the method of Gray. In the competing-risk models for engraftment, relapse, GVHD, and infectious diseases, death before these events was defined as a competing risk. The competing-risk regression model of Fine and Grey was used for univariate and multivariate analyses of cumulative incidence. A Cox proportional hazards regression model was used to analyze OS and PFS. Factors associated with a 2-sided P value of $<.10$ in the univariate analysis were included in a multivariate analysis. A backward-stepwise selection algorithm was used, and only the statistically significant variables were retained in the final model. A 2-sided P value of $<.05$ was considered statistically significant.

The following variables were evaluated in these analyses: sex, age at time of HSCT, disease risk (standard risk versus high risk), conditioning regimen for the first HSCT (CST versus RIC versus nonmyeloablative [NMA]), conditioning regimen for the second HSCT (CST versus RIC versus NMA), use of fludarabine (Flu), use of an alkylator-containing regimen, use of total body irradiation (TBI), use of antithymocyte globulin (ATG), stem cell source (PBSCs, BM, or CB) for the second HSCT, immunosuppressive drugs (primary drug: none, cyclosporine, or tacrolimus [TAC]; secondary drug: methotrexate [MTX], mycophenolate mofetil [MMF], neither MTX nor MMF, steroid, or no steroid), HLA disparities (in both graft-versus-host and host-versus-graft directions), and type of GF (primary versus secondary). Standard risk was defined as the first complete remission of acute leukemia or malignant lymphoma, the first chronic phase of chronic myelogenous leukemia, or nonmalignant disease. High risk was defined as other stages of hematologic malignancies and solid tumors. The definitions of conditioning regimens were similar to those used in previous studies [12,13]. Myeloablative conditioning regimens included at least 1 of the following: >8 Gy TBI, >140 mg/m^2 melphalan, or >6.4 mg/m^2 i.v. busulfan (or >8.0 mg/m^2 oral busulfan). NMA conditioning included conditioning regimens with 2 Gy TBI plus a purine analogue, Flu + cyclophosphamide + ATG, Flu + cytarabine + idarubicin, cladribine + cytarabine, or total lymphoid irradiation + ATG. RIC included all other conditioning regimens. Infectious diseases included both clinically and microbiologically documented infections diagnosed by a physician. Statistical analyses were performed using Stata version 11.1 (StataCorp, College Station, TX).

RESULTS

Patients

Recipient and transplantation characteristics are summarized in Table 1. Because of the limited availability of stem cell grafts in Japan, all CB recipients received only single CB unit. The median age of the recipients was 42.5 years (range, 0-75 years). Their diagnoses included AML (n = 71), ALL (n = 40), myelodysplastic syndrome (MDS; n = 52), malignant lymphoma (n = 31), nonmalignant diseases (n = 14), and others (n = 12). Eighty-two patients were classified as standard risk, and 138 were classified as high risk. The conditioning regimen at the first HSCT was CST in 137 patients, RIC in 80 patients, and NMA in 2 patients. Of the 220 patients who had GF, 200 (90.9%) had primary GF and 19 (8.7%) had secondary GF. In these 220 patients, GF was diagnosed after a median of 29 days (range, 12-176) after the first HSCT.

The median interval between the diagnosis of GF and the second HSCT was 11 days (range, 0-89 days). The stem cell source for the second HSCT was CB in 180 patients, BM in 16 patients, and PBSCs in 24 patients. In the BM and PBSC recipients, all except 1 patient with BM received stem cells from a related donor. The patients who underwent PBSCT received stem cells from an HLA 1-locus mismatched donor (n = 1; 4.5%) or a haploidentical donor (n = 21; 95.5%). The patients undergoing BMT received stem cells from an HLA-matched donor (related, n = 2; unrelated, n = 1) or an HLA 1-locus mismatched (n = 2; 12.5%) or haploidentical donor (n = 11; 68.8%). For conditioning, 5, 122 and 77 patients received CST, RIC and NMA, respectively. As for GVHD, prophylaxis included cyclosporine in 79 patients, TAC in 118 patients, and ATG in 38 patients. A short course of MTX was added in 57 patients, and a short course of MMF was added in 21 patients. No patient received posttransplantation cyclophosphamide as GVHD prophylaxis.

