置を RIST とした非血縁者間での移植の実施可能性を検討することは重要である。研究班のこれまでの研究成果、かつ現在実施中の臨床試験の結果によって、ATL に対する治療戦略への展望が得られることが期待される。

G. 研究発表

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Allogeneic Hematopoietic Stem Cell Transplantation Using Reduced-Intensity Conditioning for Adult T Cell Leukemia/Lymphoma: Impact of Antithymocyte Globulin on Clinical Outcome

Ryuji Tanosaki,[1] Naokuni Uike,[2] Atae Utsunomiya,[3] Yoshio Saburi,[4] Masato Masuda,[5] Masao Tomonaga,[6] Tetsuya Eto,[7] Michihiro Hidaka,[8] Mine Harada,[9] Ilseung Choi,[2] Takeharu Yamanaka,[10] Mari Kannagi,[11] Masao Matsuoka,[12] Jun Okamura[10]

[1] Stem Cell Transplantation Unit, National Cancer Center Hospital, Tokyo, Japan; [2] Department of Hematology, National Kyushu Cancer Center, Fukuoka, Japan; [3] Department of Hematology, Imamura Bun-in Hospital, Kagoshima, Japan; [4] Department of Hematology, Oita Prefectural Hospital, Oita, Japan; [5] Cancer Center, University of the Ryukyus, Okinawa, Japan; [6] Department of Hematology, Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University, School of Medicine, Nagasaki, Japan; [7] Department of Hematology, Hamanomachi Hospital, Fukuoka, Japan; [8] Department of Hematology, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan; [9] Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan; [10] Institute for Clinical Research, National Kyushu Cancer Center, Fukuoka, Japan; [11] Department of Immunotherapeutics, Tokyo Medical and Dental University, Medical Research Division, Tokyo, Japan; and [12] Laboratory of Virus Immunology, Institute for Virus Research, Kyoto University, Kyoto, Japan

Correspondence and reprint requests: Ryuji Tanosaki, MD, Stem Cell Transplantation Unit, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan (e-mail: rtanosak@ncc.go.jp).

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective treatment for adult T cell leukemia/lymphoma (ATLL), but shows high mortality. We evaluated the feasibility of reduced-intensity transplantation using fludarabine and busulfan, with particular focus on the clinical impact of antithymocyte globulin (ATG) in the conditioning regimen. Fourteen elderly patients with aggressive ATLL were enrolled in the current study without ATG, and were compared to those in 15 patients who were treated similarly, but with ATG, in our previous study. Engraftment was prompt, and treatment was tolerable. Overall (OS) and progression-free survival (PFS) at 3 years were 36% and 31%, respectively. HTVL-1 proviral load became undetectable by the polymerase chain reaction in 62% of patients. Compared to the previous study with ATG, complete donor chimera was significantly delayed. Although early relapse tended to be decreased, OS or PFS was not improved significantly. Analysis of combined data from both our current and previous studies disclosed that grade I-II acute GVHD was the only factor that favorably affected OS and PFS. These data suggested the presence of a graft-versus-ATLL effect and the feasibility of a transplant procedure without ATG in elderly ATLL patients, but could not demonstrate the clinical benefit of incorporating ATG.

KEY WORDS

Adult T cell leukemia/lymphoma • Hematopoietic stem cell transplantation • Allogeneic • Reduced-intensity transplantation • Antityymocyte globulin • Graft-versus-ATLL effect

INTRODUCTION

Adult T cell leukemia/lymphoma (ATLL) is a peripheral T cell malignancy that is associated with human T cell leukemia virus type 1 (HTLV-1) and a dismal prognosis [1]. It is classified into 4 subtypes according to its clinical features: acute, lymphoma, chronic, and smoldering. The former 2 subtypes have the worst prognosis, with a median survival of approximately 1 year [2-6]. On the other hand, recent reports have suggested that about 40% to 45% of patients with

Table 1. *Patient Characteristics in the Current Study in Comparison with those in the Previous Study*

