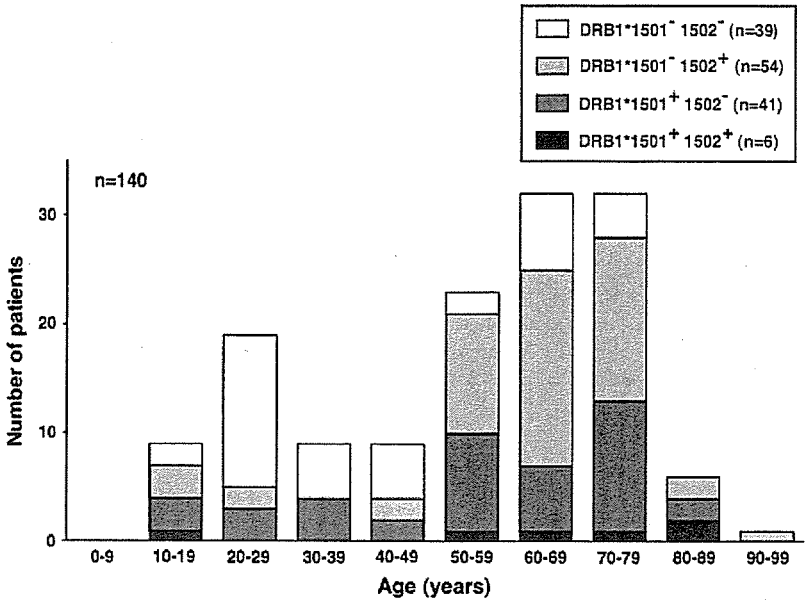

Figure 1. Age distribution of aplastic anemia (AA) patients with or without HLA-DR15. The number of AA patients with or without HLA-DR15 in different age groups is shown. DRB1*1501^{+}1502^{+}, patients with both DRB1*1501 and DRB1*1502; DRB1*1501^{+}1502^{-}, patients with DRB1*1501 but not DRB1*1502; DRB1*1501^{-}1502^{+}, patients with DRB1*1502 but not DRB1*1501; DRB1*1501^{-}1502^{-}, patients with neither DRB1*1501 nor DRB1*1502.

DRB1*1501^{+}1502^{+} patients, 85.3% (35 of 41 patients) in DRB1*1501^{+}1502^{-}, 59.3% (32 of 54 patients) in DRB1*1501^{-}1502^{+} and 53.8% (21 of 39 patients) in DRB1*1501^{-}1502^{-}.

Allele frequencies in the PNH^{+} and PNH^{-} AA patients

We next divided the 140 AA patients for whom both DRB1 alleles were determined into PNH^{+} patients (n = 92) and patients without a small population of PNH-type cells (PNH^{-} patients, n = 48), and then compared the frequency of each DRB1 allele among the three different groups including the PNH^{+} patients, PNH^{-} patients, and controls (Fig. 2). The frequency of DRB1*1501 compared to the controls was significantly higher in only the PNH^{+} patients (39 of 92 patients, 42.4%, $p_c < 0.01$), not in PNH^{-} patients (8 of 48 patients, 16.7%). On the other hand, the frequency of DRB1*1502 in comparison to the controls was higher in both the PNH^{+} patients (37 of 92 patients, 40.2%, $p_c = 0.05$) and PNH^{-} patients (24 of 48 patients, 50.0%). Frequencies of other DRB1 alleles, including DRB1*0405, were similar among PNH^{+} patients, PNH^{-} patients, and controls.

Correlation of HLA-DR15 alleles with the prevalence of increased PNH-type cells in AA patients

We analyzed the associations between the prevalence of PNH-type cells and genetic factors, such as age, sex, severity, chromosomal abnormality, and HLA-DRB1 allele to determine which factors might contribute to a slight increase in PNH-type cells in our AA patients. The presence of DRB1*1501 ($p < 0.01$, odds ratio = 3.68) was the only significant factor associated with an increase in the proportion of PNH-type cells based on a univariate analysis, and a multivariate analysis confirmed this result ($p < 0.01$). The presence of DRB1*1502 was not considered to be a contributing factor.

Favorable factors affecting response to ATG plus CsA therapy

Fifty-five of 77 patients (71.4%) improved with ATG plus CsA therapy. The factors favorably affecting the response to IST in the AA patients were examined under a univariate and multivariate analysis (Table 3). Only the presence of PNH-type cells was significantly associated with the response to IST based on a multivariate analysis. After taking into account the kinetics of the response to treatment, we made Kaplan-Meier curves to determine the probability of response to IST in three different groups of patients as defined by DRB1 alleles (Fig. 3). There were significant differences in the probability of the response to IST between the DRB1*1501^{+}1502^{-} patients and either the DRB1*1501^{-}1502^{+} patients ($p < 0.01$) or the DR15^{-} patients ($p = 0.01$) (Fig. 3A). However, these differences in the probability of response IST were no longer observed when the probability of response was compared in either the PNH^{+} patients or the PNH^{-} patients (Fig. 3B, C).

Discussion

This study demonstrated for the first time that, in addition to DRB1*1501, which is a major DRB1 allele determining

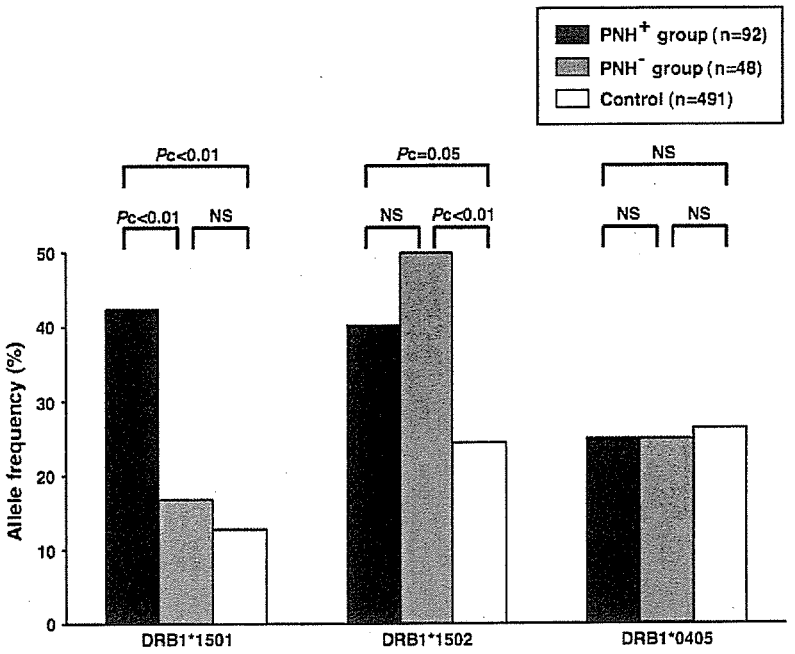

Figure 2. HLA-DRB1 allele frequencies in paroxysmal nocturnal hemoglobinuria (PNH)$^+$ and PNH$^-$ aplastic anemia (AA) patients. Frequencies of the three alleles, DRB1*1501, DRB1*1502, and DRB1*0405 are compared in the PNH$^+$ AA patients, PNH$^-$ AA patients, and controls.

the presentation of HLA-DR15 in Caucasian [2,3] and Chinese populations [4], DRB1*1502 is frequently present in Japanese AA patients. This finding, based on a large number of patients, suggests that the DR15 molecule plays a definite role in development of a subset of AA. Another novel finding in the present study was that the significantly increased frequency of HLA-DR15 was only observed in old AA patients. The frequency of HLA-DR15 reached up to 80% in AA patients 40 years of age or older. The apparent age-dependent differences in HLA-DR15 frequency suggest that the pathophysiology of AA in older patients may therefore differ from that in younger patients. Several studies of Japanese pediatric patients have revealed a relatively high incidence of MDS secondary to AA compared to adult patients [22–24]. Given the lower frequency of HLA-DR15, pediatric AA may thus display a higher proportion of bone marrow failure caused by nonimmune mechanisms than adult AA.