Neutrophil Engraftment

The cumulative incidents of neutrophil engraftment according to stem cell source are shown in Figure 1. Engraftment was achieved by day 30 after second HSCT in 39% of CBT recipients, 71% of PBSCT recipients, and 75% of BMT recipients. Engraftment was achieved at median intervals of 21 days (range, 12-97) after CBT, 18 days (range, 0-37 days) after PBSCT, and 14.5 days (range, 9-26 days) after BMT. In the univariate analysis, PBSCT and BMT were associated with a significantly higher probability of engraftment (hazard ratio [HR], 2.5; 95% confidence interval [CI], 1.5-4.3; P = .001 and HR, 2.5; 95% CI, 1.2-5.0; P = .01, respectively). In the multivariate analysis, PBSCT and BMT remained significant variables after adjustment for other independently significant variables, including the use of alkylating agents, HLA disparities, and administration of additional immunosuppressive drugs (Table 2).

Table 1. Patient and Transplantation Characteristics

	CB	BM	PBSCs	Total	*P* Value
Number of patients	180	16	24	220	
Conditioning regimen for first HSCT, n					
CST	114	9	14	137	
RIC	63	7	10	80	
NMA	2	0	0	2	
Unknown	1	0	0	1	.968
Sex of recipient, n					
Male	97	13	11	121	
Female	83	3	13	99	.069
Age of recipient, years, median	44	14	28.5	42.5	.0016
ABO mismatch, n					
Match	57	6	12	75	
Minor	42	3	5	50	
Major	51	4	3	58	
Major/minor	29	0	3	32	
Unknown	1	3	1	5	<.001
HLA disparities (graft-versus-host direction), n					
0	22	3	0	25	
1	59	2	1	62	
2	96	9	13	118	
3	2	2	8	12	
Unknown	1	0	2	3	<.001
HLA disparities (host-versus-graft direction), n					
0	14	5	0	19	
1	60	2	4	66	
2	102	7	8	117	
3	3	2	10	15	
Unknown	1	0	2	3	<.001
Disease risk, n					
0	65	6	11	82	
1	115	10	13	138	.652
Disease, n					
ALL	30	4	6	40	
AML	59	3	9	71	
MDS	45	5	2	52	
Chronic myelogenous leukemia	6	1	1	8	
Lymphoma	28	0	3	31	
Plasma cell disorder	1	0	0	1	
Nonhematologic malignancies	2	0	1	3	
Nonmalignant disease	9	3	2	14	.402
Conditioning regimen, n					
None	10	1	2	13	
CST	4	1	0	5	
RIST	105	8	9	122	
Mini	60	6	11	77	
Unknown	1	0	2	3	.074
TBI, n					
No	123	13	17	153	
Yes	56	2	4	62	
Unknown	1	1	3	5	.001
Alkylating agent, n					
No	59	5	7	71	
Yes	120	10	14	144	
Unknown	1	1	3	5	.005
Flu/cladribine, n					
No	22	2	3	27	
Yes	157	13	18	188	
Unknown	1	1	3	5	.005
Calcineurin inhibitor, n					
None	13	0	2	15	
Cyclosporine	76	1	2	79	
TAC	84	15	19	118	
Unknown	7	0	1	8	.053
Additional immunosuppressive drugs, n					
None	122	4	8	134	
MTX	32	12	13	57	
MMF	19	0	2	21	
Unknown	7	0	1	8	<.001
Steroids, n					
No	160	13	18	191	
Yes	13	3	5	21	
Unknown	7	0	1	8	.147
ATG, n					
None	153	11	13	177	
Yes	26	4	8	38	
Unknown	1	1	3	5	<.001
Engraftment failure of previous transplantation, n					
Primary	162	16	22	200	
Secondary	17	0	2	19	
Unknown	1	0	0	1	<.001
Time from graft failure to transplantation, days, median (range)	12 (0-89)	7 (0-83)	9 (0-34)	11 (0-89)	.115

There were no significant differences between PBSCT and BMT.