Characteristic	ATG − Current Study (ATL-NST-2)	ATG + Previous Study (ATL-NST-1)	P
Number of patients	14	15	
Age, years			.15
Median	56	57	
Range	50-64	51-67	
Patient sex			1.00
Male	9	8	
Female	5	7	
Subtype of ATLL			1.00
Acute	10	10	
Lymphoma	4	5	
Initial chemotherapy			.65
CHOP-based	9	12	
LSG 15	3	2	
Modified EPOCH	2	2	
Status at transplantation			.59
CR	4	3	
PR	10	10	
Refractory	0	2	
Donor HTLV-1 serology			1.00
Positive	7	7	
Negative	7	8	
CD34+ cells infused, $\times 10^6$/kg pt weight			.39
Median	3.6	4.5	
Range	1.3-9.4	1.6-8.0	

ATLL indicates adult T cell leukemia/lymphoma; CHOP, cyclophosphamide (Cy); doxorubicin (DXR); vincristine (VCR); prednisone (Pred); LSG 15, Cy, DXR, VCR, Pred, MCNU, carboplatin (CBDCA), etoposide (VP-16); Modified EPOCH, VP-16, VCR, Pred, CBDCA, DXR; CR, complete remission; PR, partial remission; HTLV-1, human T cell leukemia virus type-1; ATG, antithymocyte globulin.

these subtypes could survive without disease after allogeneic hematopoietic stem cell transplantation (allo-HSCT) using a conventional conditioning regimen [7-10]. However, treatment-related mortality (TRM) after conventional allo-HSCT is still as high as 40% to 45% because most ATLL patients are over 50 years of age and have poor morbidity, and this limits the wider application of this procedure.

To overcome this limitation, we previously conducted a phase I study of reduced-intensity allogeneic transplantation (ATL-NST-1) to examine its feasibility and safety in the treatment of 15 patients with ATLL who were aged 50 years or more [11]. The conditioning regimen consisted of fludarabine (180 mg/m^2), busulfan (8 mg/kg), and low-dose (5 mg/kg) antithymocyte globulin (ATG, Fresenius AG, Bad Homburg, Germany), as modified from a previous report [12]. Although this study confirmed its feasibility and safety, 9 of the 15 patients (60%) relapsed, and 7 of these relapsed within 100 days. This observed high rate of early relapse raised the possibility that ATG, which was used to enhance engraftment and suppress a graft-versus-host reaction, may have negatively suppressed a graft-versus-lymphoma effect to lead to the high relapse rate. Alternatively, the rapid proliferation of ATLL cells may outpace a developing donor-derived anti-ATLL activity. Therefore, in the present modified phase I study (ATL-NST-2), we eliminated ATG from the original conditioning regimen to compare the results with the previous study. Because ATLL is a rare endemic hematologic malignancy, to the best of our knowledge, these are the only on-going prospective trials that focus on reduced-intensity allo-HSCT for this disease [13].

PATIENTS AND METHODS

Patient and Donor Characteristics

Eligibility criteria for this study were identical to those in the first trial. Briefly, patients with ATLL of acute or lymphoma type [2], who were aged between 50 and 70 years, were eligible. Patients were required to be in either complete remission (CR) or partial remission (PR) at the time of registration, and to have an HLA-identical sibling donor. Patients did not have an active uncontrolled infection. Those who had a past history of CNS invasion were included. Written informed consent was obtained from all patients and donors before enrollment into the study, which was approved by the institutional review board of each participating hospital.

For this modified study, 14 patients were registered between March 2003 and February 2006 at 7 institutions. Their characteristics are given in Table 1 in comparison with those of the 15 patients treated in the first study (ATL-NST-1), who were enrolled between April 2001 and November 2002 and treated with low-dose (5 mg/kg) ATG.

Treatment

Donors received granulocyte-colony stimulating factor (G-CSF) 5 μg/kg twice daily, beginning 4 days before leukapheresis and continuing until collections were complete. The conditioning regimen consisted of fludarabine 30 mg/m^2 per day infused over 30 minutes on days −8 to −3, and busulfan 1 mg/kg orally every 6 hours for 4 times on days −6 and −5. For prophylaxis of graft-versus-host disease (GVHD), cyclosporine 3 mg/kg per day was infused continuously starting on day −1, and the dose was adjusted to between 250 and 400 ng/mL. The dose was tapered after 50 days if there was no sign of acute GVHD (aGVHD). G-CSF 5 μg/kg was administered to recipients on day 6 and thereafter until the absolute neutrophil count was $>1 \times 10^9$/L for 2 consecutive days.

