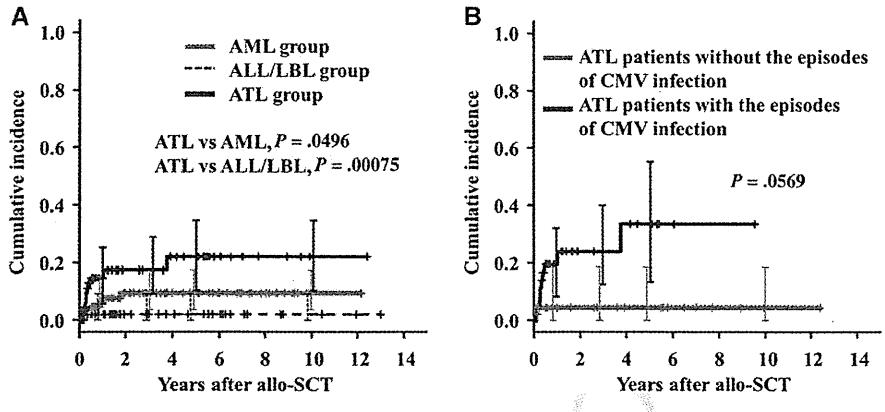

Figure 1. Cumulative incidence of infection-related death after transplantation. The 95% confidence intervals at 1, 3, 5, and 10 years are shown in each infection-related mortality. (A) Infectious mortality was higher in the adult T cell leukemia/lymphoma (ATL) group than that in the 2 other groups. (B) In the ATL group, infectious mortalities were higher in patients with episodes of cytomegalovirus (CMV) infection than in those without, but the *P* value for this association was near the borderline of significance.

$P = .1083$); multivariate analysis revealed that nonremission at allo-SCT was a significant unfavorable factor for infection-related mortality (HR 2.528; 95% CI: 1.007 to 6.345, $P = .0482$).

Although nonremission at allo-SCT remained a significant risk factor for infection-related mortality in AML group, it did not in ALL/LBL and ATL groups. Rather, in the ATL group, infection-related mortality was higher among patients who experienced a CMV infection after allo-SCT than those who did not, but the *P* value was at the borderline of significance ($P = .0569$) (Figure 1B). There was no significant relationship between episodes of CMV infection and mortality caused by infection in either the AML or ALL/LBL group (AML group, $P = .3160$; ALL/LBL group, $P = .4461$). Additionally, to exclude the bias due to the CMV-serostatus of patients, infection-related mortalities were analyzed in patients who were CMV-seropositive in each of the 3 groups. For CMV-seropositive patients, the comparison of cumulative infection-related mortalities between those with episodes of CMV infection and without showed a significant difference in the ATL group; the episodes of CMV infection have a significant negative impact on infection-related mortalities in the ATL group ($P = .0492$), but not in the AML and ALL/LBL groups ($P = .0840$ and $P = .4276$, respectively).

The difference of institution did not have any impact on the cumulative infection-related mortalities in each of the 3 groups. In the ATL group, the HTLV-1 serostatus of donor was not associated with cumulative infection-related mortalities.

The pathogens resulting in fatal infectious complications are shown in Table 4. Interestingly, despite the high incidence of CMV infection after allo-SCT, 4 patients died of CMV diseases (CMV pneumonia in 2 ATL and 2 AML patients), and no ALL/LBL patient died of any CMV disease. Of these 4 patients, one with AML and one with ATL died of recurrent CMV infection on late phase. In the patients who died of infection on late phase, 4 of 6 with ATL, 1 of 4 with AML and none with ALL/LBL died of bacterial infection. The proportion of bacteria in the pathogens resulting in fatal infectious complications on late phase after allo-SCT was likely to be higher in the ATL group than in the AML and ALL/LBL groups, but this difference was not significant. The pathogens inducing fatal complications in the 4 ATL patients on late phase were either methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa*, which were resistant to many antibiotic agents. Also, these 4 patients with ATL experienced the improvement of CMV antigenemia by GCV on post-engraftment phase (ie, before the development of fatal bacterial infections).

Survival

The outcomes of allo-SCT in each of the 3 groups are shown in Table 5. Median survival times after allo-SCT were 4.0 years and 1.0 year in the AML group and ATL group, respectively. Median survival was not reached in the ALL/LBL group (Figure 2A). Estimated OS after transplantation were 49.9% (95% CI: 38.2% to 60.5%), 58.3% (95% CI: 41.2% to 71.9%), and 34.9% (95% CI: 23.2% to 46.8%) at 5 years in the AML, ALL/LBL, and ATL groups, respectively. OS for ATL patients was significantly worse than that for AML ($P = .0089$) and ALL/LBL groups ($P = .0023$), while OS rates for AML and ALL/LBL patients were similar ($P = 0.2982$).

Univariate Analysis for Survival

Univariate analysis for survival identified several pre-transplantation and post-transplantation factors. The disease status (CR or PR) at transplantation had a significant positive impact in both the AML ($P < .0001$) and ALL/LBL groups ($P = .0050$), but not in the ATL group. The existence of aGVHD (grade II-IV) was associated with worse survival in the AML group ($P = .0007$). AML patients with cGVHD (extensive type) ($P = .0302$) and ATL with cGVHD (limited type) ($P = .0140$)

Table 4
Agents of Infection-Related Death

	Post-engraftment Phase to Days +100)	Late Phase (Days 100 to >365)
AML group (n = 91)	*MRSA* (n = 1) *Enterococcus spp* (n = 1) *Aspergillus spp* (n = 1) *Cytomegarovirus* (n = 1)	*Escherichia coli* (n = 1) *Candida spp* (n = 2) *Cytomegarovirus* (n = 1)
ALL/LBL group (n = 51)	none	*Adenovirus* (n = 1)
ATL group (n = 68)	*Enterococcus spp* (n = 1) *Stenotrophomonas maltophilia* (n = 1) *Pneumocystis jirovecii* (n = 1) *Human herpes virus-6* (n = 1) *Adenovirus* (n = 1) *Cytomegarovirus* (n = 1)	*MRSA* (n = 1) *Pseudomonas aeruginosa* (n = 3) *Pneumocystis jirovecii* (n = 1) *Cytomegarovirus* (n = 1)

MRSA indicates methicillin-resistant *Staphylococcus aureus*; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma; ATL, adult T cell leukemia/lymphoma.

Table 5
Transplantation Outcome

	AML (n = 91)	ALL/LBL (n = 51)	ATL (n = 68)
Alive (dead)	48 (43)	33 (18)	25 (43)
Cause of death			
Bacterial infection	3	-	6
Fungal infection	3	-	2
CMV disease	2	-	2
Viral infection other than CMV	-	1	2
Disease progression	24	12	21
GVHD with or without any infection	5	2	4
Bleeding	1	-	2
Organ failure without any infection	5	3	3
Secondary malignancy	-	-	1

AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma; ATL, adult T cell leukemia/lymphoma; CMV, cytomegalovirus; GVHD, grant-versus-host disease.

showed a better OS than without cGVHD. Episode of fungal infection provided a negative impact on OS for the AML (P = .0015) and ALL/LBL groups (P = .0459). Episodes of bacterial infection (P = .0102) and CMV infection (P = .0184) had a significant negative impact in the ATL group (Figure 2B, C). In CMV-seropositive patients of each of the 3 groups, episode of CMV infection negatively affected survival with a borderline difference in the ATL groups (P = .0615), but there was no relationship in the AML and ALL/LBL groups (P = .4680 and P = .4620, respectively).

There was no significant relationship between the difference of institution and OS in each of the 3 groups. For the ATL group, neither the use of anti-thymocyte globulin in the conditioning regimen nor the HTLV-1 serostatus of donor was associated with survival.

Multivariate Analysis for Survival

Multivariate analysis in all 210 patients revealed 6 factors that adversely affected OS: ATL (HR 1.944; 95% CI: 1.204 to 3.141, P = .0066), older age (HR 2.204; 95% CI 1.364 to 3.562, P = .0012), nonremission (HR 3.153; 95% CI 2.041 to 4.868, P < .0001), bacterial infection (HR 2.121; 95% CI 1.267 to 3.550, P = .0042), fungal infection (HR 2.718; 95% CI 1.507 to 4.901, P = .0009), and myeloabrative conditioning (HR 2.064; 95% CI 1.149 to 3.707, P = .0154).

To clarify the distinct unfavorable features in ATL groups, we also performed multivariate analysis for survival respectively in each of the 3 groups (Table 6). There were 4 factors that adversely affected OS in the AML group: patient age (≥ 42 years; HR 2.283; 95% CI: 1.164 to 4.476, P = .0163), lack of CR at transplantation (HR 2.975; 95% CI: 1.285 to 6.888, P = .0109), the existence of aGVHD (grade II-IV) (HR 1.731; 95% CI: 1.327 to 2.258, P < .0001), and episodes of fungal infection (HR 3.934; 95% CI: 1.357 to 11.406, P = .0117). In the ALL/LBL group, 2 factors were associated with worse

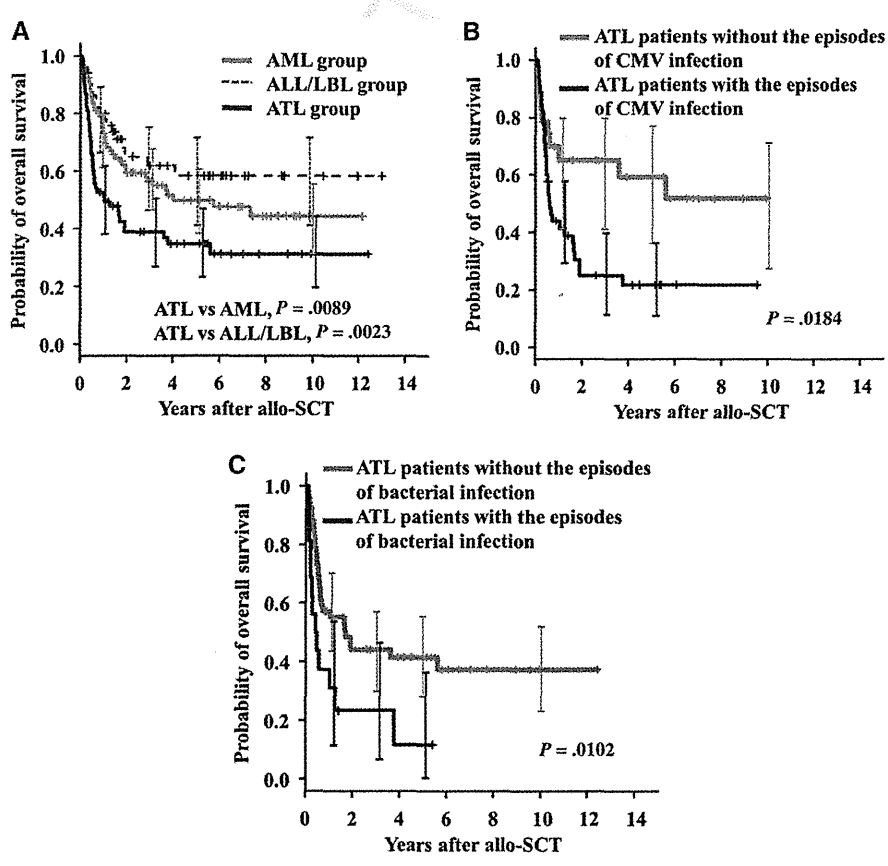

Figure 2. Kaplan-Meier estimate of overall survival after transplantation. The 95% confidence intervals at 1, 3, 5, and 10 years are shown in each overall survival (OS). (A) OS of the adult T cell leukemia/lymphoma (ATL) group was significantly worse than that of either the acute myeloid leukemia (AML) or acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) group. (B) In ATL group, the OS of patients with episodes of cytomegalovirus (CMV) infection was significantly worse than those without. (C) In the ATL group, the OS of patients with episodes of bacterial infection was significantly worse than those without.