In contrast to the findings of previous reports, DRB1*1501 appeared to confer a better chance of response to regimens including ATG than other DRB1 alleles, including DRB1*1502. We previously demonstrated that DRB1*1501 predicts the response to CsA, but not to ATG [11]. In the previous study, only 6 of 59 ATG-treated patients received CsA. The combined use of CsA and the larger number of ATG-treated patients in the present study probably accounts for the different findings regarding the role of DRB1*1501 in predicting the response to ATG therapy. DRB1*1501 may affect the response of AA to ATG therapy only when CsA is administered in combination with ATG.

Several previous studies failed to confirm the role of HLA-DR15 in predicting the response to ATG [3,10]. Most previous studies analyzed DRB1 alleles using low-resolution methods that are unable to sufficiently distinguish DRB1*1502 from DRB1*1501. DRB1*1502 accounts for 3% to 7% of the DRB1 alleles corresponding to DR15 even in Caucasians [25], and this frequency may even be higher in AA patients, particularly among AA patients 40 years of age or older. As a result, some patients with DR15 who did not respond to ATG in previous studies may have been DRB1*1502$^+$, rather than DRB1*1501$^+$. The results of this study indicate the importance of

Table 3. Pretreatment variables associated with a response to antithymocyte globulin plus cyclosporin A therapy

	p Value	
Favorable factors	univariate*	multivariate**
Gender (male vs female)	0.32	0.47
Age (at least 40 y vs younger)	0.79	0.37
Severity (severe vs moderate)	0.61	0.86
HLA-DRB1*1501 (positive vs negative)	0.03	0.19
HLA-DRB1*1502 (positive vs negative)	0.61	0.46
PNH-type cells (positive vs negative)	<0.01	<0.01

*Fisher's exact probability test.
**Wald c^2 test for a logistic regression model.
PNH = paroxysmal nocturnal hemoglobinuria.

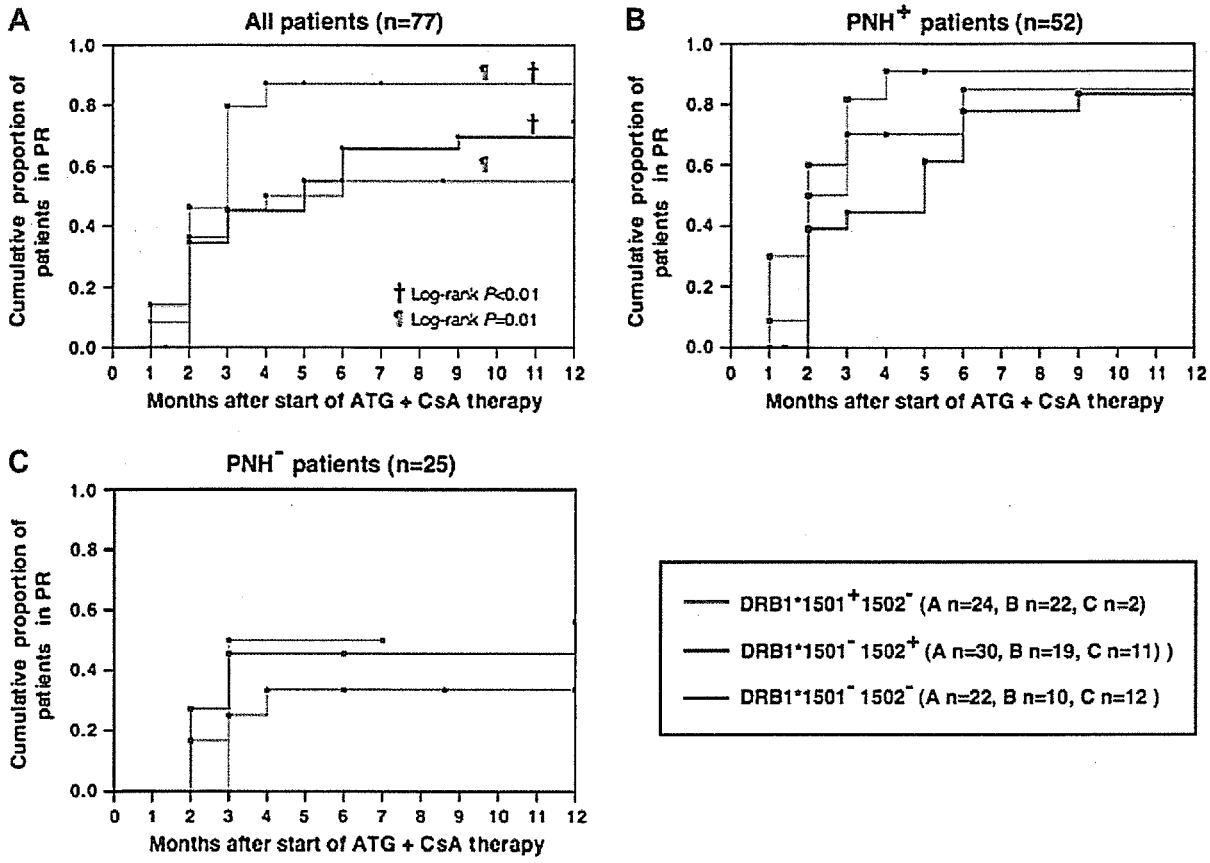

Figure 3. Kinetics of response to antithymocyte globulin (ATG) plus cyclosporin A (CsA) therapy. Kaplan-Meier curves for the response in the different groups of patients based on the DRB1 alleles are shown. DRB1*1501^{+}1502^{+} patients were not showed in this figure because only one patient (he was paroxysmal nocturnal hemoglobinuria [PNH]$^{+}$) was available for the analysis. (**A**) all patients; (**B**), PNH^{+} patients; (**C**), PNH^{-} patients.

accurately determining the DRB1 alleles using high-resolution methods to clarify the role of HLA-DR15 in predicting a response to IST.

A higher frequency of HLA-DR15 among PNH^{+} patients in comparison to PNH^{-} patients has been reported by Maciejewsky et al. [26]. The present study confirmed this finding using a different flow cytometry assay that distinguished PNH^{+} patients from PNH^{-} patients using lower levels of glycosylphosphatidyl inositol-anchored protein-deficient cells than the assay used in the previous study. Our methods also identified a significant difference between DRB1*1501 and DRB1*1502 in the minimal expansion of PNH clones. The frequencies of both alleles increased in the PNH^{+} patients in comparison to normal controls, thus supporting the preliminary results of our study of 23 patients with refractory anemia [13]. However, only DRB1*1501 represented a genetic factor significantly associated with an increase in the proportion of PNH-type cells in AA patients in the present study because the frequency of DRB1*1502 was high in both PNH^{+} and PNH^{-} AA patients, thus indicating that the minimal expansion of PNH clones is not affected by DRB1*1502. Together with the difference in the response rate to IST between DRB1*1501^{+} and DRB1*1502^{+} AA patients, all these findings suggest that DRB1*1501 and DRB1*1502, therefore, play a different role in the pathogenesis of AA.

In AA patients carrying DRB1*1501, the presentation of autoantigen by this molecule may readily induce a cell-mediated attack against hematopoietic stem cells that may be associated with minimal expansion of a PNH clones. Previous studies have demonstrated that the presence of a CD4^{+} T-cell attack against hematopoietic stem cells allows the survival of PNH-type stem cells [27,28]. On the other hand, polymorphic gene alleles of myelosuppressive cytokines, in linkage disequilibrium with DRB1*1502 may predispose individuals with HLA-DRB1*1502 toward development of AA. In keeping with this hypothesis, a recent study on diabetes mellitus patients revealed that a haplotype of TNFa12-DRB1*1502 was, therefore, more frequent in patients likely to develop insulin-dependency than in those who do not develop insulin-dependency [29]. Several reports have demonstrated TNFa12 to be associated with a higher secretion of tumor necrosis factor-α [30].