Study Endpoints

The primary objective of the study was to evaluate feasibility and safety in terms of the achievement of complete donor chimera before 91 days, defined as 90% or more peripheral blood mononuclear cells (PBMNC) of donor origin, and the occurrence of TRM within 100 days after transplantation. The degree of donor-recipient chimerism in PBMNC, CD3-positive or negative fraction, was examined after 14, 30, 60, and 90 days according to the previously published method [14]. The day of sustained engraftment was defined as the first of 3 consecutive days with the absolute neutrophil count exceeding 0.5×10^9/L.

The secondary objectives were toxicities, occurrence of aGVHD and chronic GVHD (cGVHD), overall (OS) and progression-free survival (PFS), and HTLV-1 proviral load as a surrogate marker for anti-HTLV-1 effect. Toxicities were graded using the National Cancer Institute Common Toxicity Criteria (version 3.0) [15]. Acute GVHD was diagnosed and graded according to the standard criteria [16,17]. Chronic GVHD was assessed according to the standard criteria in patients who survived >100 days after transplantation [18]. OS was defined as the duration from transplantation to death from any cause. PFS was defined as the duration from transplantation to disease progression or death from any cause. The HTLV-1 proviral load was estimated by taking blood samples before and 1, 2, 3, 6, 12, 18, and 24 months after transplantation, and HTLV-1 proviral DNA was measured by quantitative PCR amplification of HTLV-1 pX DNA using a Light Cycler System. The detection limit of the HTLV-1 proviral load was 0.5 copies/1000 cells [19].

Statistical Analysis

We hypothesized that 80% of patients were expected to survive >100 days with engraftment of 90% or more of donor chimerism after this modified treatment. Simon's 2-stage design was used [20]. In the first stage, 7 patients were to be assessed and we expected that >3 patients would fulfill the criteria. Next, 9 additional patients were to be assessed. If >10 of the total 16 patients met the criteria, we considered that our hypothesis would have been shown to be true.

Patients and disease characteristics were compared by either Fisher's exact test or the Wilcoxon rank-sum test. Estimates of time to event, including neutrophil recovery, complete donor chimera, death, relapse, and GVHD, were made by the Kaplan-Meier method. All P values are reported as 2-sided, with $P < .05$ indicating statistical significance. The hazard ratio of death or relapse with respect to clinical features was estimated by a Cox proportional hazard model. All analyses were performed using SPSS 15.0 or SAS (ver. 9) for Windows.

RESULTS

Engraftment and Toxicities

Because 12 of the 14 patients (86%) survived >100 days with complete donor chimera after transplantation, this treatment was demonstrated to be successful, and the enrollment of patients was stopped at that point. Neutrophil engraftment and complete donor chimera in PBMNC were achieved in all 14 patients before 91 days. The median number of days until engraftment and the achievement of complete donor chimera was 11 days (range: 9 to 16 days) and 60 days (14 to 90 days), respectively. TRM occurred in 3 patients; 1 subdural hemorrhage on day 21, 1 interstitial pneumonia syndrome on day 32, and 1 bronchiolitis obliterans on day 630.

In comparison with the previous study, where ATG was included in the preparatory regimen, complete donor chimera was significantly delayed in PBMNC (Figure 1; $P = .001$) and CD3-positive T cell fractions ($P = .038$). On the other hand, the speed of neutrophil recovery and the achievement of complete donor chimera in CD3-negative myelomonocytic cell fraction were almost identical between the 2 studies.