Table 6
Multivariate Analysis of Risk Factors for Overall Survival

	AML		ALL/LBL		ATL	
	P Value	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value	Hazard Ratio
Age ≥ median age	$P = .0163$	2.283	Not selected		$P = .3487$	1.363
Without CR or PR at allo-SCT	$P = .0109$	2.975	$P = .0058$	3.874	Not selected	
aGVHD (grade II -IV)	$P < .0001$	1.731	Not selected		Not selected	
Unrelated BM	Not selected		Not selected		$P = .0248$	2.568
Cord blood	Not selected		Not selected		$P = .8645$	0.936
CMV infection	Not selected		Not selected		$P = .0171$	2.514
Invasive fungal infection	$P = .0117$	3.934	$P = .0448$	3.430	Not selected	

In the ATL group, episodes of CMV infection significantly correlated with worse overall survival. However, there was no such association in either the AML or ALL/LBL group. AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma; ATL, adult T cell leukemia/lymphoma; CR, complete remission; PR, partial remission; GVHD, grant-versus-host disease; BM, bone marrow; CMV, cytomegalovirus.

survival: lack of CR at transplantation (HR 3.874; 95% CI: 1.481 to 10.134, $P = .0058$) and episodes of fungal infection (HR 3.430; 95% CI: 1.029 to 11.435, $P = .0448$). In the ATL group, 2 factors that differed from those in the AML or ALL/LBL group had a negative impact on OS with significance: the use of unrelated bone marrow (HR 2.568; 95% CI: 1.127 to 5.854, $P = .0248$) and episodes of CMV infection (HR 2.514; 95% CI: 1.178 to 5.366, $P = .0171$). Although the difference of institution was analyzed in multivariate analysis as a factor, this difference was not selected as a factor in each of 3 groups.

DISCUSSION

The success or failure of allo-SCT is mostly determined in the first 6 months after allo-SCT. Outcome closely correlates with the reconstitution of donor cell derived immunity, which affects the survival of recipients through GVHD and the graft-versus-leukemia effect, and the degree of immune competence achieved against infectious agents. Recently, some reports have indicated that the incidence of fungal infection and CMV infection has increased after engraftment, particularly among patients with severe immunodeficiency. For example, after allo-SCT using in vitro or in vivo T cell depletion, fungal infection, and reactivation of the Epstein-Barr virus and CMV are closely related to serious complications [42-49]. Also, the risk of infectious complications, including HHV-6 encephalitis and CMV diseases, is higher in patients who received cord blood transplantation [42,50-54]. These results suggest that the incidence of infectious complications depends not only on infectious disease-causing pathogens but also on the background of the patient or the cause of immunosuppression.

In our study, although the cumulative incidence of either bacterial or fungal infection was similar among the 3 groups, the ATL group showed the highest cumulative incidence of infection-related death, mainly caused by these infections. Importantly, bacteria resistant to many antibiotic agents emerged as a cause of death after 100 days in patients with ATL. It is suggested that after allo-SCT, these patients would be more susceptible to life-threatening bacterial infections even on late phase, compared to those with acute leukemia, and that the current strategy for infection would not be sufficient for allo-SCT to ATL. Hence, it seems that the development of an adoptive strategy in post-transplant patients with ATL is required.

The appearance of a CMV infection showed a negative impact for OS as an independent variable in the ATL group. Interestingly, while there were only 2 patients with ATL having CMV disease at the time of death, the risk of infectious death in patients with ATL who experienced CMV infection (including CMV antigenemia) was likely to be higher. Namely, episodes of CMV infection could predict a higher risk of death caused by not only CMV disease, but also other infections, which may help to identify the ATL patients who should receive more intensive management for infection.

It is not clear why episodes of CMV infection correlated with the outcome of patients with ATL, although multivariate analysis identified episodes of CMV infection as an independent variable only in the ATL group. It has been shown that episodes of CMV infection were associated with a worse outcome in post-transplant patients with defective cellular immunity [43,44,55]. Therefore, it is speculated that persistent compromised cellular immunity after transplantation led to the higher susceptibility of CMV and other infections among ATL patients, resulting in worse outcomes than leukemia patients. Considering that the reactivation of CMV itself and the prolonged administration of GCV could induce greater immune suppression [56,57], we hypothesize that the direct and indirect influence of CMV infection adversely promoted immunosuppression attendant on ATL patients. It remains to be elucidated how immunologic recovery was delayed after transplantation in ATL patients. Since the immune system recovery following allo-SCT was not sufficiently evaluated in our study, the monitoring of immune function after transplant, such as analysis of lymphocyte subset and quantitative estimation of immunoglobulin, should be considered in a future study.

It is possible that CMV-serostatus affected the result of statistical analysis in our study, because CMV-serostatus, which was unexamined in 37.6% patients, was not included in the statistical analysis. Therefore, to remove the bias of this point, the analysis for ATL patients with CMV-seropositive revealed that CMV infection was also identified as a risk factor in infection-related mortality and OS. Considering that it has been reported that about 90% of the Japanese population tests CMV-seropositive, the difference of CMV-serostatus would not have a big impact in our study. However, a larger analysis for matched patients' background regarding with CMV-serostatus would help to confirm our findings.

The ATL group showed that the highest cumulative incidence of infection-related mortality and the various pathogens causing death, indicating that it was difficult to establish the uniform management to reduce the fetal infectious complications for post-transplant patients with ATL. However, it is speculated that more intensive management for bacterial infection might provide the reduction of

infection-related death in some post-transplant patients with ATL, since ATL group would be more likely to show the higher risk of fatal antibiotic-resistant bacterial infection, even on late phase in our study. Therefore, appropriate antibiotic treatment using prolonged bacterial surveillance culture should be considered, particularly in ATL patients with persistent compromised cellular immunity. Moreover, because of a limitation of treatment active on multi-drug resistant gram negative rods, particularly *Pseudomonas aeruginosa*, at the present situation, the introduction of new treatment options, including antibiotic combination therapy using a "break-point checker board plate" and developing antibiotic agents such as colistin [58-62], are expected in patients who developed such infection after allo-SCT.

Our results showed the higher risk of fatal infectious complications in post-transplant patients with ATL. However, the number of patients is limited and the detailed treatment protocols were not completely uniform. Thus, it is possible that these factors exerted a bias and affected results. For instance, the small number of patients in our study resulted in wide and overlapping confidence intervals despite P values <.05. Our finding should be interpreted carefully, and they should be confirmed in larger prospective studies.

In conclusion, we found that the clinical features of infectious complications after allo-SCT in ATL patients are different from those in AML and ALL/LBL patients. Because allo-SCT offers the best chance of prolonged survival by inducing graft-versus-ATL effect, developing supportive care to minimize fatal infectious complications would be important, in particular, for post-transplant patients with ATL. Our data suggested that ATL patients require more intensive management for infections according to individualized risk such as the appearance of CMV infection. Such a strategy may be beneficial in reducing transplantation-related mortality in post-transplant patients with ATL.

ACKNOWLEDGEMENTS

We thank the patients who willingly entered this study; the physicians, nurses, and other support staff who cared for the patients during the transplantation procedures; and the clinical investigation team at each participating institution who provided data collection and follow-up.

Financial disclosure: This study was supported in part by a Grant-in-Aid from the Ministry of Health, Labour, and Welfare of Japan.

Conflict of Interest Statement: There are no conflicts of interest to report.

Authorship Statement: H.I., J.T., T.F., and Y. M-i contributed to the study concept/design. H.I., J.T., T.F., H.T., S.S., K.A., Y.S., E.M., R.Y., Y.O., D.I., Y.I., S.Y., T.H., Y. Mo., and Y.Mi. performed data collection/analysis. H.I., S.H., and Y. Mi. performed statistical analysis. H.I., J.T., T.F., H.T., and Y. Mi. drafted the manuscript and created figures/tables. H.I., J.T., T.F., H.T., S.S., K.A., Y.S., E.M., R.Y., Y.O., D.I., Y.I., S.Y., T.H., Y. Mo., S.H., and Y.Mi. reviewed the manuscript and read and approved the final version of the manuscript.

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blood

2013 121: 219-225
Prepublished online October 24, 2012;
doi:10.1182/blood-2012-07-444372

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Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.

Reguiar Article

TRANSPLANTATION

Treatment of relapsed adult T-cell leukemia/lymphoma after allogeneic hematopoietic stem cell transplantation: the Nagasaki Transplant Group experience

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Key Points

- ATL patients who relapsed after allogeneic HSCT have a very high mortality rate and present a serious therapeutic challenge.
- No large study exists that assesses the role of salvage therapies for relapsed ATL after HSCT; this is the first report summarizing the outcome.