HLA-DR15 molecules derived from DRB1*1502 differ from those derived from DRB1*1501 in only one amino acid at position 86 (valine for DRB1*1502 and glycine for DRB1*1501) of the β-chain [31]. This structural similarity indicates that antigenic epitopes presented by these molecules are common [32,33]. For most autoimmune diseases where DRB1*1501 is associated with susceptibility in patients from Western countries, DRB1*1502 is expected to play the same role as DRB1*1501 in Japanese patients. However, in Japanese patients with multiple sclerosis, the frequency of DRB1*1502 is not increased in comparison to that in the controls [34,35]. As a result, DRB1*1502 appears to contribute to development of some autoimmune diseases via different mechanisms to DRB1*1501. In AA patients carrying DRB1*1501, certain antigens of which presentation requires position 86 of the β-chain to be glycine may likely induce an immune system attack to hematopoietic progenitor cells. It is also possible that DRB5*0101 and DRB5*0102, which are in complete linkage disequilibrium with DRB1*1501 and DRB1*1502, respectively, in the Japanese population [19] may be responsible for the difference because DRB5*0101 differs from DRB5*0102 by three amino acids in the antigen-peptide binding domain.

Our data may be relevant to the management of AA. Although the incidence of HLA-DR15 is significantly higher in AA patients than in the normal controls, only DRB1*1501 was found to be a predictive marker for a good response to ATG plus CsA therapy. AA patients with DRB1*1502 who do not show an increased proportion of PNH-type cells may not benefit from IST. HLA-DR typing has been considered to be useful for predicting a good response to IST in AA patients [7,8], but this costly test may not be necessary in the circumstance where the highly sensitive flow cytometry is available because the presence of a small population of PNH-type cells is the only significant factor that affects the response to ATG plus CsA therapy based on the findings of our multivariate analysis. Prospective studies are called for to confirm these findings.

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Clinical significance of a blood eosinophilia in adult T-cell leukemia/lymphoma: A blood eosinophilia is a significant unfavorable prognostic factor

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Abstract

We investigated the clinical significance of a blood eosinophilia in a cohort of 158 consecutive patients with adult T-cell leukemia/lymphoma (ATLL), and multivariate analysis revealed that a blood eosinophilia was an independent and a significant unfavorable prognostic factor. Interestingly, a blood eosinophilia was independent of serum LDH level, which might reflect the tumor burden. The present study shows that measurement of the blood eosinophil count is useful for predicting the prognosis and for determining a suitable treatment strategy for ATLL patients.

Keywords: ATLL; Eosinophilia; Interleukin-5; Th1/Th2 balance; CCR4

1. Introduction

Adult T-cell leukemia/lymphoma (ATLL) patients are in a severely immunocompromised state, leading to frequent and severe infectious complications and to an unfavorable outcome [1,2]. The human immune system depends on balanced production of cytokines by two distinct T helper (Th) cell subsets: Th1 and Th2 cells [3,4]. Th1 cells produce interferon (IFN)-γ, and interleukin (IL)-2, while Th2 cells produce IL-4 and IL-5. Th1 cells play a critical role in cellular immunity, while Th2 cells are involved in humoral immunity. Eosinophilia is induced by overproduction of IL-5 [5], and thus the ATLL patients with a blood eosinophilia seem to have shifted their Th1/Th2 balance in favor of a Th2 response. Since Th1 cells are likely to play a key role in the initiation and persistence of an anti-tumor response, while a predominant differentiation to Th2 has been associated with a relative defect in the anti-tumoral and anti-infectious responses [6], the hypothesis that a blood eosinophilia in ATLL patients might be an indicator of poor prognosis was proposed. In fact, a blood eosinophilia is a significant prognostic factor in the other hematological neoplasm, cutaneous T-cell lymphoma [7]. Furthermore, we have recently examined the levels of serum cytokines including IFN-γ, TNF-α, IL-2, -4, -5, -6, -10, and TGF-β1 in 94 ATLL patients, 39 asymptomatic HTLV-1 carriers, and 50 healthy adult volunteers, in order to clarify whether elevated levels of particular cytokines are associated with the prognosis of ATLL patients. Multivariate analysis indicated that high IL-5 and IL-10 levels were independent and significant unfavorable prognostic factors among the ATLL patients, and most importantly, there was a signifi-

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cant relationship between a high serum IL-5 level and a blood eosinophilia (a blood eosinophil absolute count > 500 μL^{-1}) among the ATLL patients [8]. In addition, it is generally known that a blood eosinophilia is sometimes seen in ATLL patients [1,9,10]. These findings prompted us to undertake the present study. We retrospectively investigated the clinical significance of a blood eosinophilia in a cohort of 158 consecutive patients with ATLL.

2. Materials and methods

2.1. Patients

This study included 158 consecutive ATLL patients for whom there was sufficient clinical information and follow-up, who were diagnosed between 1989 and 2005 at two independent hospitals in Japan (Imamura Bun-in Hospital and Nagoya City University Hospital). The diagnosis and classification of ATLL clinical subtypes were made according to the criteria proposed by the Japan Lymphoma Study Group [2]. The clinical characteristics of the ATLL patients who were analyzed in this study included age, sex, clinical subtype, performance status (PS), presence or absence of B symptoms, white blood cell count (WBC), lymphocyte count, eosinophil count, hemoglobin level (Hb) and platelet count (Plt) in the peripheral blood, serum calcium level, serum albumin level, serum lactate dehydrogenase (LDH) level, and involved sites [lymph node (LN), bone marrow (BM), peripheral blood, lung, liver, spleen, gastrointestinal tract, kidney, central nervous system (CNS), bone, and skin]. We designated a blood eosinophil absolute count exceeding 500 μL^{-1} as a blood eosinophilia throughout the present study [11]. ATLL patients with the acute and lymphoma subtypes receive an aggressive clinical course, while ATLL patients with the chronic and smoldering subtypes survive longer [1,2]. Thus, we designated the acute and lymphoma subtypes of ATLL as the aggressive variant, and the chronic and smoldering subtypes of ATLL as the indolent variant in the present study. For these analyses, we used the clinical characteristics recorded at the time the blood examination was performed, and all blood samples were obtained at the time of initial diagnosis of ATLL. Although the treatments administered to the ATLL patients enrolled in this study varied, combination chemotherapy protocols including doxorubicin such as the RCM protocol [12], the LSG15 protocol [13], or the cyclophosphamide–doxorubicin–vincristine–prednisone (CHOP) regimen were administered to the majority of the patients.

2.2. Statistical analysis

The significance of differences in clinical characteristics between the two groups was assessed by Fisher's exact test. For survival analyses, the starting time was the date of blood collection, and a census was taken of all patients who were still alive at the date of the last follow-up. Kaplan–Meier curves were plotted to assess overall survival (OS), and different survival curves were compared using the log-rank test. Prognostic factors were examined by univariate and multivariate analyses using the Cox proportional hazard model. The variables for univariate analysis were age, sex, clinical variant, PS, presence or absence of B symptoms, WBC, lymphocyte count, eosinophil count, Hb count and Plt count in the peripheral blood, serum calcium level, serum albumin level, serum LDH level, and presence or absence of extranodal involvement at more than one site. Variables considered for possible inclusion in the regression analysis were those that showed a significant difference in the univariate analysis. All statistical analyses were performed using StatView software (SAS Institute, version 5.0, Cary, NC). In this study, $P < 0.05$ was considered significant.

3. Results

3.1. Patient characteristics

Among the 158 ATLL patients enrolled in the present study, there were 90 males and 68 females with an age range of 38–89 years (median age, 62 years), and the event (patient's death) was observed in 109 patients (69.0%). The OS curve of all ATLL cases is shown in Fig. 1A. The 50% OS ± standard error was 11.4 ± 0.3 months, which was nearly in agreement with values obtained in previous clinical trials in Japan [14]. The OS was significantly shorter in ATLL patients with the aggressive variant than in those with the indolent variant (50% OS, 10.5 months versus 22.5 months) (Fig. 1B). The OS was significantly shorter in ATLL patients with a blood eosinophilia than in those without a blood eosinophilia (50% OS, 8.9 months versus 12.1 months) (Fig. 1C). Among the ATLL patients with the aggressive variant, a blood eosinophilia was significantly associated with shorter survival (50% OS, 8.9 months versus 10.8 months) (Fig. 1D).