Concerning nonhematologic toxicities, no patients experienced grade 3 or 4 toxicities, except 3 TRM as described above. CMV antigenemia was observed in 11 patients (79%) at least once within 100 days after transplantation, although none developed a CMV disease. Other infectious complications within 100 days after transplantation included mild hemorrhagic

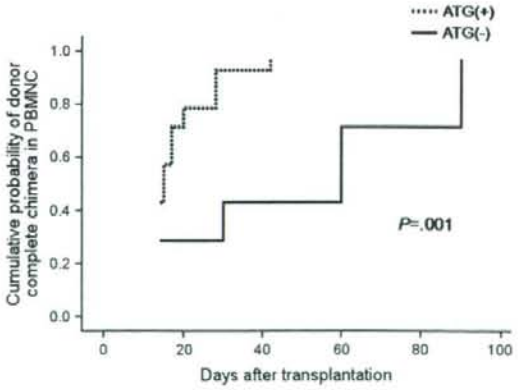

Figure 1. Kaplan-Meier estimate of the cumulative probability of achieving complete donor chimera in the mononuclear cell fraction in peripheral blood. PBMNC indicates peripheral blood mononuclear cell; ATG, antithymocyte globulin; ATG(+), patients treated with a conditioning regimen that included ATG in the previous study (n = 15); ATG(−), patients treated without ATG in the current study (n = 14). The achievement of complete donor chimera was significantly delayed in the current study compared to the previous study ($P = .001$).

Table 2. *Clinical Outcomes of the Current and the Previous Studies*

	ATG				
	−		+		
	Current Study (n = 14)		Previous Study (n = 15)		
Characteristic	No.	%	No.	%	P
Complete donor chimera≤90 days	14	100	14	93	.78
Death					
Overall	8	57	10	67	.88
All TRM	3	21	4	27	.60
TRM ≤100 days	2	14	1	7	1.00
ATLL	5	36	6	40	.88
Relapse					
Overall	6	43	9	60	.45
≤100 days	3	21	7	47	.25
Acute GVHD	12	86	10	67	.27
I	4	29	1	7	
II	5	36	4	27	
III	3	21	3	20	
IV	0	0	2	13	
Chronic GVHD*	10/12	83	6/13	46	.063
CMV antigenemia	11	79	13	87	.65
EB-LPD	0	0	2	13	
No. of pts with undetectable PCR for HTLV-I*†	8/13	62	8	53	.96

ATLL indicates adult T-cell leukemia/lymphoma; TRM, treatment-related mortality; GVHD, graft-versus-host disease; CMV, cytomegalovirus; EB-LPD, Epstein-Barr virus-associated lymphoproliferative disorders; PCR, polymerase chain reactions; HTLV-1, human T cell leukemia virus type-1; ATG, antithymocyte globulin.

*The number of evaluated patients is shown on the right side of the slash in each column.

†The number of patients whose HTLV-1 provirus could not be detected at lease once was counted.

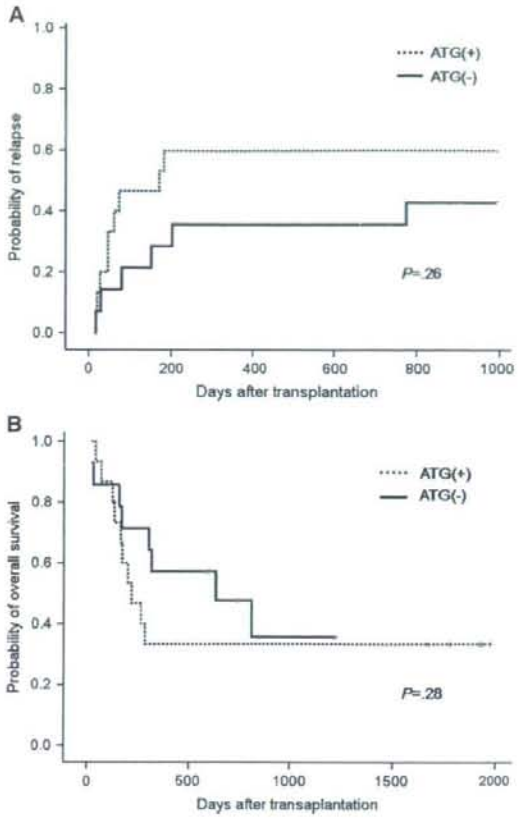

Figure 2. Cumulative incidence estimates of relapse and Kaplan-Meier survival estimates in comparison between the absence (the current study) and presence (the previous study) of ATG in the conditioning regimen. (A) Total and early relapse within 100 days tended to be decreased in the current study, but not significantly different ($P = .26$). (B) There was no significant difference in overall survival rate between with and without ATG ($P = .28$).