Adult T-cell leukemia/lymphoma (ATL) relapse is a serious therapeutic challenge after allogeneic hematopoietic stem cell transplantation (allo-SCT). In the present study, we retrospectively analyzed 35 patients who experienced progression of or relapsed persistent ATL after a first allo-SCT at 3 institutions in Nagasaki prefecture (Japan) between 1997 and 2010. Twenty-nine patients were treated by the withdrawal of immune suppressants as the initial intervention, which resulted in complete remission (CR) in 2 patients. As the second intervention, 9 patients went on to receive a combination of donor lymphocyte infusion and cytoreductive therapy and CR was achieved in 4 patients. Of 6 patients who had already had their immune suppressants discontinued before the relapse, 3 patients with local recurrence received local cytoreductive therapy as the initial treatment, which resulted in CR for more than 19 months. Donor lymphocyte infusion–induced remissions of ATL were durable, with 3 cases of long-term remission of more than 3 years and, interestingly, the emergence or progression of chronic GVHD was observed in all of these cases. For all 35 patients, overall survival after relapse was 19.3% at 3 years. The results of the present study suggest that induction of a graft-versus-ATL effect may be crucial to obtaining durable remission for ATL patients with relapse or progression after allo-SCT. (*Blood.* 2013;121(1):219-225)

Introduction

Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell neoplasm caused by a specific retrovirus, human T-cell lymphotropic virus type I (HTLV-1).[1-4] Patients with the aggressive type of ATL (the acute, lymphoma, and unfavorable chronic types) generally have a poor prognosis because of chemotherapy resistance and predisposition to opportunistic infections.[5-10] In Japan, allogeneic hematopoietic stem cell transplantation (allo-SCT) has been explored as an alternative treatment that can provide long-term remission[11,12]; overall survival (OS) at 3 years has been reported to be approximately 33%-45% in these patients.[13-20] However, the relapse rate after allo-SCT is approximately 40%[13] and relapsed patients have a very poor prognosis. Treatment options include withdrawal of immune suppressants (IS), chemotherapy, local radiation therapy, lymphocyte infusions (DLIs) from the original donor, and second allo-SCT, but there are limited data describing the outcome of each treatment.[12,17,19,21,22]

It has been shown that the graft-versus-ATL (GVATL) effect plays an important role in the prevention of relapse[13,19,21,23,24] and therapy that could induce the GVATL reaction may improve postrelapse outcome. DLI, a therapy that would induce a GVL reaction, has gained a prominent role in the management of leukemia patients who relapse after allo-SCT.[25-28] The best responses to DLI occur in patients with chronic myelogenous leukemia, which yields complete remission (CR) in approximately 80% of patients with relapsed chronic myelogenous leukemia after transplantation. However, the benefit of DLI for relapsed acute leukemia is often limited, partly because of the rapid growth of leukemia cells and poor response to the GVL reaction. Considering the similar characteristics of ATL cells, the role of GVATL-based therapy (ie, withdrawal of IS and DLI) as salvage therapy remains controversial.

Submitted July 18, 2012; accepted October 20, 2012. Prepublished online as *Blood* First Edition paper, October 24, 2012; DOI 10.1182/blood-2012-07-444372.

There is an Inside *Blood* commentary on this article in this issue.

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In the present study, we retrospectively analyzed 35 patients, including 9 who received DLIs for progression of or relapsed ATL after allo-SCT, and found that the outcomes of those treated with salvage chemotherapy and treatments intended to induce an immune-mediated GVATL effect could be promising for at least some of them.

Methods

Patients and donors

Eighty-one patients with ATL received allo-SCT between September 1997 and December 2010 at 3 institutions in Nagasaki prefecture (Japan). Thirty-five of 81 patients experienced persistence of ATL or relapse of ATL after allo-SCT and these patients were candidates for salvage treatment. Data on these 35 patients were collected and updated as of July 2011.

Before transplantation, all 35 patients received conventional chemotherapy. Because transplantation was performed following the protocol of each institution, the conditioning regimen and prophylaxis for GVHD varied among institutions.

Five related donors showed a positive result for the anti–HTLV-1 Ab. The PBMCs of these donors were subjected to Southern blot analysis to examine monoclonal integration of the HTLV-1 provirus into the genome and all 5 donors were confirmed as carriers of HTLV-1.

Our study was approved by the ethical committees of the participating hospitals. The outline was followed and clinical information about the patients was available to be retrospectively analyzed when informed consent was obtained according to the Declaration of Helsinki.

Treatment for the relapse or progression of ATL after allo-SCT

The relapse was defined by reappearance of abnormal lymphocytes in peripheral blood or local failure diagnosed by biopsies. In 22 cases, HTLV-1 provirus load in peripheral blood was monitored using quantitative PCR, however, an increase in HTLV-1 provirus load was not used to diagnose a relapse. When relapse or progression of persistent ATL after allo-SCT was confirmed, IS was withdrawn if the patients were still receiving IS for the prophylaxis or treatment for GVHD. Indication for DLI was determined by attending physicians following the policy of each institution. Collected cells were given intravenously on the same day of the collection or cryopreserved for later use. Salvage chemotherapy and/or local radiation therapy were also administered before DLI at the discretion of the attending physician. Donor leukocytes from the original donor were obtained by leukocyte apheresis. Cells were infused without further manipulation. Calculation of the number of T cells infused was performed by FACScan analysis of buffy coat cells using anti-CD3–specific mAbs. No donor received G-CSF mobilization.

Definition of therapeutic response and GVHD

Response to treatmentation was divided into 4 categories: CR, partial remission (PR), stable disease (SD), and progressive disease (PD). Responses were defined as follows: CR, disappearance of all disease; PR, $\geq$ 50% reduction of measurable disease; SD, failure to attain CR or PR and no PD; and PD, new or increased lesions.

The clinical manifestations of acute GVHD were graded I to IV according to the criteria described by Przepiorka et al.[29] Chronic GVHD was classified as limited or extensive as described by Filipovich et al.[30]

Statistical analysis

Descriptive statistics were used for summarizing variables related to patient demographics and transplant characteristics. Comparisons among the groups were performed by use of the χ^2 statistic or Fisher exact test as appropriate for categorical variables and the Mann-Whitney U test for continuous variables. OS was calculated from the first day of relapse or progression of persistent ATL to the date of death or the last follow-up. The analysis included the overall study population of 35 patients to evaluate the impact of DLI-based strategies on outcome. The Kaplan-Meier method was used to estimate OS after relapse. The 95% confidence interval of 3-year OS was calculated. The following variables were analyzed by Fisher exact test to determine significantly associated factors for the response of DLI: donor type (HLA-matched related or alternative), HTLV-1 serostatus of donor (positive or negative), chemotherapy or radiotherapy (pre-DLI or post-DLI), time of allo-SCT (1997-2003 or 2004-2010), disease status at allo-SCT, disease status at DLI, T-cell dose, GVHD at relapse/progression (present or absent), GVHD after withdrawing IS (present or absent), post-DLI GVHD (progressive or stable), and time from transplantation to relapse (within 6 months or longer than 6 months). All tests were 2-sided and $P < .05$ was considered significant in all analyses. All statistical analyses were performed with Prism Version 5.0 software (GraphPad).

Results

Characteristics of patients and disease status at transplantation

Patient characteristics including transplantation procedures and clinical outcomes of allo-SCT are summarized in Table 1. Nine of 35 patients (25.7%) received DLI as a part of the treatment for relapse or progression of persistent ATL after allo-SCT (DLI group), whereas 26 patients (74.3%) received other types of treatment without DLI (non-DLI group). Among other characteristics, the 2 groups were well matched in terms of age, HTLV-1 serostatus of donor, disease status at allo-SCT, acute GVHD, chronic GVHD, and intervals from allo-SCT to relapse. All DLI recipients showed that the subtype at diagnosis was the acute type. In the non-DLI group, one patient received conditioning containing antithymocyte globulin. No patient received an ex vivo T cell–depleted graft. Nine patients who experienced relapse after cord blood transplantation were treated without DLI. The clinical outcome after relapse or progression is summarized in Figure 1.

Clinical characteristics and outcome of patients who received DLI

The characteristics of 9 patients in the DLI group are summarized in Table 2. In the DLI group, after allo-SCT, ATL was noticed before or at the time of hematopoietic recovery in 2 patients (unique patient number [UPN] 1 and UPN 5). The other 7 patients attained or maintained CR with hematopoietic reconstitution after allo-SCT. The median time from transplantation to relapse or progression was 2.8 months (range, 0.4-100.7) and the median time from relapse or progression to DLI was 1.2 months (range, 0.4-8.0). All 9 patients had their IS terminated as the first intervention, but no patients achieved CR by the discontinuation of IS alone. One patient (UPN 1) achieved SD by the mere discontinuation of IS. Six patients received cytoreductive therapy (chemotherapy or local radiation therapy) before the first DLI (pre-DLI therapy). No patients achieved CR by any pre-DLI therapy. The response to pre-DLI therapy could not be evaluated in 1 patient (UPN 1) because the interval between pre-DLI therapy and the first DLI was not long enough for evaluation (the patient received pre-DLI therapy for 3 days before the initial DLI).

A total of 20 DLIs were performed in 9 patients. The median of initial and total T-cell doses was 8.2×10^6/kg (range, 5.0-12.0) and 40.0×10^6/kg (range, 5.5-221.0), respectively. The median follow-up duration after relapse/progression and initial DLI was 16.9 months (range, 11.8-148.4) and 16.3 months (range, 4.3-68.1), respectively. Basically, the DLIs were repeated if CR was not

Table 1. Patient characteristics and disease status at transplantation

Characteristic	DLI performed		P
	Yes	No	
No. of patients	9	26	
Median age at allo-SCT, y	54 (range, 41-62)	51 (range, 39-63)	.496
Sex, n			
Male	8	10	.018
Female	1	16	
Subtype of ATL at diagnosis, n			
Acute	9	20	.304
Lymphoma	0	6	
Type of donor, n			
HLA-matched related	7	13	.072
HLA-mismatched related	1	0	
HLA-matched unrelated, BM	1	4	
Unrelated, cord blood	0	9	
Source of stem cells, n			
BM	5	11	.109
Peripheral blood	4	6	
Cord blood	0	9	
HTLV-1 serostatus of donor, n			
HTLV-1 Ab positive	1	4	1.000
HTLV-1 Ab negative	8	22	
Status at allo-SCT, n			
CR	3	6	.930
Partial remission	2	6	
Primary induction failure	2	8	
Relapse	2	6	
Conditioning for allo-SCT, n			
Myeloablative			.456
TBI-based	3	7	
Non TBI-based	0	4	
Reduced intensity			
Fludarabine-based	6	15	
GVHD prophylaxis, n			
Cyclosporine	4	2	.063
Tacrolimus	0	5	
Cyclosporine + short-term methotrexate	3	12	
Tacrolimus + short-term methotrexate	2	7	
GVHD after allo-SCT, n			
Acute			.490
No	6	13	
Grade 1	0	3	
Grade 2-4	3	10	
Chronic			.239
No	3	17	
Yes	3	5	
Not evaluated	3	4	
Attaining CR after allo-SCT, n			
Yes	7	23	.586
No	2	3	
Interval from allo-SCT to relapse, mo (range)	2.8 (0.4-100.7)	3.6 (0.4-45.9)	.836
Time of allo-SCT			
1997-2003	2	8	1.000
2004-2010	7	18	

TBI indicates total body irradiation.

obtained and 7 patients received multiple infusions with sequential T-cell dose escalation. Five of 6 patients who received pre-DLI therapy showed clinical response to DLI (4 CRs and 1 PR). In 3 CR patients who received multiple infusions, the effect of first DLI was PR in 2 patients (UPN 3 and 5) and SD in 1 patient (UPN 4). Four patients (UPN 6, 7, 8, and 9) did not experience any response even after the administration of multiple DLIs with escalated T-cell doses. The total number of DLIs given to UPN 2 and UPN 4 were 3 and 4, respectively. Two patients (UPN 4 and 5) were alive in CR at the time of analysis with follow-up times from relapse or progression of 47.7 and 69.4 months, respectively. The other 2 patients who achieved CR died of bacterial infection without relapse (UPN 1) and of progression of ATL (UPN 3) at 45.0 and 19.9 months after relapse, respectively. One patient with PR after DLI (UPN 2) experienced a relapse at 1.2 months from the first DLI and died of ATL at 16.9 months from the first relapse after allo-SCT. Among patients with CR or PR after DLI, the median remission duration was 37.0 months (range, 1.2-68.5).