3.2. Associations between a blood eosinophilia and clinical characteristics among the ATLL patients

The clinical characteristics of the ATLL patients with or without a blood eosinophilia are summarized in Table 1. A blood eosinophilia was significantly associated with a younger age (≤60 years) ($P = 0.0315$), leukocytosis (>10.0×10^3 μL^{-1}) ($P < 0.0001$), lymphocytosis (>4.0×10^3 μL^{-1}) ($P = 0.0238$), and hypoalbuminemia (<3.0 g/dL) ($P = 0.0385$). Regarding the involvement sites, a blood eosinophilia was significantly associated with favored tumor involvement of the liver ($P = 0.0129$), spleen ($P = 0.0124$) and skin ($P = 0.0290$). None of the other clinical characteristics were associated with a blood eosinophilia among the ATLL patients.

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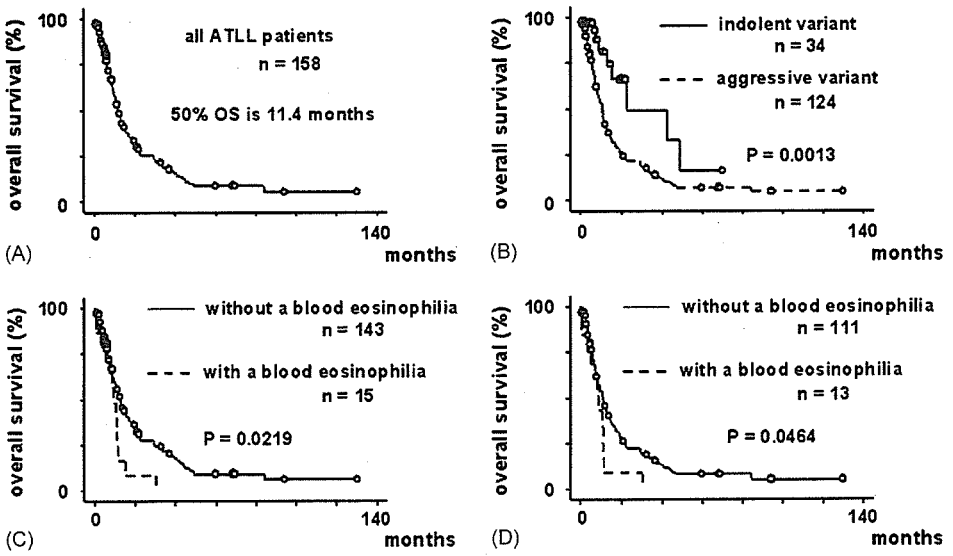

Fig. 1. Overall survival (OS) of ATLL patients. (A) OS curve of all patients with ATLL enrolled in this study ($n = 158$). (B) OS curves of the 124 ATLL patients with the aggressive variant and the 34 ATLL patients with the indolent variant. The 50% survival times were 10.5 and 22.5 months, respectively. The ATLL patients with the aggressive variant showed a significantly worse prognosis. (C) OS curves of the ATLL patients according to a blood absolute eosinophil count. The ATLL patients with a blood eosinophilia (a blood absolute eosinophil count $> 500\ \mu L^{-1}$) showed a significantly worse prognosis. (D) OS curves of the ATLL patients with the aggressive variant ($n = 124$) according to a blood absolute eosinophil count. The ATLL patients with the aggressive variant with a blood eosinophilia showed a significantly worse prognosis.

3.3. Prognostic factors in ATLL patients

Univariate Cox proportional hazard analysis identified the following unfavorable prognostic factors with respect to the ATLL patients' survival: the aggressive variant, worse PS (2–4), presence of B symptoms, a blood eosinophilia, a high serum calcium level (>11 mg/dL), hypoalbuminemia, a high LDH level (greater than twice the upper limit of normal), and extranodal involvement of more than one site (Table 2). Multivariate analysis demonstrated that worse PS, a blood eosinophilia, and a high LDH level were independent and significant unfavorable prognostic factors (Table 2).

3.4. Associations between a blood eosinophilia and clinical characteristics among the ATLL patients with the aggressive variant

The clinical characteristics of the aggressive ATLL patients with or without a blood eosinophilia were also analyzed. A blood eosinophilia was significantly associated with leukocytosis ($>10.0 \times 10^3\ \mu L^{-1}$) ($P < 0.0001$) and lymphocytosis ($>4.0 \times 10^3\ \mu L^{-1}$) ($P = 0.0296$) among the ATLL patients with the aggressive variant (data not shown). Regarding the involvement sites, a blood eosinophilia was significantly associated with favored tumor involvement of the liver ($P = 0.0152$), spleen ($P = 0.0296$) and skin ($P = 0.0181$) among the ATLL patients with the aggressive variant (data not shown). None of the other clinical characteristics were associated with a blood eosinophilia among the ATLL patients with the aggressive variant.

3.5. Prognostic factors for ATLL patients with the aggressive variant

Univariate Cox proportional hazard analysis identified the following unfavorable prognostic factors with respect to the aggressive ATLL patients' survival: worse PS, presence of B symptoms, a blood eosinophilia, and a high LDH level (Table 3). Multivariate analysis demonstrated that worse PS and a high LDH level were independent and significant unfavorable prognostic factors among the ATLL patients with the aggressive variant (Table 3).

4. Discussion

In the present study, we found that a blood eosinophilia was an independent and significant unfavorable prognostic factor in patients with ATLL. This study is in agreement with our previous study showing that there was a significant relationship between a blood eosinophilia and a high serum IL-5 level, and that a high serum IL-5 level was an independent and significant unfavorable prognostic factor among the patients with ATLL [8]. Interestingly, a blood eosinophilia did not seem to directly reflect the tumor burden, since it was neither significantly associated with an increased serum LDH level nor with extranodal involvement at more than one site. In addition, the incidences of blood eosinophilia in indolent and aggressive variants of ATLL patients were not significantly different. Since it was reported that the ATLL cells of some, but not all, patients with ATLL express IL-5 [15–17], the main source of serum IL-5 in patients with a high serum

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Table 1
Clinical characteristics according to peripheral eosinophil count

Characteristics	Eosinophil count		*P* value
	>500 μL^{-1}, *n* (%) [15 (9.5)]	≤500 μL^{-1}, *n* (%) [143 (90.5)]	
Age (year)			
>60	4 (26.7)	81 (56.6)	
≤60	11 (73.3)	62 (43.4)	0.0315
Sex			
Male	12 (80.0)	78 (54.5)	
Female	3 (20.0)	65 (45.5)	n.s.
Clinical variant			
Aggressive	13 (86.7)	111 (77.6)	
Indolent	2 (13.3)	32 (22.4)	n.s.
Performance status			
2–4	5 (33.3)	49 (34.3)	
0–1	10 (66.7)	94 (65.7)	n.s.
B symptom			
+	6 (40.0)	37 (25.9)	
−	9 (60.0)	106 (74.1)	n.s.
WBC ($\times 10^3$ μL^{-1})			
>10.0	14 (93.3)	56 (39.2)	
≤10.0	1 (6.7)	87 (60.8)	<0.0001
Lymphocyte ($\times 10^3$ μL^{-1})			
>4.0	10 (66.7)	50 (35.0)	
≤4.0	5 (33.3)	93 (65.0)	0.0238
Hb (g/dL)			
<10	3 (20.0)	16 (11.2)	
≥10	12 (80.0)	127 (88.8)	n.s.
Plt ($\times 10^3$ μL^{-1})			
<100	3 (20.0)	14 (9.8)	
≥100	12 (80.0)	129 (90.2)	n.s.
Ca (mg/dL)			
>11.0	2 (13.3)	24 (16.8)	
≤11.0	13 (86.7)	119 (83.2)	n.s.
Albumin (g/dL)			
<3.0	5 (33.3)	17 (11.9)	
≥3.0	10 (66.7)	126 (88.1)	0.0385
LDH			
>2N	8 (53.3)	52 (36.4)	
≤2N	7 (46.7)	91 (63.6)	n.s.
Involvement sites			
Lymph node	12 (80.0)	106 (74.1)	n.s.
Bone marrow	9 (60.0)	63 (44.1)	n.s.
Peripheral blood	12 (80.0)	106 (74.1)	n.s.
Lung	1 (6.7)	3 (2.1)	n.s.
Liver	6 (40.0)	18 (12.6)	0.0129
Spleen	9 (60.0)	36 (25.2)	0.0124
Gastrointestinal tract	1 (6.7)	29 (20.3)	n.s.
Central nervous system	0 (0)	2 (14)	n.s.
Bone	1 (6.7)	3 (2.1)	n.s.
Skin	8 (53.3)	35 (24.5)	0.0290
Extra lymph node involvement at more than one site	10 (66.7)	63 (44.1)	n.s.

n, number; WBC, white blood cell count; Hb, hemoglobin; Plt, platelet count; Ca, calcium level; LDH, lactate dehydrogenase; Aggressive: acute and lymphoma subtypes of ATLL; Indolent: chronic and smoldering subtypes of ATLL; LDH > 2N, the LDH level is greater than twice the upper limit of normal at the laboratory of the respective hospital; ns., not significant.