cystitis because of adenovirus in 3, and mild pneumonia because of pseudomonas aeruginosa in 1 patient.

aGVHD and cGVHD

The incidence of aGVHD was not significantly increased in the current study ($P = .27$); grade I to IV was 86%, grade II to IV 57%, grade III to IV 21%, whereas in the previous study these values were 67%, 60%, and 34%, respectively. Chronic GVHD developed in 10 of 12 patients (83%) who could be evaluated, and it tended to be increased in the current study compared to the previous study (Table 2; $P = .063$).

Relapse

Six patients relapsed (within 100 days in 3 [50%]). Total and early relapse within 100 days tended to occur less frequently in the current study than in the first study, but these differences were not statistically significant (Figure 2A; $P = .26$ and .25, respectively). Two patients relapsed in the CNS on days 78 and 778. Another patient, who relapsed on the skin on day 30, responded to withdrawal of cyclosporine and is currently alive without disease 592 days after transplantation.

Kinetics of HTLV-I Proviral Load

In 13 patients who could be examined serially for HTLV-1 proviral load in the peripheral blood, this value decreased after transplantation and reached an undetectable level within 6 months in 8 patients (62%), including 3 patients who were transplanted from an HTLV-1 carrier donor. There was no significant difference in these kinetics between the 2 studies (Table 2 and Figure 3). In 2 patients, it is still undetectable at 12 and 18 months after transplantation.

OSI and PFS

OS and PFS at 3 years were 36% (95% confidence interval [CI], 21% to 51%) and 31% (95% CI, 17% to

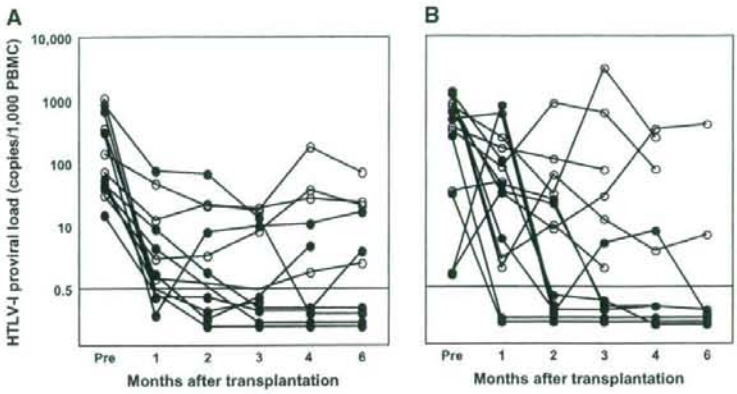

Figure 3. The kinetics of the HTLV-1 proviral load within 6 months after RIST. The panel on the left (A) indicates the kinetics of HTLV-1 proviral load in the current study, whereas the panel on the right (B) shows the kinetics in the previous study. The HTLV-I proviral load was expressed as copy numbers per 1000 mononuclear cells (MNC). A load of <0.5 copies per 1000 MNC was considered to be undetectable. Closed circles indicate patients whose proviral load became undetectable at least once, whereas open circles indicate patients whose proviral load remained detectable.

45%), respectively, with a median follow-up time of 792 days (range: 592 to 1222 days) in surviving patients. There was no significant difference in OS (Figure 2B; $P = .49$) or PFS ($P = .28$) between the 2 studies.

Factors that Affect OS and PFS in a Combined Analysis of Both Studies

We examined the effects of various factors, including the use of ATG in the conditioning regimen, age, gender, type of ATLL, disease status at transplantation, donor's HTLV-1 status, and aGVHD as a time-dependent variable, on OS and PFS in a total of 29 patients who had been enrolled into the 2 studies. The Kaplan-Meier estimate revealed marked differences in OS and PFS among patients who were stratified retrospectively according to the grade of aGVHD (Figure 4). In a univariate analysis, only aGVHD of grade I to II was identified as a prognostic factor with a positive impact for both OS and PFS (Table 3). The use of low-dose ATG in the conditioning regimen did not significantly influence OS or PFS in this particular setting.