OS and PFS

The median follow-up period for surviving patients after second HSCT was 481 days (range, 82-1825 days). The probability of 1-year OS after the second HSCT was 58% with PBSCs, 38% with BM, and 28% with CB (Figure 2A). In the multivariate analysis, after adjustment for age, disease risk, use of calcineurin inhibitors, and use of steroids in GVHD prophylaxis, the probability of 1-year OS was significantly greater after PBSCT than after CBT (HR, 0.45; 95% CI, 0.21-0.95; $P = .036$). The probability of 1-year PFS after the second HSCT was 48% with PBSCs, 34% with BM, and 24% with CB (Figure 2B). After adjustment

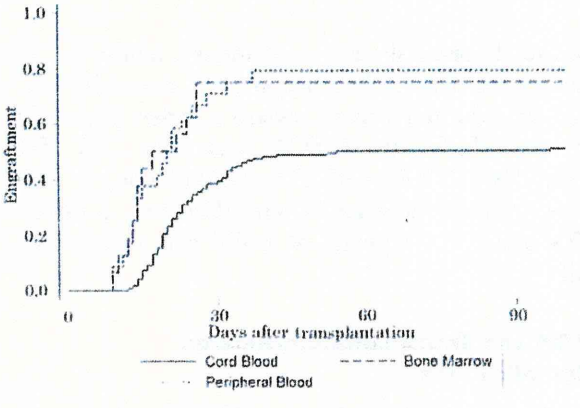

Figure 1. Cumulative incidence of engraftment after a second HSCT in patients according to stem cell source.

Table 2. Multivariate Analysis for Engraftment, OS, and PFS

	HR (95% CI)	P Value
Engraftment		
Stem cell source		
CB	Reference	
BM	2.81 (1.21-6.53)	.016
PBSCs	7.77 (4.16-14.51)	<.001
Alkylating agent		
None	Reference	
Yes	2.69 (1.64-4.41)	<.001
HLA disparities (host-versus-graft direction)		
0	Reference	
1	0.47 (0.22-1.03)	.06
2	0.46 (0.22-0.97)	.041
3	0.21 (0.08-0.61)	.004
Additional immunosuppressive drugs		
None	Reference	
MTX	0.19 (0.06-0.63)	.006
MMF	0.99 (0.66-1.48)	.945
OS		
Stem cell source		
CB	Reference	
BM	0.95 (0.46-1.95)	.881
PBSCs	0.45 (0.21-0.95)	.036
Disease risk		
Normal	Reference	
High	1.74 (1.21-2.49)	.003
Steroids		
None	Reference	
Yes	2.31 (1.37-3.91)	.002
Each additional year older	1.01 (1.00-1.02)	.003
Calcineurin inhibitor		
Cyclosporine	Reference	
None	0.97 (0.53-1.75)	.915
TAC	0.63 (0.44-0.90)	.011
PFS		
Stem cell source		
CB	Reference	
BM	0.95 (0.46-1.96)	.886
PBSCs	0.52 (0.25-1.05)	.066
Disease risk		
Normal	Reference	
High	1.85 (1.29-2.66)	.001
Calcineurin inhibitor		
Cyclosporine	Reference	
None	0.99 (0.55-1.79)	.971
TAC	0.61 (0.43-0.88)	.008
Steroids		
None	Reference	
Yes	2.01 (1.19-3.40)	.009
Each additional year older	1.01 (1.00-1.02)	.014

for age, disease risk, use of calcineurin inhibitors, and use of steroid as GVHD prophylaxis, the multivariate analysis indicated a trend toward a higher probability of 1-year PFS after PBSCT than after CBT (HR, 0.52; 95% CI, 0.25-1.05; $P = .066$) (Table 2). There were no statistically significant differences in OS and PFS between recipients of BMT and recipients of CBT.