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Table 2
Prognostic factors affecting overall survival among all ATLL patients

Variable	Unfavorable	Univariate		Multivariate	
		Hazard ratio (95%[a]CI)	*P* value	Hazard ratio (95%[a]CI)	*P* value
Clinical variant	Aggressive	2.838 (1.433–5.621)	0.0028	–	
Performance status	2–4	2.132 (1.454–3.126)	0.0001	1.879 (1.251–2.821)	0.0024
B symptom	Present	2.081 (1.396–3.101)	0.0003	–	
Blood eosinophilia	>500 μL^{-1}	1.988 (1.102–3.588)	0.0225	1.887 (1.029–3.462)	0.0403
Calcium	>11 mg/dL	1.689 (1.036–2.755)	0.0357	–	
Albumin	<3.0 g/dL	1.736 (1.027–2.933)	0.0395	–	
LDH	>2N	2.232 (1.523–3.271)	<0.0001	1.760 (1.173–2.641)	0.0063
Extranodal involvement	≥2	1.829 (1.250–2.675)	0.0019	–	

[a] CI, confidence interval.

Table 3
Prognostic factors affecting overall survival among the ATLL patients with the aggressive variant

Variable	Unfavorable	Univariate		Multivariate	
		Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
Performance status	2–4	1.881 (1.263–2.802)	0.0019	1.662 (1.102–2.508)	0.0155
B symptom	Present	1.715 (1.136–2.589)	0.0102	–	
Blood eosinophilia	>500 μL^{-1}	1.867 (1.009–3.455)	0.0469	–	
LDH	>2N	1.884 (1.265–2.806)	0.0018	1.668 (1.106–2.516)	0.0147

IL-5 level seems to be ATLL cells. Thus, patients with ATLL cells that express IL-5 seem to have a blood eosinophilia and an unfavorable prognosis, regardless of the tumor burden. We surmise that the IL-5 produced by ATLL cells may induce a much greater shift in the Th1/Th2 balance in favor of a Th2 response in some ATLL patients, placing the host in a highly immunocompromised state.

In ATLL patients with the aggressive variant, a blood eosinophilia was a significant unfavorable prognostic factor, but it was not an independent prognostic factor. Multivariate Cox proportional hazard analysis including two factors, a blood eosinophilia and a high LDH level, showed that a blood eosinophilia was not an independent prognostic factor in ATLL patients with the aggressive variant.

We showed here that a blood eosinophilia was significantly associated with favored tumor involvement of the liver, spleen and skin, not only in all ATLL patients but also in ATLL patients with the aggressive variant. These observations were consistent with our previous report that a high IL-5 level was significantly associated with favored tumor involvement of the liver and skin in ATLL patients, and favored tumor involvement of the skin in ATLL patients with the aggressive variant [8]. With respect to the association between a blood eosinophilia and liver/spleen involvement in ATLL patients, we have neither data of our own nor any reports by other investigators that might suggest possible explanations of this, and thus further investigations are warranted. In contrast, we have some possible explanations for the association between a blood eosinophilia and skin involvement in ATLL patients, as follows. The CC chemokine receptor 4 (CCR4) is expressed on Th2 cells [18], and the specific ligand, thymus and activation-regulated chemokine (TARC)/CCL17 for CCR4, is abundant in inflamed skin [19–21]. It is important to note that we have previously reported that CCR4 expression was significantly associated with skin involvement in ATLL, and CCR4 expression was an independent and significant unfavorable prognostic factor in ATLL [22]. These observations suggest that the TARC/CCL17, which is produced abundantly in the lymphoma-affected skin, strongly stimulates and attracts not only CCR4 positive ATLL cells, which may produce IL-5, but also Th2 cells, which produce IL-5, thus contributing to a blood eosinophilia.

In conclusion, a blood eosinophilia is an independent and significant unfavorable prognostic factor in patients with ATLL, and it seems to reflect the fact that the host's Th1/Th2 immune balance favors a Th2 response. Measurement of a blood eosinophil count, which is usually part of a routine blood examination in any hospital and can be performed quickly and easily using a small blood sample, is useful for predicting the prognosis and for determining a suitable treatment strategy for ATLL patients.

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Allogeneic Bone Marrow Transplantation from Unrelated Human T-Cell Leukemia Virus-I–negative Donors for Adult T-Cell Leukemia/Lymphoma: Retrospective Analysis of Data from the Japan Marrow Donor Program

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an HLA-matched related donor has been suggested to improve the poor prognosis of adult T-cell leukemia/lymphoma (ATLL). However, the infusion of HTLV-I–infected cells from HTLV-I–positive related donors could lead to the development of donor-derived ATLL under immunosuppressive conditions. Although most ATLL patients lack a suitable HLA-matched related donor and require an HTLV-I–negative unrelated donor, little information is currently available regarding the outcome of unrelated bone marrow transplantation (UBMT) for ATLL. To evaluate the role of UBMT in treating ATLL, we retrospectively analyzed data from 33 patients with ATLL treated by UBMT through the Japan Marrow Donor Program (JMDP). Overall survival (OS), progression-free survival, and cumulative incidence of disease progression and progression-free mortality at 1 year after UBMT were 49.5%, 49.2%, 18.6%, and 32.3%, respectively. Multivariate analysis identified recipient age as an independent prognostic factor for OS (P = .044). Patients age ≥50 years who showed nonremission at transplantation tended to have higher rates of treatment-related mortality. Our observations suggest that UBMT could represent a feasible treatment option for ATLL patients and warrant further investigation based on these risk factors.

KEY WORDS

Adult T-cell leukemia/lymphoma • Allogeneic hematopoietic stem cell transplantation • Unrelated donor • Graft-versus-adult T-cell leukemia/lymphoma

INTRODUCTION

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell neoplasm caused by human T-cell leukemia virus type I (HTLV-I) [1,2]. ATLL is generally classified into 4 clinical subtypes based on clinical and laboratory features: acute, chronic, smoldering, and lymphoma type. Clinically, acute- and lymphoma-type ATLL show an aggressive course, with tumor

burden, severe hypercalcemia, multiorgan failure, and poor performance status. ATLL has an extremely poor prognosis, with a median survival of about 6 months for the acute type and about 10 months for the lymphoma type; these patients are usually highly immunocompromised and develop various opportunistic infections. [3] Furthermore, their tumor cells are usually resistant to conventional chemotherapies, because overexpression of multidrug-resistance genes leads to intrinsic drug resistance. [4,5] Intensified chemotherapy [6,7] and autologous stem cell transplantation [8] likewise have failed to improve the prognosis. Thus, alternative treatment strategies for ATLL are needed.

Some cases of successful treatment with allogeneic stem cell transplantation (allo-HSCT) from an HLA-matched related donor have been reported, and a graft-versus-ATLL (GvATLL) effect has been implicated for improving treatments outcomes in transplant patients undergoing transplantation for ATLL. [9–11] However, more than 2/3 of patients with ATLL lack HLA-matched related donors. Furthermore, approximately 2/3 of the siblings of patients with ATLL are HTLV-I carriers [12], and allo-HSCT from an HTLV-I–positive donor may carry a risk of promoting the development of ATLL through the addition of a new HTLV-I load on the immunocompromised host. [13,14] Although most ATLL patients lack a suitable HLA-matched related donor and require an unrelated donor to benefit from allo-HSCT, few reports are available concerning the results of unrelated donor bone marrow transplantation (UBMT) for ATLL [9,11,15–18], and the number of patients in these few reports has been too small on which to base any solid conclusions. Therefore, to clarify the feasibility and efficacy of UBMT from an HTLV-I-negative donor for ATLL, we retrospectively analyzed registered data and clinical outcomes of UBMT for ATLL through the Japan Marrow Donor Program (JMDP).