One patient (UPN 9) who received pre-DLI therapy and 3 patients (UPN 6, 7, and 8) who did not receive pre-DLI therapy did not achieve any remission. These 4 patients died of ATL within 9 months after the first DLI.

Factors significantly associated with clinical responses to DLI were the administration of pre-DLI therapy ($P = .018$) and absence of GVHD at relapse or progression of ATL ($P = .018$). The distribution of the T-cell dose of the first DLI tended to be skewed toward higher numbers in patients who responded (median 10.0×10^6/kg, range $5.5\text{-}12.0 \times 10^6$/kg) relative to those without a response (median 6.0×10^6/kg, range $5.0\text{-}8.2 \times 10^6$/kg; $P = .0617$). The other factors, including year of transplantation, were not significantly associated with the response. Interestingly, 3 of 5 patients who achieved remission by DLIs had skin involvement at the time of relapse or progression, but this association was not significant ($P = .1667$).

Six patients experienced the emergence or progression of GVHD after DLIs. Three of 4 CR patients (UPN 1, 4, and 5) had chronic GVHD with oral lichenoid change as a common symptom and had been kept in continuous remission for more than 2 years after the first DLI. Two patients (UPN 1 and 9) developed chronic GVHD, including bronchiolitis obliterans and cryptogenic organizing pneumonia, respectively. In 4 patients (UPN 1, 2, 5, and 8), IS was resumed for the treatment of chronic GVHD after DLI.

Treatments for patients in the non-DLI group

Of 26 patients who did not receive DLI, 6 patients had IS discontinued before the relapse or progression of persistent ATL after allo-SCT and all received cytoreductive therapy. Three of these 6 patients (UPN 10, 11, and 12) achieved CR and were alive at the time of analysis, with follow-up times from relapse or progression of 63.9, 118.6, and 19.0 months, respectively (Table 3). The common characteristic of these 3 patients is that they all experienced local relapse (ie, CNS relapse, localized lymph node relapse, or localized bone relapse) and received local cytoreductive therapies (ie, local radiation therapy or intrathecal injections).

For 20 patients with IS at the time of relapse or progression, withdrawal of IS was performed as a first intervention. A total of 5, 1, and 2 patients developed severe acute GVHD (grade II-IV), limited type chronic GVHD, and extensive type chronic GVHD after the withdrawal of IS, respectively. Discontinuation of IS alone resulted in CR for 2 patients, along with the emergence of GVHD. One of these patients (UPN 13) remained in CR for 46.7 months with limited type chronic GVHD (oral lichenoid change), although the other eventually died of acute GVHD. Seventeen patients received either chemotherapy (n = 16) or local radiation therapy (n = 1) as an initial therapy after discontinuation of IS. These salvage treatments resulted in SD in 2 patients and PD in 15 patients. These 17 patients could not receive DLI for the following reasons: in 5 patients who had cord blood as the donor

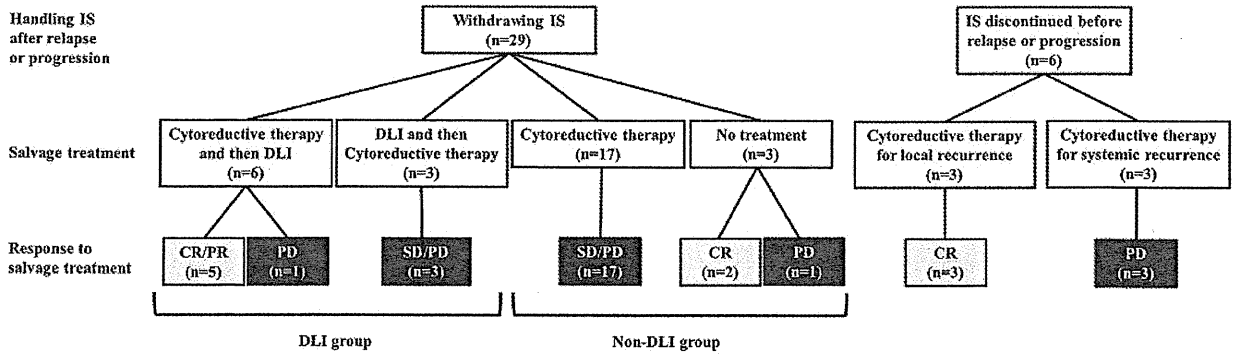

Figure 1. Clinical course of posttransplantation patients with relapse or progression of ATL after allo-SCT.

source of SCT, DLI was not applicable; in 4 patients, attempts at collecting lymphocytes from an unrelated donor was unsuccessful; in 3 patients, severe GVHD (acute GVHD grade II-IV or extensive type chronic GVHD) emerged after the discontinuation of IS and DLI was not warranted; and in 5 patients, disease progressed very rapidly and resulted in death within 1 month after the relapse. Eleven of 17 patients received additional salvage treatments after the initial cytoreductive therapy, including second allo-SCT from unrelated cord blood (n = 1). All 17 patients died of disease progression; the patient who received the second cord blood transplantation died of disease progression at day 8 after transplantation.

OS

For all patients, the median survival time after relapse or progression was 6.2 months and estimated OS after relapse or progression was 19.3% (95% confidence interval [CI]: 8.2%-33.9%) at 3 years. Median survival times after relapse or progression were 16.9 months in the DLI group and 3.9 months in the non-DLI group (Figure 2). Estimated OS rates after relapse or progression were 33.3% (95% CI, 7.8%-62.3%) and 14.4% (95% CI, 4.1%-30.9%) at 3 years in DLI and non-DLI groups, respectively.

Discussion

Relapse of ATL after allo-SCT is one of the main causes of treatment failure after allo-SCT and remains a significant therapeutic challenge. In the present study, the most common initial intervention for these patients was the withdrawal of IS. The remission (CR + PR) rate by this procedure alone was only 7% (2 of 29), suggesting that mere discontinuation of IS may not provide enough effect for ATL. However, the fact that one of these patients achieved long-term durable remission strongly suggested the existence of the GVATL effect; similar observations have been reported from other groups.[13,19,21,24] In the present study, administration of donor lymphocytes was performed for patients who did not achieve CR by the withdrawal of IS. DLI with or without cytoreductive therapy induced remission (CR + PR) for 5 of 9 patients with median OS of 16.9 months (OS from relapse or progression). Considering the extremely poor outcomes of relapsed ATL patients after allo-SCT, a treatment strategy including DLI seems to be a potential therapeutic option to obtain a response that may lead to a long-term durable remission. However, generally, the prognosis of patients with relapsed ATL or progressive ATL after allo-SCT is still not satisfactory, even with the salvage treatments containing DLI.

It has been reported previously that achieving hematologic remission with DLI is generally a difficult task, especially in patients with a high tumor burden and rapidly proliferating leukemic cells.[25-28,31,32] Therefore, debulking with cytoreductive therapy before DLI was thought to be advantageous.[33] In this analysis, DLI brought CR in 4 patients who responded to pre-DLI therapy. Using pre-DLI therapy, 2 patients (UPN 3 and 5) and 1 patient (UPN 4) obtained PR and SD, respectively, and 1 patient (UPN 1) achieved SD after discontinuation of IS. Five patients (UPN 2, 6, 7, 8, and 9) who did not receive pre-DLI treatment were all in PD before the DLI, and the responses were either SD or PD. These results suggest that the patients with better disease control will be more likely to benefit from DLI. Our data imply that once patients obtain any remission by cytoreductive therapy, DLI is the treatment of first choice if possible.

The regimens for pre-DLI therapy are yet to be established. Such regimens are challenging, as the condition of relapsed patients may vary widely because they often suffer from preexisting transplantation-related complications (eg, infections, organ damage, and GVHD). We believe that intensity of CHOP (vincristine, cyclophosphamide, doxorubicin, and prednisone) is sufficient in this setting because the primary purpose of pre-DLI chemotherapy is to slow down the speed of progression.

In acute lymphoblastic leukemia, it has been suggested that the administration of DLI at the time of detecting minimal residual disease (MRD) could be more effective.[31] However, in ATL, detecting MRD using HTLV-1 provirus load[34] is often limited because the provirus load itself may not reflect the true amount of leukemia cells (HTLV-1–infected donor derived T cells may also exist). ATL cell–specific inverse PCR is capable of detecting real MRD, but it has not been put into clinical practice.