NRM and Transplantation-Related Complications

The cumulative incidence of NRM at 1 year after the second HSCT was 29% with PBSCs, 38% with BM, and 60% with CB (Figure 2C). After adjustment for age and use of steroids, the incidence of 1-year NRM was significantly lower after PBSCT than after CBT (HR, 0.43; 95% CI, 0.21-0.87; $P = .019$). The cumulative incidents of grade II-IV acute GVHD were 47% after PBSCT, 31% after BMT, and 19% after CBT (Figure 2D), and the corresponding cumulative incidents of grade III-IV acute GVHD were 44%, 0%, and 12% (Figure 2E). After adjustment for the use of TBI in multivariate analysis, PBSCT was associated with a significantly higher incidence of grade II-IV (HR, 2.8; 95% CI, 1.3-6.3; $P = .011$) (Table 3). After adjustment for the use of steroids as GVHD prophylaxis and the type of conditioning regimen in multivariate analysis, PBSCT was associated with a significantly higher incidence of grade III-IV (HR, 7.3; 95% CI, 2.9-18.7; $P < .001$).

The cumulative incidents of infectious disease at 1 year after the second HSCT were 23% with PBSC, 15% with BM, and 58% with CB (Figure 3). PBSCT and BMT were associated with a significantly lower incidence rate of infectious disease (HR, 0.33; 95% CI, 0.14-0.81; $P = .015$ and HR, 0.21; 95% CI, 0.05-0.87; $P = .032$, respectively). The significant risk factors in the multivariate analyses are listed in Table 3. The major cause of death in our cohort was infectious disease (n = 72); other causes of death were relapse or progression of primary disease (n = 31), organ failure (n = 26), acute GVHD (n = 8), and others (n = 15).

DISCUSSION

In this study, we retrospectively analyzed the outcomes of 220 patients who underwent a second allogeneic HSCT after GF. The largest sample size found in the literature allowed us to analyze the effect of stem cell source on outcome. Neutrophil engraftment was significantly faster after PBSCT and BMT than after CBT. Patients with GF are at increased risk for developing a lethal infectious disease because of prolonged severe pancytopenia, and thus the faster neutrophil recovery after PBSCT and BMT is a highly beneficial effect. The differences in engraftment rate of stem cells from different sources in the present study may be greater than those observed after the first HSCT in previous studies [2-5], possibly because many patients died before engraftment after the second CBT. Infectious disease was the main cause of death in our cohort.

The clinical outcomes after salvage CBT in the present study are comparable to those reported by Waki et al. [8]. The 1-year OS was 28% in the present study and 33% in the study of Waki et al. The engraftment rate was lower in our cohort; however, this difference may be attributable to the fact that Waki et al. excluded patients who died before engraftment within 28 days after second HSCT. Our engraftment rate after PBSCT was comparable to that reported in the