PATIENTS AND METHODS

Patients and Transplantation Procedure

The subjects of this retrospective study consisted of 33 patients with ATLL (acute type, n = 20; lymphoma type, n = 7; not described, n = 6) who received UBMT from a donor mediated and recruited through the JMDP between September 1999 and January 2004. The clinical indications for UBMT were determined by each individual institution. The median time from diagnosis of ATLL to UBMT was 8 months (range, 5–28 months). At the time of transplantation, 13 patients were in complete remission (CR), 2 patients were in partial remission (PR), and 14 patients were in nonremission (NR); disease status at the time of transplantation was not described in 4 patients. CR status was reported in detail for 13 patients, with 11 patients in first CR (CR1) and 2 patients in second CR (CR2) (Table 1). All unrelated donors were HTLV-I antibody–negative. Serologic typing for HLA-A, -B, and -DR was performed using a standard 2-stage complement-dependent test of microcytotoxicity. [19] Alleles at the HLA-A, -B, and -DRB1 loci were identified by high-resolution DNA typing as described previously. [20] Serologic typing revealed that 22 patients were matched at the HLA-A, -B, and -DR loci. Four patients were mismatched at 1 HLA-DR locus, and 1 patient was mismatched at 2 loci of HLA-A and -DR. DNA typing revealed that 13 patients were matched at HLA-A, -B and -DRB1 loci. Ten patients were mismatched at 1 locus; 9 patients were mismatched at the HLA-DRB1 locus, and the remaining patient was mismatched at 1 HLA-A locus. Another 4 patients were mismatched at 2 loci. HLA typing data were not described in 6 patients. Patient and donor characteristics are summarized in Table 2.

Table 1. *Patient characteristics*

Characteristic	Value
Median age at transplantation, years (range)	49 (range, 24–59)
Sex, n	
Male	18
Female	15
Performance status, n	
0–1	21
2–4	4
ND	8
Subtypes of ATLL, n	
Acute	20
Lymphoma	7
ND	6
Disease status at transplantation, n	
CR or PR	15
NR	14
ND	4
Duration from diagnosis to UBMT, n	
Within 1 year	21
Beyond 1 year	11
ND	1
Conditioning, n	(TBI-containing, 22; non–TBI-containing, 11)
CST	27
RIST	6
Cell dose, n	
$< 3.0 \times 10^8$/kg	16
$\geq 3.0 \times 10^8$/kg	14
ND	3
GVHD prophylaxis, n	
CsA + MTX	13
TCR + MTX	20

ND indicates not described; CR, complete remission; PR, partial remission; NR, nonremission; UBMT, unrelated bone marrow transplantation; TBI, total body irradiation; CST, conventional stem cell transplantation; RIST, reduced-intensity stem cell transplantation; GVHD, graft-versus-host disease; CsA, cyclosporine; MTX, methotrexate; TCR, tacrolimus.

Table 2. *Patient and donor characteristics*

Characteristic	Value
HLA-A, -B, and -DRB1 allele mismatches, n	
0	13
1	10
2	4
ND	6
Sex of donor/patient, n	
Male/male	13
Female/female	8
Female/male	5
Male/female	7
Extent of ABO match, n	
Match	19
Minor mismatch	4
Major mismatch	7
Major/minor	2
ND	1

ND indicates not described.

Transplantation was performed according to the protocol of each institution; therefore, conditioning regimens and prophylaxis against graft-versus-host disease (GVHD) differed among patients. Conditioning regimens were myeloablative in 27 patients; total body irradiation (TBI) was incorporated in 22 patients. Reduced-intensity conditioning regimens were used in 6 patients. GVHD prophylaxis included cyclosporine (n = 13) and tacrolimus (n = 20) combined with methotrexate. All recipients received bone marrow transplantation, which was not manipulated.

Assessment of Engraftment, GVHD, Survival, and Progression-Free Mortality

The day of sustained engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count exceeding 0.5×10^9/L. Acute GVHD was diagnosed and graded according to the standard criteria described previously. [21,22] Chronic GVHD was evaluated according to standard criteria [23] in patients who survived more than 100 days after transplantation. Overall survival (OS) was defined as the duration (in days) from transplantation to death from any cause. Progression-free survival (PFS) was defined as days from transplantation to disease progression or death from any cause. Progression-free mortality was defined as death without disease progression.

Data Management and Statistical Considerations

Data were collected by the JMDP using a standardized report form. Follow-up reports were submitted at 100 days, 1 year, and every subsequent year after transplantation. The cumulative incidence of disease progression and progression-free mortality were evaluated using Gray's method, [24] considering each other risk as a competing risk. OS and PFS were estimated using the Kaplan-Meier method. Potential confounding factors considered in the analysis were age, sex, disease status, duration from diagnosis to transplantation, Eastern Cooperative Oncology Group (ECOG) performance status, [25] conditioning regimen, number of bone marrow cells transplanted, and presence of grade II–IV acute GVHD. Proportional hazard modeling was used to evaluate any influence of these factors on OS, treating development of acute GVHD as a time-dependent covariate. Factors associated with at least borderline significance ($P < .05$) in univariate analyses were subjected to multivariate analyses using backward-stepwise proportional hazards modeling. P values $P < .10$ were considered statistically significant.

RESULTS

Engraftment and GVHD

Transplantation outcomes are summarized in Table 3. The median number of cells transplanted was 2.44×10^8 nucleated cells/kg of recipient body weight (range, $0.58–3.58 \times 10^8$ nucleated cells/kg of recipient body weight). Five patients (15%) died within 20 days. Neutrophil engraftment was achieved in 28 patients. Late graft failure occurred in 1 of these 28 patients, although the patient showed engraftment on

Table 3. *Transplantation outcome*

	Value
Alive/dead, n	19/14
Median follow-up for survivors, days (range)	139 (87–600)
Cause of death	
Progression, n	2
Death without progression, n	9
Median days after transplantation (range)	32 (10–71)
Late graft failure, n	1
GVHD, n	1
Infection, n	3
TMA, n	2
VOD, n	1
Arrhythmia, n	1
Not described, n	3
Disease progression, n	5
Median days after transplantation (range)	122 (61–223)
Engraftment, n	
Engraftment	28
Death within 20 days	5
Late graft failure	1
Acute GVHD, n	
None	3
Grade I	8
Grade II	12
Grade III	3
Grade IV	2
Chronic GVHD, n	
None	14
Limited	1
Extensive	3

GVHD indicates graft-versus-host disease; TMA, thrombotic microangiopathy; VOD, venooculusive disease.

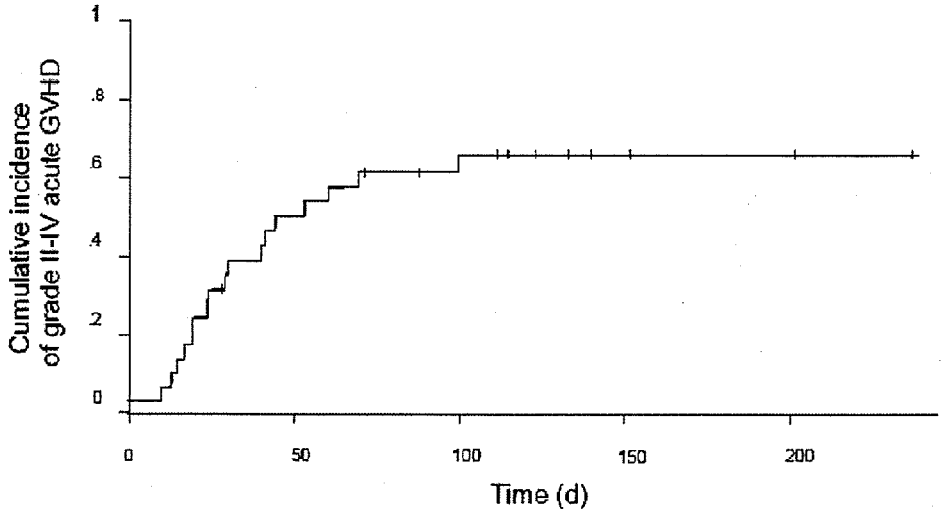

Figure 1. Cumulative incidence of grade II–IV acute GVHD in patients who achieved neutrophil engraftment.

day 14. Acute GVHD developed in 25 of the 28 patients who achieved engraftment (89%): grade I GVHD in 8 patients, grade II in 12 patients, grade III in 3 patients, and grade IV in 2 patients. The cumulative incidence of grade II–IV acute GVHD was 61% (Figure 1). Chronic GVHD developed in 4 of 18 patients, with limited disease in 1 patient and extensive disease in the other 3 patients.