GVHD was closely correlated with disease response to DLI. Four patients (UPN 1, 4, 5, and 13) with long-term remission experienced emergence or progression of GVHD after DLI and no patient showed response to DLI without GVHD, suggesting that GVHD exerts a potent GVATL effect. In the present study, the types of GVHD observed after DLI were chronic, mostly with oral lichenoid changes. Kami et al reported 2 cases of ATL with posttransplantation relapses who received a single DLI and gained CR but died of exacerbation of the preexisting chronic GVHD.[12] In addition, Kamimura et al reported 2 cases of successful DLI in ATL relapse after allo-SCT and also observed exacerbation of chronic GVHD with oral lichenoid changes.[22] Together with our observations, chronic GVHD seems to be associated with GVATL. Similarly, in the case of acute myeloid leukemia, it has been reported that the development of chronic GVHD was associated

Table 2. DLI and patient outcome

UPN	Age, y*	Sex, recipient/ donor	Type of donor	Status at allo-SCT	Year of allo-SCT	Time of relapse after allo-SCT, mo	Tumor lesion at relapse	Pre-DLI therapy	Status at DLI	Time of DLI after relapse, mo	T-cell dose, × 10^6/kg		Response to DLI	GVHD after DLI (type of cGVHD)	OS after relapse, mo	Cause of death
											Initial	Total				
1	56	M/ F	R-PBSC	CR	2005	1.0	Skin	Oral VP-16	NE	8.0	5.5	5.5	CR	Progression (extensive)	45.0	Infection
2	63	M/M	R-PBSC	CR	2004	2.4	Skin, hypodermis	Half-dose CHOP	PD	0.6	10.0	110.0	PR	Emergence (extensive)	16.9	PD
3	41	M/M	R-BM	PIF	2004	2.8	CNS	IT	PR	0.4	10.0	40.0	CR	Absent	19.9	PD
4	53	M/M	R-BM	PR	2009	100.7	Skin	RT	SD	1.0	12.0	221.0	CR	Emergence (limited)	47.7+	-
5	55	M/ F	R-PBSC	Relapse	2002	0.4	PB, liver, pleural effusion	Half-dose CHOP	PR	0.9	10.0	10.0	CR	Emergence (extensive)	69.4+	-
6	63	M/ F	R-BM	PR	2008	3.1	PB	No	PD	2.3	6.9	33.0	PD	Absent	8.7	PD
7	44	F/ F	R-PBSC	Relapse	1997	10.6	Bone, liver	No	PD	1.2	5.0	15.0	SD	No progression	9.2	PD
8	55	M/M	UR-BM	CR	2010	11.0	Lymph nodes	No	PD	1.4	5.0	65.0	SD	Progression (extensive)	5.7	PD
9	53	M/ F	R-BM	PIF	2009	1.1	Hypodermis	RT	PD	5.0	8.2	40.8	PD	Progression (extensive)	12.1	PD

cGVHD indicates chronic GVHD; R-PBSC, related peripheral blood stem cell; R-BM, related BM; UR-BM, unrelated BM; PB, peripheral blood; PIF, primary induction failure; NE, not evaluated; VP-16, etoposide; IT, intrathecal injection of cytarabine, methotrexate and prednisone; and RT, local radiation therapy.

*Age indicates age at time of relapse or progression.

Table 3. Outcome of patients maintaining CR for more than 1 year after relapse without DLI

UPN	Age at time of relapse, y	Sex, recipient/ donor	Type of donor	Status at allo-SCT	Year of allo-SCT	Time of relapse after allo-SCT, mo	Tumor lesion at relapse	IS at relapse	GVHD at relapse	GVHD after withdrawing IS (type of cGVHD)	Response to withdrawing IS	Salvage treatment	Response to salvage treatment	OS after relapse, mo
10	57	F/M	R-BM	PIF	2005	4.6	CNS	None	Absent		PD	IT only	CR	63.9+
11	55	F/ F	R-BM	PR	2000	14.3	Bone	None	Absent		PD	RT	CR	118.6+
12	63	F/ F	UR-CB	PIF	2007	45.9	Lymph nodes	None	Absent		PD	RT	CR	19.0+
13	50	F/M	R-BM	PR	2005	0.9	Lymph nodes	CsA	Absent	Emergence (limited)	CR	Not done	-	46.7+

R-BM indicates related BM; UR-CB, unrelated cord blood; PIF, primary induction failure; CsA, cyclosporine A; IT, intrathecal injection of cytarabine, methotrexate and prednisone; and RT, local radiation therapy.

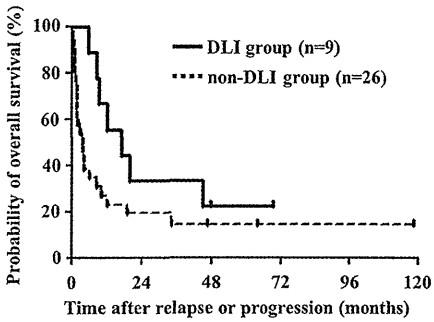

Figure 2. OS after relapse or progression. Median survival times after relapse or progression were 16.9 and 3.9 months in patients treated with and without DLI, respectively.

with superior outcome, whereas the development of acute GVHD had a negative effect on survival.[28] Furthermore, it has also been reported that in the case of nonmyeloablative transplantation for acute myeloid leukemia, relapse rates are lower in patients developing chronic GVHD.[35] Because the development of mild to moderate acute GVHD, not chronic GVHD, has been reported to be associated with a lower risk of disease progression and confers a beneficial influence on the survival of patients who received allo-SCT,[23] the type of GVHD that is associated with durable remission may be different in the settings of allo-SCT and DLI. A definitive assessment of the contribution of the GVATL effect linked with chronic GVHD for the relapse or progression of ATL would require a study with a larger number of patients.

It is of interest that the site of ATL at relapse involved the skin in 3 of 5 patients who responded to DLIs and 2 of 3 patients with skin lesions maintained long-term remissions. It is possible that the relapse in skin is a nonaggressive (ie, low-level) disease and DLI may be effective against these type of diseases. Aggressiveness of ATL at the time of relapse may be a factor determining the effect of DLI. In addition, it is known that GVL-based therapy could induce durable responses in posttransplantation relapsed patients with cutaneous T-cell lymphoma, which is another type of mature T-cell lymphoma.[36-40] Based on these previous results and together with our findings, it is suggested that mature T-cell lymphomas with skin lesions are good targets for GVL-based therapy.

The results of the present study found several factors associated with the efficacy of GVATL-based therapy. However, the number of patients in our study was limited and the treatment protocols used in this cohort of patients were not uniform, so it is possible that these factors exerted a bias and affected the results. Our findings should be interpreted carefully and should be confirmed in prospective studies.

Reinduction chemotherapy alone to treat posttransplantation relapse of ATL has been reported to be largely ineffective. In the present study, however, local cytoreductive therapy alone induced long-durable remission in 3 patients with local recurrence. Interestingly, Simone et al[41] have recently reported that local radiotherapy is useful for the management of ATL patients who have not received allo-SCT. For local relapse, whether posttransplantation or not, local cytoreductive therapy should be considered as one of the treatment options.

In conclusion, the results of our analysis suggest a role of GVATL-based therapy for patients with progression of or relapsed persistent ATL after allo-SCT, but also point out the limitations of GVATL-based therapy. Further experimental and clinical research is required to enhance the GVATL effect to overcome the obviously high capacity of leukemic cells that escape from an allogeneic immune reaction. Such research may lead to more effective and less toxic methods of using adoptive GVATL-based therapy for this disease.

Acknowledgments

The authors thank the many hematologists in the Department of Hematology, Atomic Bomb Disease and Hibakusya Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, for the diagnosis and treatment of patients with ATL.

This study was supported in part by a grant-in-aid from the Ministry of Health and Welfare of Japan and a grant-in-aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Authorship

Contribution: H.I., J.T., T.F., and Y. Miyazaki conceived and designed the study; H.I., H. Tsushima, J.T., T.F., H. Taniguchi, S.S., K.A., Y.S., E.M., R.Y., Y.O., D.I., Y.I., S.Y., T.H., Y. Moriuchi, and Y. Miyazaki collected and analyzed the data; H.I., H. Tsushima, and Y. Miyazaki performed the statistical analysis, wrote the manuscript, and created the figures and tables; and all authors critically reviewed the manuscript and read and approved the final version of the manuscript.

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

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blood

2012 120: 1734-1741
Prepublished online June 11, 2012;
doi:10.1182/blood-2012-03-414490

Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study

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Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.

Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study

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Adult T-cell leukemia-lymphoma (ATL) is an intractable mature T-cell neoplasm. We performed a nationwide retrospective study of allogeneic hematopoietic stem cell transplantation (HSCT) for ATL in Japan, with special emphasis on the effects of the preconditioning regimen. This is the largest study of ATL patients receiving HSCT. Median overall survival (OS) and 3-year OS of bone marrow or peripheral blood transplantation recipients (n = 586) was 9.9 months (95% confidence interval, 7.4-13.2 months) and 36% (32%-41%), respectively. These values for recipients of myeloablative conditioning (MAC; n = 280) and reduced intensity conditioning (RIC; n = 306) were 9.5 months (6.7-18.0 months) and 39% (33%-45%) and 10.0 months (7.2-14.0 months) and 34% (29%-40%), respectively. Multivariate analysis demonstrated 5 significant variables contributing to poorer OS, namely, older age, male sex, not in complete remission, poor performance status, and transplantation from unrelated donors. Although no significant difference in OS between MAC and RIC was observed, there was a trend indicating that RIC contributed to better OS in older patients. Regarding mortality, RIC was significantly associated with ATL-related mortality compared with MAC. In conclusion, allogeneic HSCT not only with MAC but also with RIC is an effective treatment resulting in long-term survival in selected patients with ATL. (*Blood*. 2012;120(8):1734-1741)

Introduction

Adult T-cell leukemia-lymphoma (ATL) is an aggressive peripheral T-cell neoplasm caused by human T-cell lymphotropic/leukemia virus type-1. It has a very poor prognosis.[1-4] A recent phase 3 trial for previously untreated patients with aggressive ATL (acute, lymphoma, or unfavorable chronic type) aged 33 to 69 years demonstrated that the dose-intensified multidrug regimen VCAP-AMP-VECP resulted in a median overall survival (OS) and OS at 3 years of 12.7 months and 24%, respectively. The OS plot for this treatment did not reach a plateau.[5] Alternatively, based on a meta-analysis, Bazarbachi et al proposed that zidovudine (AZT) and interferon (IFN)–α should be considered the standard for first-line therapy in patients with acute, chronic, or smoldering types of ATL. They reported median OS and 5-year OS for acute-type ATL treated with AZT/IFN-α to be 9 months and 28%, respectively, whereas these values were 7% and 0%, respectively, for lymphoma-type ATL.[6] These results indicate that conventional chemotherapeutic agents alone, even including AZT/IFN-α, yield few or no long-term remissions or potential cures in ATL patients.