DISCUSSION

In our previous study, which incorporated low-dose ATG, we showed that elderly patients with aggressive ATLL could be transplanted safely, and that laboratory-evaluated graft-versus-HTLV-1 activity and clinically observed graft-versus-ATLL (GV-ATLL) effect were important after allo-HSCT [11]. Nevertheless, disease relapse was the main cause of treatment failure, and 9 of the 15 patients (60%) relapsed, 7 of whom relapsed within 100 days after transplantation. The early relapse was considered to be because of the highly resistant nature of ATLL. It was speculated that the disease activity could not be controlled by reduced-intensity conditioning therapy per se, unless a GV-ATLL effect appears earlier. However, GVHD and a related GV-ATLL effect might have been suppressed by ATG included in the conditioning regimen.

In this modified phase I study, we again showed that a reduced-intensity conditioning regimen, regardless of the use of ATG or not, was feasible and safe in elderly patients with ATLL. Total and early relapse within 100 days after transplantation tended to be decreased, although there were no significant differences, as we had not expected. A univariate analysis also failed to show any differences in OS or PFS between patients in the 2 studies treated with and without ATG. It is considered that the reason why we could not show the impact of ATG was because of the small number of patients in these cohorts and the relatively low dose of ATG used in the previous study.

The speed of achieving complete donor chimera was significantly delayed if ATG was not used in the conditioning regimen, as has been reported [21]. It was speculated that, without ATG, host T cells tended to remain reactive to donor-derived allo-antigen and to compete with donor cells in the early phase after transplantation, and would require more time to be completely replaced by donor cells. Because the frequency of aGVHD was not significantly different between with and without ATG in the conditioning regimen, the development of aGVHD may not be associated with the achievement of complete donor chimera.

As shown here, there were no significant differences between the 2 study groups in most patients'

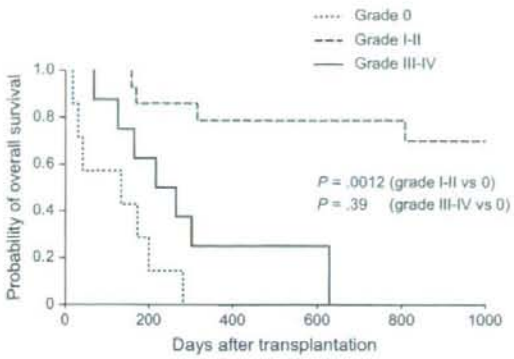

Figure 4. Kaplan-Meier estimate of overall survival for all patients treated in both studies according to the grade of aGVHD. Patients with grade I-II aGVHD had a significantly better overall survival compared to those without aGVHD ($P = .0012$). Severe aGVHD (grade III-IV) did not affect favorably in respect of overall survival compared to those without aGVHD ($P = .39$).

characteristics. Therefore, it is reasonable to analyze rare patients in both studies combined together. In the total of 29 patients included in both studies, the median survival time was 304 days, and OS and PFS at 3 years were 36% (95% CI, 27 to 45%) and 25% (95% CI, 16 to 34%), respectively, with a median follow-up of 1222 days (range: 592 to 1973) in the surviving patients. Moreover, our study revealed the characteristics of ATLL in response to transplantation; despite the frequent occurrence of early relapse, a significant number of patients survived thereafter. Four patients who had a relapse subsequently responded to a rapid discontinuation of the immunosuppressive agent and had a sustained remission for 152, 562, 1498, and 1945 days after relapse, suggesting that this disease entity is particularly susceptible to immune modulation [22,23].