Survival and disease progression

The 1-year OS and PFS were 49.5% (95% confidence interval [CI], 31.2%–78.5%) and 49.2% (95% CI, 33.6%–72.1%), respectively (Figure 2). Disease progression was observed in 5 patients, and the median number of days from transplantation to disease progression was 122 (range, 61–223 days). As of the last follow-up, 14 deaths had been reported. Primary cause of death was disease progression in 2 patients and was not described in 3 patients, but the other 9 deaths were not due to disease progression (see Table 3). Primary causes of transplantation-related death within 100 days after transplantation were late graft failure in 1 patient, GVHD in 1 patient, infection in 3 patients (with methicillin-resistant *Staphylococcus aureus*–positive sepsis in 1 patient and pulmonary infection in 2 patients), thrombotic microangiopathy (TMA) in 2 patients, veno-occlusive disease (VOD) in 1 patient, and arrhythmia in 1 patient.

Univariate and Multivariate Analyses for OS

Pretransplantation and posttransplant factors were calculated for OS (Table 4). In univariate analyses, OS was not significantly associated with sex, duration from diagnosis to transplantation, ECOG performance status, conditioning regimen, number of bone marrow cells transplanted, or presence of grade II–IV acute GVHD. On the other hand, patient age and disease status at transplantation were identified as significant independent risk factors. In multivariate analyses, only patient age at transplantation was identified as exerting a significant independent risk impact on OS (≥50 years vs <50 years; relative risk, 3.47; 95% CI, 1.03–11.6; $P = .044$). Disease status at transplantation exerted a marginally significant impact on OS (NR vs CR or PR; relative risk, 3.17; 95% CI, 0.96–10.5; $P = .059$) (Figure 3).

Influence of Pretransplantation Factors on Disease Progression and Progression-Free Mortality

The cumulative incidence of disease progression and progression-free mortality at 1 year were 18.6% and 32.3%, respectively (Figure 4). To clarify how age and disease status at transplantation affected OS, we evaluated the relationship between these factors and the incidence of progression-free mortality. The cumulative incidence of progression-free mortality was significantly higher in patients age ≥50 years at transplantation (50% vs 18%; $P = .048$; Figure 5A). NR at transplantation exerted a marginally significant effect on increased progression-free mortality (54% vs 20%; $P = .070$; Figure 5B).

DISCUSSION

This study analyzed the data and evaluated treatment outcomes for 33 patients with ATLL who received UBMT. Two important findings were identified regarding UBMT for ATLL. First, UBMT from HTLV-I–negative donors for ATLL represents a feasible treatment. Second, recipient age (≥50 years) and NR disease status at transplantation were independent risk factors for OS, and patients with ATLL displaying these risk factors tended to exhibit higher frequencies of treatment-related mortality.

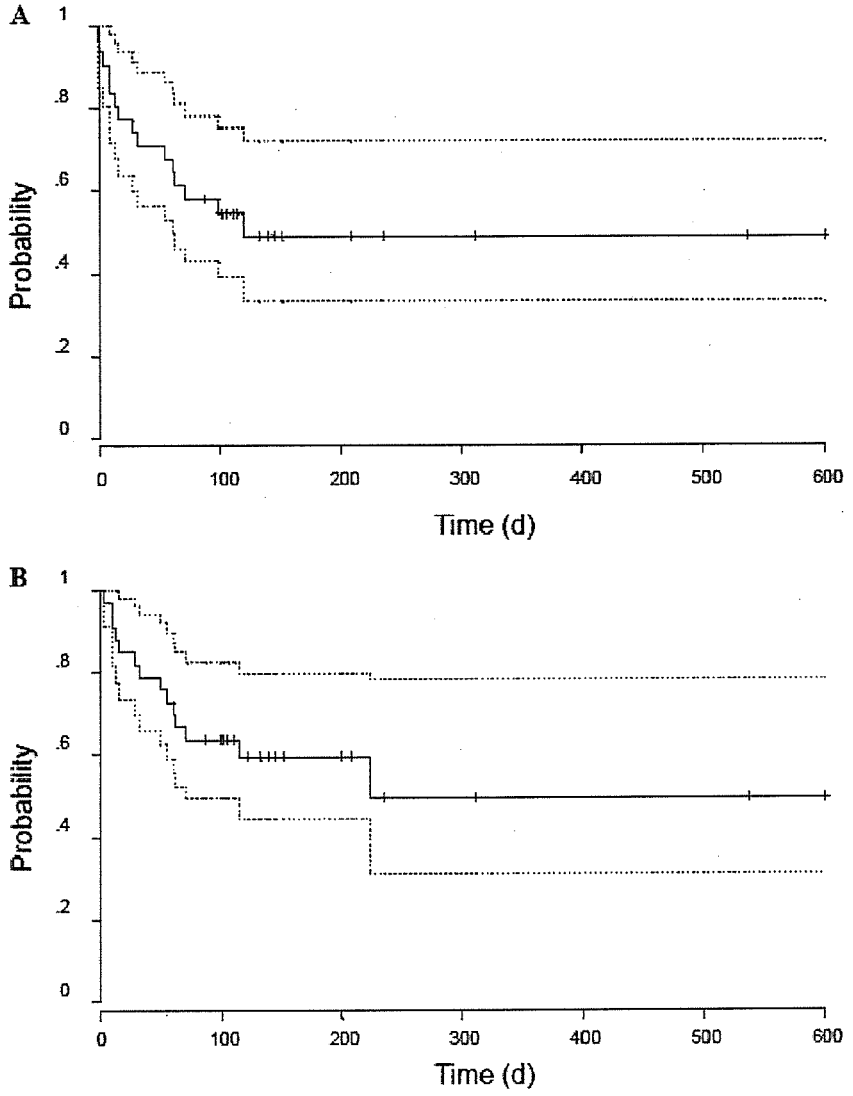

Figure 2. Probability of progression-free survival (A) and overall survival (B) after unrelated bone marrow transplantation for adult T-cell leukemia/lymphoma. Dashed lines represent 95% confidence intervals.

Table 4. *Prognosis factors in univariate and multivariate analyses*

	Univariate		Multivariate	
	Relative risk (95% CI)	*P*	Relative risk (95% CI)	*P*
Age ≥50 versus <50 years	4.03 (1.23–13.3)	.022	4.03 (1.23–13.3)	.022
Male versus female	0.97 (0.34–2.80)	.95		
PS 0–1 versus 2–4	0.44 (0.11–1.70)	.23		
NR versus CR or PR	3.37 (1.03–11.0)	.044		.059
UBMT within 1 year versus beyond 1 year	0.54 (0.15–2.00)	.35		
RIST versus CST	0.71 (0.19–2.59)	.60		
TBI versus non-TBI	1.35 (0.45–4.04)	.59		
Cell dose < 3.0 × 10^8/kg versus ≥ 3.0 × 10^8/kg	0.98 (0.31–3.05)	.97		
GVHD II–IV present versus absent	1.91 (0.50–7.26)	.34		

CI indicates confidence interval; PS, performance status; NR, nonremission; CR, complete remission; PR, partial remission; UBMT, unrelated bone marrow transplantation; RIST, reduced-intensity stem cell transplantation; CST, conventional stem cell transplantation; TBI, total body irradiation; GVHD, graft-versus-host disease.