Although early experience in myeloablative chemoradiotherapy together with autologous hematopoietic stem cell rescue for ATL was associated with a high incidence of relapse and fatal toxicities,[7] allogeneic hematopoietic stem cell transplantation (HSCT) has been explored as a promising alternative treatment that can provide long-term remission in a proportion of patients with ATL.[8-10] Therefore, we previously performed a nationwide retrospective study of ATL patients who received allogeneic HSCT in Japan before December 31, 2005, with special emphasis on the effect of the graft source: 296 patients received bone marrow (BM) and/or peripheral blood stem cells (PBSCs) and 90 received cord blood.[11] We concluded that allogeneic HSCT using currently available sources is an effective treatment in selected patients with ATL, although greater effort is warranted to reduce treatment-related

Submitted March 9, 2012; accepted June 4, 2012. Prepublished online as *Blood* First Edition paper, June 11, 2012; DOI 10.1182/blood-2012-03-414490.

There is an Inside Blood commentary on this article in this issue.

The online version of the article contains a data supplement.

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mortality (TRM). In addition, the use of unrelated cord blood as a stem cell source was associated with lower survival, with a median OS and unadjusted 3-year probability of OS of 2.6 months and 17% (95% confidence interval [CI], 9%-25%), respectively. Because the results suggested that allogeneic BM and PBSCs could be considered to be the more standard donor forms, rather than unrelated cord blood, for transplantation in ATL, as a next step, here we report results of a nationwide retrospective study of Japanese ATL patients receiving allogeneic HSCT, especially focusing on bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT), with special emphasis on the effects of the preconditioning regimen. Our current analysis included the previous cohort[11] (January 1996–December 2005) with updated clinical information as well as data on one patient who received allogeneic HSCT in February 1992 and patients who received allogeneic HSCT after December 2005. It is thought that allogeneic HSCT with reduced intensity conditioning (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 than conventional myeloablative conditioning (MAC). In this context, RIC might be suitable for ATL because several reports have suggested the existence of graft-versus-T-cell lymphotropic/leukemia virus type-1 or graft-versus-ATL effects.[12-18] In addition, RIC might be associated with reduced TRM, which has represented a significant obstacle to successful allogeneic HSCT for ATL patients.[11] Furthermore, ATL has a long latency and occurs in older individuals at a median age of nearly 60 years.[19,20] There is the possibility that HSCT with RIC can provide clinical benefits for those older patients who hardly benefit from allogeneic HSCT with MAC. Here, we performed multivariate analyses of OS and treatment-related or ATL-related mortality after allogeneic BMT and PBSCT and have identified factors influencing transplantation outcomes in ATL patients.

Methods

Collection of data

Data on patients with ATL who had received their first allogeneic BMT, PBSCT, or BMT + PBSCT between February 1992 and December 2009 were collected from nationwide survey data of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). Cases with missing preconditioning or survival data were excluded, with the result that 586 patients were included in the analysis. Data collected for analysis included the patients' clinical characteristics such as age at transplantation, sex, disease status at transplantation, date of transplantation, time from ATL diagnosis to transplantation, performance status (PS) according to the Eastern Cooperative Oncology Group criteria at transplantation, source of stem cells, relationship between recipient and donor, ATL clinical subtype,[1] preconditioning regimens, date alive at last follow up, date and cause of death, and incidence and severity of acute graft-versus-host disease (GVHD). When serologic or molecular typing for HLA-A, HLA-B, and HLA-DR were identical between the recipient and the related donor, we determined the relationship as HLA-matched related. As a control, data on patients with ATL who had received their first unrelated cord blood transplantation (CBT) between March 2001 and December 2009 were collected from the nationwide survey data of the JSHCT. Cases with missing survival data were excluded, resulting in the inclusion of 174 patients in the present study. The study was approved by the data management committees of the JSHCT, 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 transplantation until death, and patients who remained alive at the time of the last follow-up were censored. For analysis, patients were divided into 2 age groups, either $>$ or $\leq$ 55 years, because the Japanese Clinical Oncology Group is currently conducting a phase 2 study of strategies including allogeneic HSCT other than CBT with MAC for ATL patients aged 20 to 55 years (UMIN000004147). Reported causes of death were reviewed and categorized into ATL-related or TRM. ATL-related mortality was defined as death caused by relapse or progression of ATL in patients who survived for at least 1.0 month after transplantation 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[21] by the physicians who performed transplantations at each institution. Patients undergoing allogeneic BMT or PBSCT were divided into 2 groups based on the preconditioning regimens, with 1 group being MAC and the other group RIC. MAC or RIC was defined according to the proposals by Giralt et al[22] and Bacigalupo et al,[23] with a slight modification. In the present study, MAC was defined as any regimen that includes (1) $\geq$ 5 Gy of total body irradiation (TBI) as a single fraction or $\geq$ 8 Gy fractionated, (2) busulfan (BU) $>$ 8 mg/kg orally or the intravenous equivalent, or (3) melphalan (Mel) $>$ 140 mg/m^2. All other regimens were classified as RIC. MAC was further subdivided into 4 groups as follows: TBI (n = 208), BU (n = 46), Mel (n = 21), and other types (n = 3). RIC also was subdivided into 3 groups: fludarabine (Flu) + BU (n = 165), Flu + Mel (n = 86), and other types (n = 49).

Statistical analysis

Descriptive statistics were used for summarizing variables related to patient demographics and transplant characteristics. Comparisons among the groups were performed by Fisher exact test as appropriate for categorical variables. The probability of OS was estimated according to the Kaplan-Meier method. The Cox proportional hazard model was used for multivariate analyses for OS using all independent variables in the model and then using a stepwise selection method by minimizing the Akaike Information Criterion (AIC). The AIC penalizes overparametrization, and variables are retained only when the model improves enough to balance the number of parameters. The lower the AIC, the better the predictive model fits the data.[24] Our inspection of plots of OS estimates versus follow-up time indicated that the assumption of proportional hazards for all variables used seemed to be valid. In the Cox proportional hazard model, incidence and severity of acute GVHD was treated as a time-varying covariate[25] as described previously.[12] Fine and Gray proportional hazard modeling was used to estimate the effect of the same variables used in multivariate analysis of OS on the cumulative incidence of TRM and ATL-related mortality, respectively.[26,27] All analyses including competing risk analysis[28,29] were performed using the cmprsk package of R Version 2.9.0 for Windows statistics software. Statistical significance was set at $P < .05$.

Results

Patients' characteristics

Among 586 ATL patients who received allogeneic BMT or PBSCT (mean age, 52 years; median, 53 years; range, 15-72 years), 280 received MAC (mean age, 48 years, median, 49 years; range, 15-69 years) and the remaining 306 received RIC (mean age, 56 years; median, 57 years; range, 28-72 years). Characteristics of these ATL patients are shown in Table 1. In comparison with MAC recipients, significantly more RIC recipients belonged to the older age group (56-72 years), more often received PBSCs as the stem cell source and more frequently had a related donor transplantation. There was no significant difference between MAC and RIC recipients regarding PS distribution from 0 to 4, but unknown PS was observed in significantly more MAC recipients than RIC recipients. There were no significant differences between MAC and

Table 1. Characteristics of ATL patients receiving allogeneic HSCT

Characteristic	MAC	RIC	P
Total patients, no. (%)	280	306	
Age range at transplantation, y			< .001
15-55	248 (89)	124 (41)	
56-72	32 (11)	182 (59)	
Sex			.135
Female	120 (43)	151 (49)	
Male	160 (57)	155 (51)	
Disease status at transplantation			.206
CR	96 (34)	112 (37)	
Non-CR	160 (57)	179 (58)	
Unknown	24 (9)	15 (5)	
Year.month of transplantation			.473
1992.2-2004.12	71 (25)	78 (25)	
2005.1-2006.11	69 (25)	77 (25)	
2006.11-2008.5	76 (27)	68 (22)	
2008.5-2009.12	64 (23)	83 (27)	
Time from diagnosis to transplantation, mo			.569
0.5-4.9	74 (26)	72 (24)	
4.9-6.9	66 (24)	79 (26)	
6.9-10.1	74 (26)	71 (23)	
≥10.1	65 (23)	81 (26)	
PS at transplantation			.004
0	102 (36)	119 (39)	
1	121 (43)	143 (47)	
2	29 (10)	25 (8)	
3	4 (1)	12 (4)	
4	3 (1)	2 (1)	
Unknown	21 (8)	5 (2)	
Source of stem cells			< .001
BM	212 (76)	186 (60)	
Peripheral blood	68 (24)	118 (39)	
BM + peripheral blood	0 (0)	2 (1)	
Relationship between recipient and donor			.019
HLA-matched related	96 (34)	117 (38)	
HLA-mismatched related	21 (8)	42 (14)	
HLA-unknown related	1 (0)	1 (0)	
Unrelated	162 (58)	146 (48)	
ATL clinical subtype			.253
Chronic, smoldering	10 (4)	6 (2)	
Acute	163 (58)	170 (56)	
Lymphoma	79 (28)	87 (28)	
Unknown	28 (10)	43 (14)	

RIC recipients regarding sex, disease status at transplantation (in complete remission [CR], not in CR, or unknown), and ATL clinical subtypes (chronic/smoldering, acute, lymphoma, or unknown). There were also no significant differences between MAC and RIC recipients regarding the date of transplantation and time from diagnosis to transplantation, both of which were equally distributed in quartiles among the 586 cases.

The 174 ATL patients who received unrelated CBT were aged 54 years, on average, with a median of 55 years and range of 27 to 79 years. There were 69 females and 105 males, with an ATL status at transplantation of CR (n = 50), not in CR (n = 115), and unknown (n = 9).

As for infectious complications, 145 of the 280 MAC recipients had bacterial infection, and 94 did not. Information on bacterial infection was missing for the remaining 41 MAC recipients. As for fungal infection, 23 and 219, respectively, did and did not have fungal infection; no such information was available on 38 patients. As to viral infection, 65 and 177, respectively, did and did not experience a viral infection, with such data missing on the remaining 38 patients. When we examined data on infectious complications in the RIC recipients, we found that of the 306 RIC recipients 134 had bacterial infection and 121 did not, with data unavailable for the remaining 51 patients. Twenty-three RIC recipients had fungal infection and 232 did not; no such information was available for 51 patients. As to viral infection, 57 and 199 patients, respectively, had and did not have viral infection; no information was available on the remaining 50 patients.

OS of patients receiving allogeneic HSCT

The unadjusted 3-year probability of OS was 36% (95% CI, 32%-41%) in the 586 ATL patients receiving allogeneic BMT or PBSCT and 21% (95% CI, 15%-29%) in the 174 patients receiving unrelated CBT. The median OS of the former was 9.9 months (95% CI, 7.4-13.2 months) and of the latter, 4.3 months (95% CI, 3.2-6.5 months; Figure 1A).