Patients who developed grade I-II aGVHD had significantly better OS and PFS than other patients. Because the development of severe GVHD is considered to be too toxic for ATLL patients who are elderly, highly immune-compromised, and/or often have preexisting infectious complications, the regulation of immune reaction should be important for controlling the disease activity. We also confirmed that allogeneic transplantation not only has an anti-ATLL effect, but also anti-HTLV-1 activity. Eleven of the 14 patients (79%) who received graft from an HTLV-1-negative donor and 5 of the 14 patients (36%) from an HTLV-1-carrier donor became negative for HTLV-1 proviral load in the peripheral blood at least once within 6 months after transplantation, with no meaningful difference between the 2 studies.

The frequency of infectious complications in our studies was quite high, regardless of the use of ATG in the conditioning regimen, because 24 of the total

Table 3. *Univariate Analysis of Factors that Influence Overall and Progression-Free Survival*

Parameter and Group	HR	95% CI	P
OS			
ATG			
Absence versus presence	0.72	0.28 to 1.83	.49
Patient age			
>55 versus ≤55	1.92	0.72 to 5.15	.19
Patient sex			
Male versus female	0.67	0.26 to 1.71	.40
Subtype			
Lymphoma versus acute	0.77	0.27 to 2.17	.61
Status at transplantation			
PR versus CR	1.26	0.41 to 3.84	.69
Donor's HTLV-I status			
Carrier versus noncarrier	1.15	0.46 to 2.91	.77
Acute GVHD			
Grade I-II versus grade 0	0.07	0.01 to 0.35	.0012
Grade III-IV versus grade 0	0.59	0.17 to 2.00	.39
PFS			
ATG			
Absence versus presence	0.62	0.26 to 1.48	.28
Patient age			
>55 versus ≤55	2.27	0.85 to 6.12	.10
Patient sex			
Male versus female	0.81	0.32 to 2.07	.66
Subtype			
Lymphoma versus acute	0.70	0.27 to 1.81	.46
Status at transplantation			
PR versus CR	1.22	0.45 to 3.34	.70
Donor's HTLV-I status			
Carrier versus noncarrier	1.06	0.45 to 2.49	.90
Acute GVHD			
Grade I-II versus grade 0	0.15	0.05 to 0.49	.0014
Grade III-IV versus grade 0	0.39	0.13 to 1.13	.08

OS indicates overall survival; ATG, anti-thymocyte globulin; PR, partial remission; CR, complete remission; HTLV-1, human T cell leukemia virus type-1; GVHD, graft-versus-host disease; PFS, progression-free survival; HR, hazard ratio.

29 patients (83%) developed CMV antigenemia, although all were successfully treated with gancyclovir and none progressed to CMV disease. This high rate may reflect profound immunodeficiency underlying the process of ATLL, as has been reported [24,25]. Moreover, 2 patients developed EBV-lymphoproliferative disorders and both were in the first study: there were none in the second study without ATG.

In conclusion, allogeneic reduced-intensity HSCT using fludarabine and busulfan with or without low-dose ATG was shown to be feasible and safe even in elderly patients with ATLL, and the results suggested that its efficacy may be because of a GV-ATLL effect. A combined analysis suggests that the use of ATG could provide too much immune suppression to patients who are already intensely immune-compromised. To confirm these findings, a multicenter phase II study of reduced-intensity HSCT using fludarabine and busulfan without ATG is currently underway.

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Authors' Disclosures of Potential Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conception and design: Jun Okamura, Ryuji Tanosaki, Naokuni Uike, Atae Utsunomiya, AND Mari Kannagi. *Collection and assembly of data:* Ilseung Choi and Jun Okamura. *Data analysis and interpretation:* Takeharu Yamanaka, Ryuji Tanosaki, Ilseung Choi, Naokuni Uike, and Atae Utsunomiya. *Manuscript writing:* Ryuji Tanosaki, Naokuni Uike, Atae Utsunomiya, Ilseung Choi, Takeharu Yamanaka, and Jun Okamura. *Final approval of manuscript:* Ryuji Tanosaki, Naokuni Uike, Atae Utsunomiya, Yoshio Saburi, Masato Masuda, Masao Tomonaga, Tetsuya Eto, Michihiro Hidaka, Mine Harada, Ilseung Choi, Takeharu Yamanaka, Mari Kannagi, Masao Matsuoka, and Jun Okamura.

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