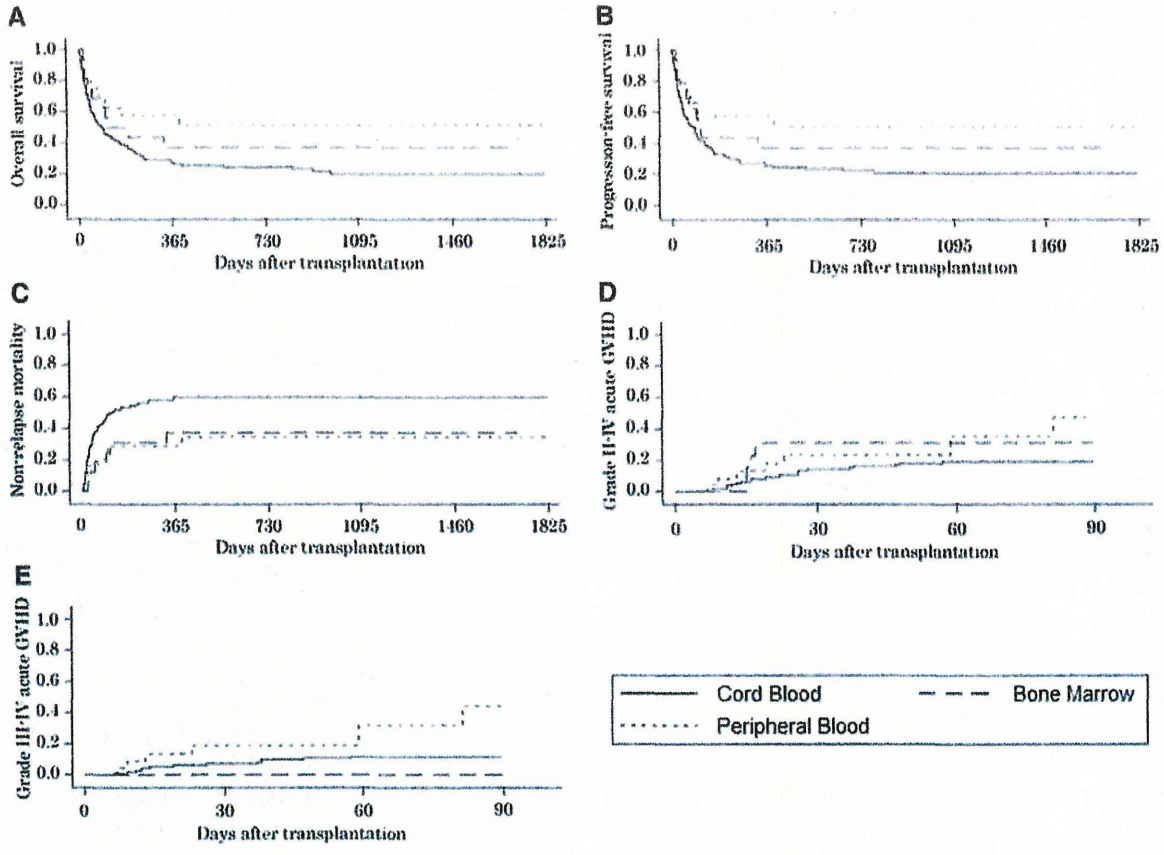

Figure 2. Probability of 1-year OS (A), probability of 1-year PFS (B), cumulative incidence of NRM (C), cumulative incidence of grade II-IV acute GVHD (D), and cumulative incidence of grade III-IV acute GVHD (E) in patients according to stem cell source.

previous NMDP study, but our OS was greater [9]. The poor OS in the NMDP study might be attributable to the longer interval between the diagnosis of GF and the second HSCT (median, 48 days) because they included only patients who underwent unrelated HSCT, which takes more time to coordinate. In addition, the proportion of patients who received a conventional conditioning regimen was significantly higher in the NMDP study than in the present study, possibly contributing to the higher NRM rate in the NMDP study [14]. Most patients in the present study received an RIC or NMA regimen, which might have reduced the incidence of NRM.

The risk of severe GVHD is a major concern when selecting HLA-mismatched PBSCs as the stem cell source for a second HSCT, even with the advantage of faster engraftment. In fact, PBSCT was associated with significantly higher rates of grade II-IV and grade III-IV acute GVHD, as expected given that the majority of PBSC grafts were obtained from HLA-mismatched donors. The incidence rate of NRM was significantly lower after PBSCT, however. In addition, 21 of 22 PBSCT recipients with available HLA information (95%) received stem cells from a 2-3 HLA antigen-mismatched donor. The main cause of death after second HSCT, especially before engraftment, was infectious disease; therefore, an early, significant reduction in the rate of infectious disease after the second HSCT contributed to the reduction in NRM. In addition, our study cohort comprised exclusively Japanese patients, who have a lower incidence of acute GVHD compared with Caucasian patients and can better tolerate HLA-mismatched HSCT without ex vivo T cell depletion [15-17]. The superiority of PBSC compared with CB awaits confirmation in Caucasian patients.

