATL but for other intractable T-cell neoplasms.

This study has several limitations. First, acute GVHD might be intentionally induced for some patients considered at high risk of relapse by treating clinicians. Secondly, the information on the day when each grade of GVHD occurred was not available. Therefore, we treated the development of acute and chronic GVHD in their worst severity as a time-varying covariate. To validate the results, we also performed the landmark analysis and obtained consistent results. Thirdly, the relatively small number of patients with chronic GVHD might mask or bias the effect of chronic GVHD on outcomes. Lastly, the effect of multiple testing should be taken into account for the interpretation of the secondary endpoints.

In conclusion, the development of acute GVHD was associated with lower disease-associated mortality after allogeneic HCT for ATL as compared with the absence of acute GVHD. However, improved survival can be expected only among a group of patients who developed mild-to-moderate acute GVHD

because those who developed severe acute GVHD were at high risk of treatment-related mortality. New strategies that enhance the allogeneic anti-ATL effect without exacerbating GVHD are required to improve the outcomes of patients undergoing allogeneic HCT for ATL.

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Authorship

Contribution: T.I. and T.U. designed the research and organized the project; M. Hishizawa, J.K., T.I., and T.U. reviewed data, analyzed data, and wrote the paper; J.K., T.I., and K.M. performed statistical analysis; Y.A., R.S., and H.S. collected data from JSHCT; T.K. and Y. Morishima collected data from JMDP; T.

N-I. and S. Kato collected data from JCBBN; A.U., S.T., T.E., Y. Moriuchi., R.T., F.K., Y. Miyazaki., M.M., K.N., M. Hara, M.T., S.Kai., and J.O. interpreted data, reviewed and approved final manuscript.

T.U., the senior author, was deceased during the preparation of this manuscript.

In addition to authors, other members who contributed data on allogeneic HSCT for ATL to JSHCT, JMDP, and JCBBN are listed in the supplemental Appendix.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

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