The unadjusted 3-year probability of OS was 39% (95% CI, 33%-45%) in the 280 ATL patients receiving MAC and 34% (95% CI, 29%-40%) in the 306 patients receiving RIC. The median OS of the former was 9.5 months (95% CI, 6.7-18.0 months), and of the latter 10.0 months (95% CI, 7.2-14.0 months; Figure 1B).

Multivariate analysis of factors influencing OS in ATL patients receiving allogeneic BMT or PBSCT

Of the 586 ATL patients receiving allogeneic HSCT other than unrelated CBT, 4 were excluded because of lack of data on the time from diagnosis to transplantation, 2 were excluded because of receiving BMT and PBSCT together, and 2 were excluded because of lack of data on HLA. Multivariate analysis of OS was therefore conducted on a total of 578 patients (Table 2). The following 10 variables were analyzed: age (15-55 or 56-72 years), sex, disease status (CR, not CR, or unknown), date of transplantation (1992.2-2004.12, 2004.12-2006.10, 2006.10-2008.4, or 2008.4-2009.12), time

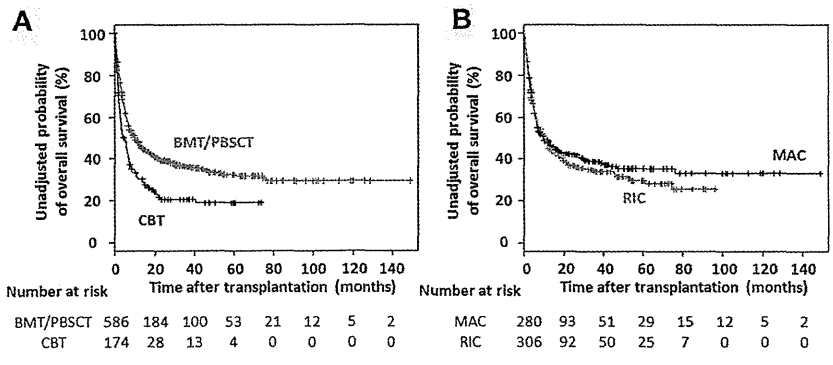

Figure 1. OS of ATL patients receiving allogeneic HSCT. (A) Kaplan-Meier curves of estimated OS in ATL patients receiving allogeneic BMT, PBSCT, or unrelated CBT. (B) Kaplan-Meier curves of estimated OS in ATL patients receiving allogeneic BMT or PBSCT with MAC or RIC.

Table 2. Multivariate analysis of factors influencing OS in ATL patients receiving allogeneic HSCT

Variable	No.	HR	95% CI	P
Age range at transplantation, y				
15-55	368	1.000		Reference
56-72	210	1.334	(1.035-1.719)	.026
Sex				
Female	267	1.000		Reference
Male	311	1.376	(1.113-1.702)	.003
Disease status at transplantation				
CR	205	1.000		Reference
Non-CR	335	1.940	(1.511-2.490)	< .001
Unknown	38	1.744	(1.114-2.731)	.015
PS				
0	219	1.000		Reference
1	260	1.498	(1.171-1.916)	.001
2-4	74	4.057	(2.957-5.565)	< .001
Unknown	25	1.489	(0.863-2.570)	.153
Relationship between recipient and donor				
HLA-matched related	210	1.000		Reference
HLA-mismatched related	62	1.296	(0.917-1.831)	.142
Unrelated	306	1.276	(1.009-1.613)	.042
Preconditioning regimen				
MAC	278	1.000		Reference
RIC	300	1.087	(0.845-1.398)	.515

from diagnosis to transplantation (0.5-4.9, 4.9-6.9, 6.9-10.1, or 10.1-143.2 months), PS (0, 1, 2-4, or unknown), source of stem cells (BM or PBSCs), relationship between recipient and donor (HLA-matched related, HLA-mismatched related, or unrelated), ATL clinical subtype (chronic/smoldering, acute, lymphoma, or unknown), and preconditioning regimen (MAC or RIC). Five variables, age, sex, disease status, PS, and relationship between recipient and donor, were retained by stepwise Cox regression analysis by minimizing the AIC, as was the preconditioning regimen, which received special emphasis in this study. Of these 6 variables, the following 5 significantly affected OS: older age (56-72 years compared with 15-55 years; hazard ratio [HR], 1.334; 95% CI, 1.035-1.719), male sex (HR, 1.376; 95% CI, 1.113-1.702), not being in CR compared with CR (HR, 1.940; 95% CI, 1.511-2.490), worse PS (1 compared with 0; HR, 1.498; 95% CI, 1.171-1.916, 2-4 compared with 0; HR, 4.057; 95% CI, 2.957-5.565), and transplantation from an unrelated donor compared with HLA-matched related donor (HR 1.276; 95% CI, 1.009-1.613).

Multivariate analysis of factors influencing OS including acute GVHD in ATL patients receiving allogeneic BMT or PBSCT

Of the 586 ATL patients receiving allogeneic HSCT other than unrelated CBT, 2 were excluded because of lack of data on HLA and 57 were excluded because of missing any data on the time from transplantation to onset of acute GVHD or the severity of acute GVHD. Thus, multivariate analysis on 527 ATL patients was performed using the following 7 variables: age, sex, disease status, PS, relationship of the donor to the recipient, preconditioning regimen, and incidence and severity of acute GVHD. Of these, 5 variables significantly affected OS; they were male sex (HR, 1.472; 95% CI, 1.168-1.855), not in CR (HR, 1.943; 95% CI, 1.491-2.532), worse PS (1 compared with 0; HR, 1.534; 95% CI, 1.182-1.991, 2-4 compared with 0; HR, 3.223; 95% CI, 2.256-4.605), transplantation from an unrelated donor compared with that from an HLA-matched related donor (HR, 1.449; 95% CI, 1.115-1.882), and acute GVHD. HRs for death of recipients having grades 1 or 2 and 3 or 4 acute GVHD compared with recipients having no acute GVHD were 0.753 (95% CI, 0.576-0.984), and 1.538 (95% CI, 1.123-2.107), respectively (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). This result suggesting that an appropriate level of acute GVHD contributed to better OS but that severe GVHD contributed to inferior OS was consistent with our previous report.[12] In contrast, the inclusion of a posttransplant time-varying covariate, acute GVHD, into the present study resulted in a decrease in the number of evaluable patients. In addition, the inclusion of patients who died so early after transplantation that onset of acute GVHD would not yet have occurred provided unacceptable bias leading to the finding that recipients without acute GVHD had worse OS compared with recipients with acute GVHD. Thus, we conducted the present subsequent analyses that aimed to clarify the significance of the preconditioning regimen MAC versus RIC in ATL patients by only including time-fixed covariates that were present pretransplantation.

Interactions of the preconditioning regimen with age, disease status, and PS for OS

Statistical interactions between the preconditioning regimens and age, disease status, or PS at transplantation for OS were tested by adding an interaction term into the multivariate analysis that included the following 6 variables: age, sex, disease status,

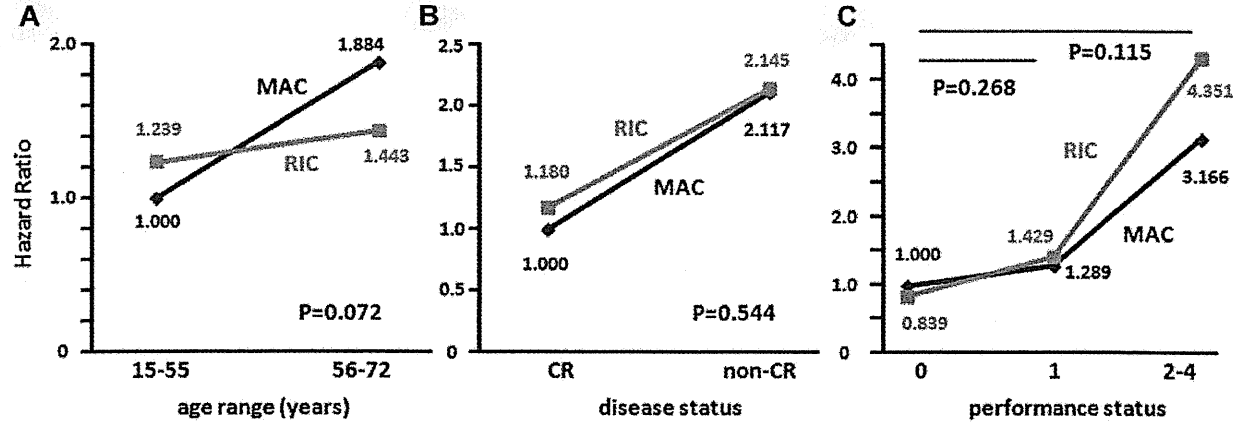

Figure 2. Interactions of the preconditioning regimen with age, disease status, and performance status for OS. Statistical interactions between the preconditioning regimens (MAC or RIC) and age range (15-55 vs 56-72 years; A), disease status (CR vs non-CR; B), and performance status (0 vs 1 or 2-4; C) were analyzed.

Table 3. Multivariate analysis of factors influencing OS in the subgroup of ATL patients receiving transplantation after MAC

Variable	No.	HR	95% CI	P
Age range at transplantation, y				
15-55	246	1.000		Reference
56-72	32	1.667	(1.051-2.643)	.030
Sex				
Female	120	1.000		Reference
Male	158	1.458	(1.053-2.019)	.023
Disease status at transplantation				
CR	95	1.000		Reference
Non-CR	159	2.071	(1.409-3.043)	< .001
Unknown	24	1.536	(0.822-2.870)	.178
PS				
0	102	1.000		Reference
1	120	1.322	(0.909-1.922)	.144
2-4	36	3.073	(1.920-4.919)	< .001
Unknown	20	1.109	(0.565-2.175)	.764
Relationship between recipient and donor				
HLA-matched related	96	1.000		Reference
HLA-mismatched related	21	1.165	(0.618-2.196)	.637
Unrelated	161	1.323	(0.920-1.902)	.131
Type of MAC				
TBI-based	208	1.000		Reference
BU-based	46	0.757	(0.475-1.206)	.242
Mel-based	21	1.388	(0.819-2.353)	.223
Others	3	0.666	(0.158-2.817)	.581

PS, relationship of the donor to the recipient, and preconditioning regimen. Among the 578 patients for whom multivariate analysis for OS was conducted (Table 2), when the HR for death of MAC recipients of a younger age (15-55 years) was determined as 1.000, the HRs of MAC recipients in the older age group (56-72 years) and RIC recipients in the younger and older age groups were 1.884, 1.239, and 1.443, respectively ($P_{interaction} = 0.072$; Figure 2A). When the HR for death of MAC recipients with CR at transplantation was determined as 1.000, HRs of MAC recipients with non-CR and RIC recipients with CR and non-CR were 2.117, 1.180, and 2.145, respectively ($P_{interaction} = 0.544$; Figure 2B). When the HR for death of MAC recipients with PS 0 at transplantation was determined as 1.000, HRs of MAC recipients with PS 1 and RIC recipients with PS 0 and 1 were 1.289, 0.839, and 1.429, respectively ($P_{interaction} = 0.268$), and HRs of MAC and RIC recipients with PS 2 to 4 were 3.166 and 4.351, respectively ($P_{interaction} = 0.115$; Figure 2C).