Regarding the conditioning regimen for salvage PBSCT, we performed univariate analysis only because of the limited number of patients. The cumulative incidents of engraftment were 100% with a Flu-based regimen including an alkylator, 78% with a Flu-based regimen without an alkylator, and 0% without any conditioning regimen. The use of a Flu-based regimen including an alkylator was associated with a significantly higher probability of engraftment compared with a Flu-based regimen without an alkylator (HR, 4.5; 95% CI, 1.6-12.8; $P = .0051$). The probability of 1-year OS was 82% with a Flu-based regimen including an alkylator, but only 44% with a Flu-based regimen without an alkylator ($P = .27$). Alkylators

Table 3. Multivariate Analysis for NRM, Acute GVHD, and Infectious Disease

	HR (95% CI)	P Value
NRM		
Stem cell source		
CB	Reference	
BM	0.54 (0.25-1.15)	.111
PBSCs	0.43 (0.21-0.87)	.019
Steroids		
None	Reference	
Yes	2.41 (1.59-3.66)	<.001
Each additional year older	1.01 (1.00-1.02)	.015
Grade II-IV acute GVHD		
Stem cell source		
CB	Reference	
BM	1.74 (0.54-5.62)	.352
PBSCs	2.83 (1.27-6.27)	.011
TBI		
None	Reference	
Yes	2.43 (1.29-4.61)	.006
Grade III-IV acute GVHD		
Stem cell source		
CB	Reference	
BM	<0.01	<.001
PBSCs	7.34 (2.87-18.74)	<.001
Steroids		
None	Reference	
Yes	<0.01	<.001
Conditioning regimen		
None	Reference	
CST	16.12 (1.34-193.80)	.028
RIST	1.93 (0.20-18.75)	.573
Mini	0.94 (0.09-9.60)	.961
All infectious diseases		
Stem cell source		
CB	Reference	
BM	0.21 (0.05-0.87)	.032
PBSCs	0.33 (0.14-0.81)	.015
Additional immunosuppressive drugs		
None	Reference	
MTX	1.09 (0.64-1.85)	.748
MMF	2.25 (1.23-4.10)	.008
Disease risk		
Normal	Reference	
High	0.63 (0.41-0.98)	.039

included cyclophosphamide in 7 patients and melphalan in 3 patients. The majority of patients (79%) received TAC-based GVHD prophylaxis. Therefore, PBSCT with a Flu + alkylator combination regimen followed by TAC-based GVHD prophylaxis seemed to be the preferable course of treatment.

Some limitations of this study warrant considereation. A major limitation is the study's retrospective nature and use of registry data, which make it impossible to identify the decisions made by the physicians regarding stem cell source, conditioning regimen, timing of second HSCT, and so on. Consequently, our analysis might include uncontrolled confounding variables, even though we performed multivariate analysis. Another important limitation is the lack of chimerism data at the time of GF, which prevented us from differentiating GF without donor hematopoiesis from GF with donor hematopoiesis but poor graft function.

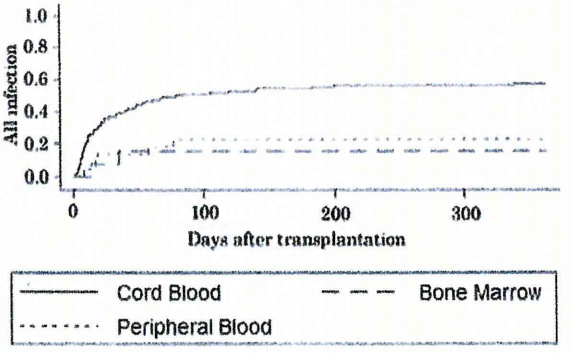

Figure 3. Cumulative incidence of infectious disease in patients according to stem cell source.

In conclusion, this retrospective analysis found that PBSCT was associated with greater and faster engraftment than CBT and led to a significantly better survival, although it did have a higher rate of acute GVHD. Considering the difficulty in performing a randomized controlled trial to compare the effects of stem cell source in patients with GF, PBSCT with a conditioning regimen including Flu and an alkylator may be the preferable salvage therapy, even using PBSCs from a mismatched related/haploidentical donor if necessary, in the emergent situation of GF after CBT.

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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

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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

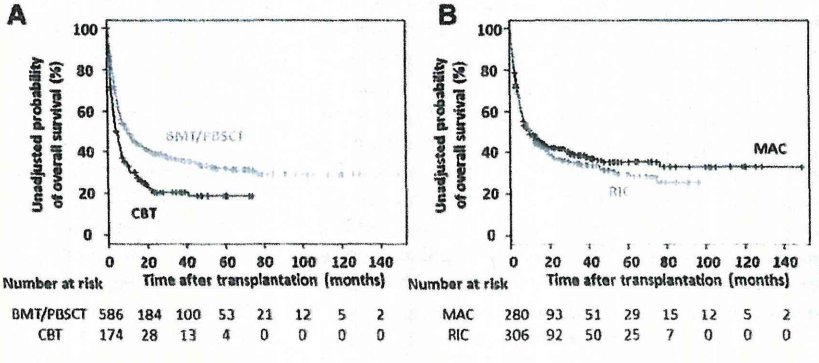

Figure 1. OS of ATL patients receiving allogeneic HSCT. (A) Kaplan-Meier curves of estimated OS in ATL patients receiving allogeneic BMT, PBSCT, or unrelated CBT. (B) Kaplan-Meier curves of estimated OS in ATL patients receiving allogeneic BMT or PBSCT with MAC or RIC.

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,

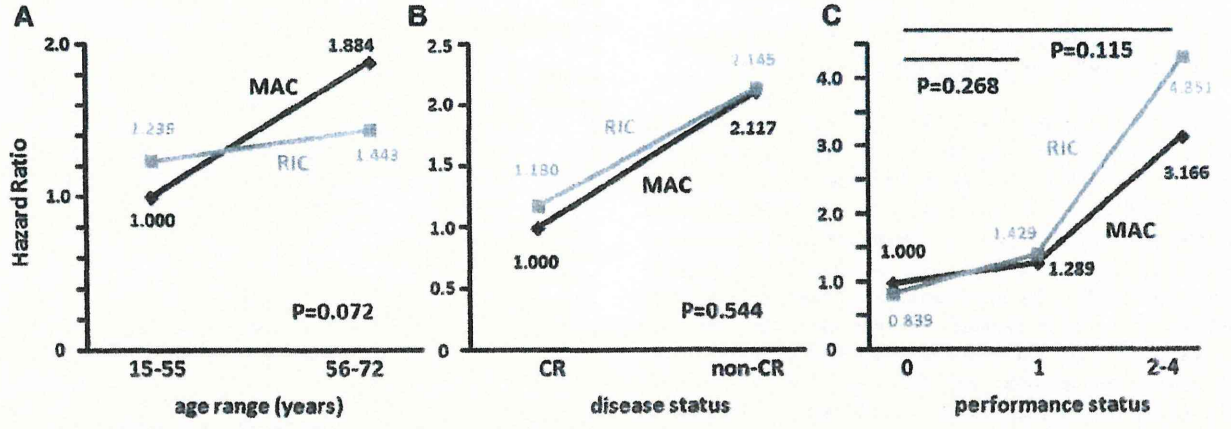

Figure 2. Interactions of the preconditioning regimen with age, disease status, and performance status for OS. Statistical interactions between the preconditioning regimens (MAC or RIC) and age range (15-55 vs 56-72 years; A), disease status (CR vs non-CR; B), and performance status (0 vs 1 or 2-4; C)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