Multivariate analysis of factors influencing OS in the subgroup of ATL patients who had transplantation after MAC

Of the 280 ATL patients who received MAC, 1 patient was excluded because of missing data on the time from diagnosis to transplantation and one was excluded because of lack of data on HLA. Multivariate analysis was therefore conducted on 278 patients and included the variables of age, sex, disease status, PS, and relationship of the donor to recipient, which were found to have significantly affected OS in the entire subject population (Table 2). Also included was a sixth variable, the type of MAC (TBI, BU, Mel-based, or others). Of these 6 variables, 4 significantly affected OS, namely, older age (HR, 1.667; 95% CI, 1.051-2.643), male sex (HR, 1.458; 95% CI, 1.053-2.019), not in CR (HR, 2.071; 95% CI, 1.409-3.043), and worse PS (2-4 compared with 0; HR, 3.073; 95% CI, 1.920-4.919; Table 3).

Multivariate analysis of factors influencing OS in the subgroup of patients receiving transplantations after RIC

Of the 306 ATL patients receiving RIC, 3 were excluded because of lack of data on the time from diagnosis to transplantation, 2 were excluded because of receiving BMT and PBSCT together, and 1 was excluded because of lack of data on HLA. Thus, multivariate analysis on 300 ATL patients was performed using the following 6 variables: age, sex, disease status, PS, relationship of the donor to the recipient, and type of RIC (Flu + BU, Flu + Mel-based, or others). Of these, 4 significantly affected OS, namely, male sex (HR, 1.475; 95% CI, 1.100-1.978), not in CR (HR, 1.743; 95% CI, 1.249-2.432), worse PS (1 compared with 0; HR, 1.803; 95% CI, 1.293-2.516, 2-4 compared with 0; HR, 6.175; 95% CI, 3.908-9.756), and type of RIC (Flu + Mel compared with Flu + BU based; HR, 0.645; 95% CI, 0.453-0.918; Table 4).

Multivariate analysis of TRM and ATL-related mortality

Among the 586 ATL patients receiving allogeneic BMT or PBSCT, 14 could not be assigned to either the TRM or ATL-related mortality category because detailed information regarding cause of death was missing. The Fine and Gray proportional hazards model was applied to the remaining 572 patients to identify variables affecting TRM and ATL-related mortality, respectively. The variables included age, sex, disease status, PS, and relationship between recipient and donor, which was shown to significant affect OS in the entire patient population (Table 2), and the preconditioning regimen, namely, MAC or RIC. Among these variables, sex and PS were significantly associated with TRM. The HR for TRM of male patients was 1.383 (95% CI, 1.026-1.863). HRs for TRM of recipients with PS 1 and PS 2 to 4 compared with PS 0 were 1.509 (95% CI, 1.075-2.118) and 3.004 (95% CI, 1.915-4.714), respectively. Conversely, disease status, PS, and the preconditioning regimen were significantly associated with ATL-related mortality. HR for ATL-related mortality of recipients not in CR was

Table 4. Multivariate analysis of factors influencing OS in the subgroup of patients receiving transplantation after RIC

Variable	No.	HR	95% CI	P
Age range at transplantation, y				
15-55	122	1.000		Reference
56-72	178	1.127	(0.834-1.523)	.435
Sex				
Female	147	1.000		Reference
Male	153	1.475	(1.100-1.978)	.009
Disease status at transplantation				
CR	110	1.000		Reference
Non-CR	176	1.743	(1.249-2.432)	.001
Unknown	14	1.959	(0.998-3.843)	.051
PS				
0	117	1.000		Reference
1	140	1.803	(1.293-2.516)	< .001
2-4	38	6.175	(3.908-9.756)	< .001
Unknown	5	4.979	(1.849-13.409)	.001
Relationship between recipient and donor				
HLA-matched related	114	1.000		Reference
HLA-mismatched related	41	1.279	(0.836-1.959)	.257
Unrelated	145	1.237	(0.895-1.710)	.198
Type of RIC				
Flu + BU-based	165	1.000		Reference
Flu + Mel-based	86	0.645	(0.453-0.918)	.015
Others	49	0.854	(0.557-1.310)	.470

Table 5. Multivariate analysis of TRM and ATL-related mortalities in patients receiving allogeneic HSCT

	TRM				ATL-related mortality			
Variable	No.	HR	95% CI	P	No.	HR	95% CI	P
Age range at transplantation, y								
15-55	116/362	1.000		Reference	93/362	1.000		Reference
56-72	79/210	1.403	(0.954-2.064)	.085	62/210	0.955	(0.658-1.385)	.810
Sex								
Female	75/262	1.000		Reference	66/262	1.000		Reference
Male	120/310	1.383	(1.026-1.863)	.033	89/310	1.226	(0.886-1.697)	.220
Disease status at transplantation								
CR	58/205	1.000		Reference	32/205	1.000		Reference
Non-CR	121/330	1.238	(0.906-1.691)	0.180	114/330	2.203	(1.469-3.302)	< .001
Unknown	16/37	1.507	(0.873-2.603)	0.140	9/37	1.511	(0.663-3.444)	.330
PS								
0	54/213	1.000		Reference	44/213	1.000		Reference
1	91/260	1.509	(1.075-2.118)	.017	74/260	1.272	(0.872-1.856)	.210
2-4	41/75	3.004	(1.915-4.714)	< .001	30/75	1.679	(1.035-2.723)	.036
Unknown	9/24	1.214	(0.614-2.403)	0.580	7/24	1.965	(0.802-4.818)	.140
Relationship between recipient and donor								
HLA-matched related	62/206	1.000		Reference	60/206	1.000		Reference
HLA-mismatched related	18/62	0.924	(0.532-1.606)	0.780	26/62	1.392	(0.873-2.220)	.160
Unrelated	115/304	1.429	(1.033-1.975)	.031	69/304	0.843	(0.589-1.209)	.350
Preconditioning regimen								
MAC	100/274	1.000		Reference	61/275	1.000		Reference
RIC	95/298	0.786	(0.538-1.148)	0.210	94/304	1.579	(1.080-2.308)	.019

2.203 (1.469-3.302). The HR for ATL-related mortality of recipients with PS 2 to 4 compared with PS 0 was 1.679 (95% CI, 1.035-2.723), and the HR of patients receiving RIC compared with MAC was 1.579 (95% CI, 1.080-2.308; Table 5).

Cumulative incidence of TRM and ATL-related mortality

Among the 572 ATL patients receiving allogeneic BMT or PBSCT, the cumulative incidence of TRM one year after transplantation was 32.7% (95% CI, 27.1-38.4) in MAC recipients and 29.2% (95% CI, 24.0-34.5) in RIC recipients. These figures at 3 years were 37.7% (95% CI, 31.8-43.6) and 33.3% (95% CI, 27.7-38.9), respectively (Figure 3). The cumulative incidence of ATL-related mortality 1 year after transplantation was 18.5% (95% CI, 14.1-23.4) for MAC and 25.0% (95% CI, 20.1-30.1) for RIC recipients and was 22.5% (95% CI, 17.5-27.9) and 33.2% (95% CI, 27.6-38.9), respectively, at 3 years (Figure 3).

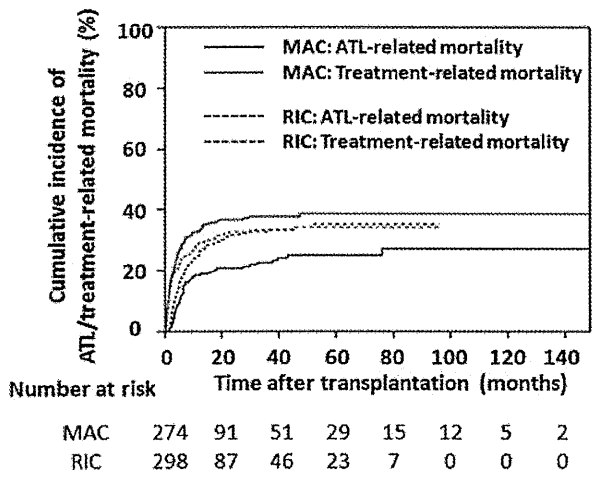

Figure 3. Cumulative incidence of ATL-related and TRMs in patients receiving BMT or PBSCT. Probabilities of ATL-related and TRMs in recipients of MAC or RIC were estimated using cumulative incidence curves to accommodate competing events.

Discussion

To the best of our knowledge, the present study is the largest retrospective study of ATL patients receiving allogeneic HSCT. Results showed that for allogeneic BMT or PBSCT for ATL, RIC was applied more frequently in older patients, as is reasonable and expected. RIC patients more often received PBSCT and had related donors. We surmise this was because RIC was initially proposed in the setting of PBSCT from HLA-matched sibling donors.[30]

The OS plot of ATL patients receiving allogeneic HSCT reached a plateau, leading to long-term survival of a subgroup of ATL patients. Recipients of CBT had a significantly worse prognosis than recipients of BMT or PBSCT, which was consistent with our previous report.[11] Direct comparison of transplantation outcomes between unrelated CBT and the other types of allogeneic HSCT was not possible because the selection of the graft source is an individual process strongly influenced by donor availability and the patient's ATL status. However, even considering such potential biases, the outcome of unrelated CBT seems clearly unsatisfactory. Thus, novel strategies to further improve the outcomes of unrelated CBT are warranted.

Among ATL patients receiving allogeneic BMT or PBSCT, multivariate analysis revealed 5 significant independent variables affecting OS, namely, age, sex, disease status, PS, and relationship between the recipient and donor. Of these factors, younger age, good ATL disease status, and PS at transplantation contributing to better OS were to be expected. The contribution to a better OS of HSCT from HLA-A, -B, and -DR–matched related donors also would be expected. The reason why the female sex was an independent favorable factor is not fully understood but is consistent with results of our previous study.[11] With respect to preconditioning, there was no significant difference in OS between MAC