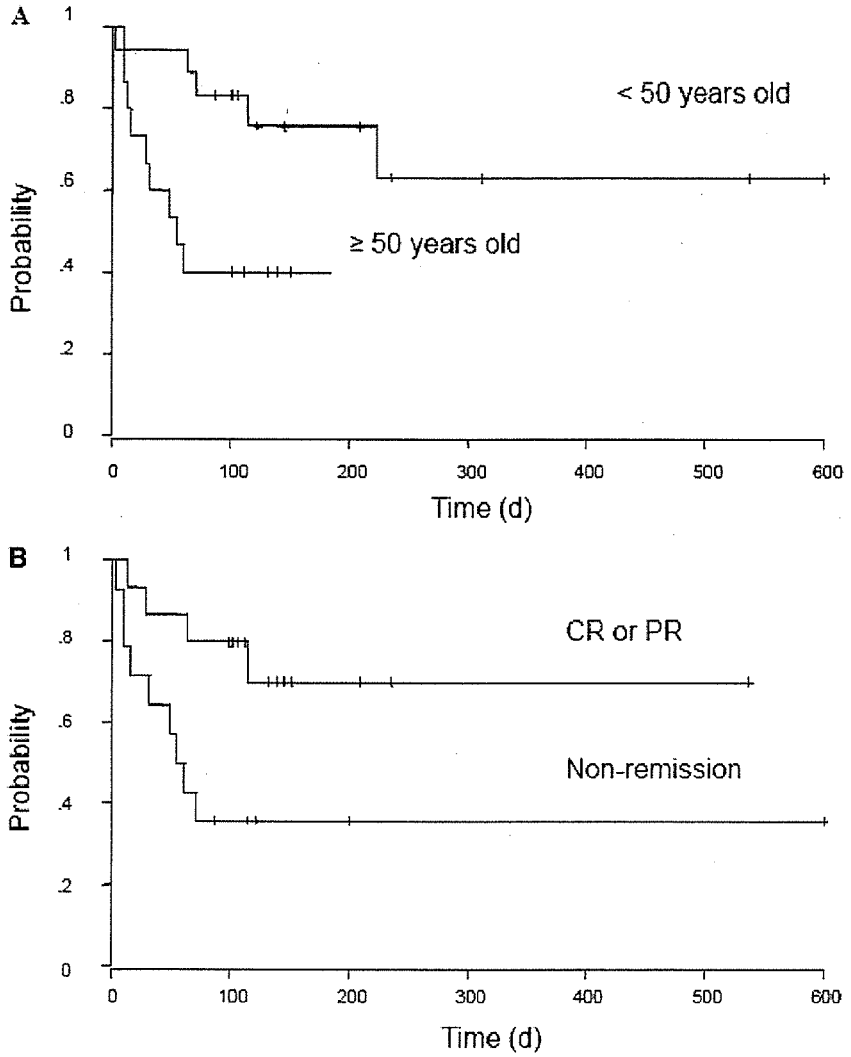

Figure 3. Overall survival according to pretransplantation factors, age (A) and disease status at transplantation (B).

ATLL has an extremely poor prognosis, with projected 2- and 4-year survival rates of 16.7% and 5.0% for the acute type and 21.3% and 5.7% for the lymphoma type, respectively. [3] Neither intensified chemotherapy nor autologous stem cell transplantation have improved the prognosis. Encouraging results for allo-HSCT for ATLL from HLA-matched related donors have been reported by several groups; thus, allo-HSCT may improve the poor prognosis of ATLL. However, the number of patients in most reports has been too small to allow evaluation of the efficacy of allo-HSCT for ATLL. The present results were derived from a large number of patients who underwent transplantation (33 patients) performed through the JMDP. Longer follow-up is, of course, needed to confirm the curative potential of allo-HSCT for ATLL. However, the good survival rates noted here suggest that allo-HSCT is an effective treatment for ATLL, and that patients with ATLL will benefit from allo-HSCT through HTLV-I–negative unrelated donors, because the OS and PFS rates at 1 year after UBMT were 49.5% and 49.2%, respectively. Compared with the results for patients with non-Hodgkin's lymphoma in the National Marrow Donor Program, the incidence of grade III–IV acute GVHD in the present study was low (18% vs 30%). [26] The outcome in the present study appears to be favorable, possible due to the lower incidence of grade III–IV acute GVHD. This observation is compatible with previous studies showing a lower incidence of acute GVHD in Japanese patients compared with Western patients, which might reflect the less diverse genetic background of in the Japanese population. [27,28]

Frequency of relapse after transplantation differs between autologous and allo-HSCT for ATLL. The use of high-dose chemotherapy with autologous HSCT has been reported in only 9 patients, all of whom relapsed or died from transplantation-related mortality. [8] In contrast, the cumulative incidence of

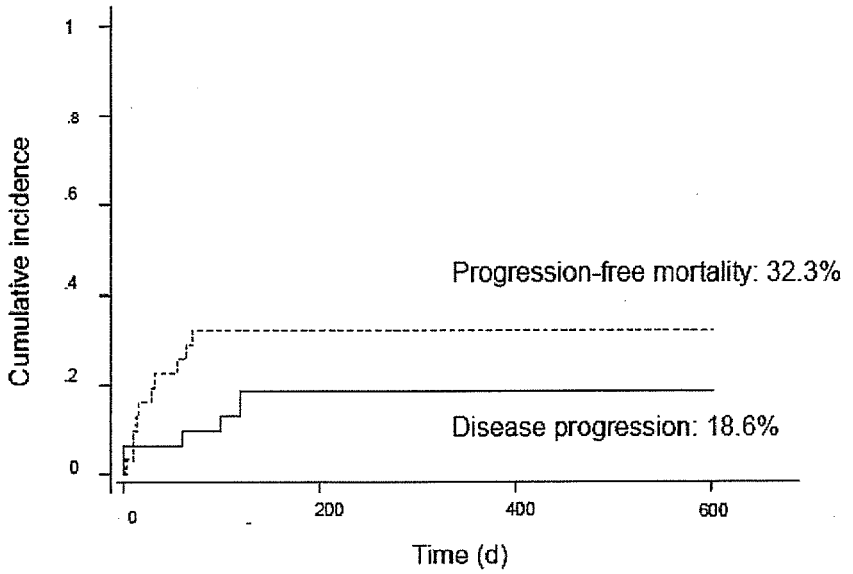

Figure 4. Cumulative incidence of disease progression (—) and progression-free mortality (---) after transplantation.

disease progression was lower after UBMT in this study. Interestingly, patients with ATLL displaying acute or chronic GVHD reportedly did not relapse. [9] In another report, patients with ATLL who relapsed after allo-HSCT reachieved CR after tapering or discontinuation of immunosuppressive agents and donor lymphocyte infusions. [10,11] Reactivation in tax-specific CD8-positive cytotoxic T lymphocytes (CTLs), which has been recently shown in patients with ATLL after allo-HSCT, may indicate a potential contribution of CTLs to anti-ATLL immunity and induction of a GvATLL effect. [29] These results strongly suggest that a GvATLL effect could work on some patients with ATLL to prevent relapse after allo-HSCT. In the present study, neither univariate nor multivariate analysis showed a survival benefit for acute GVHD. We were unable to analyze the relationship between chronic GVHD and relapse, because of the low number of patients with chronic GVHD. In fact, the number of patients may have been insufficient to confirm GvATLL in this study. On the other hand, the absence of benefit from GVHD in preventing relapse suggests that a GvATLL effect could occur in patients with ATLL after allo-HSCT without clinically obvious GVHD. [11]

Transplantation-related mortality was a significant problem in this study. Five patients (15%) died within 20 days, from infection in 3 patients and TMA in 2 patients. Nine patients (27%) died within 100 days, due to infection in 3 patients, TMA in 2 patients, and VOD in 1 patient. Patients with ATLL might have an increased risk of frequent opportunistic infection, because they have an associated T-cell immunodeficiency. Furthermore, ATLL is usually systemic in distribution, and the accumulated organ damages as a result of repeated cytotoxic chemotherapy seen in patients before transplantation may have contributed to the onset of TMA. In univariate and multivariate analysis, recipient age (≥50 years) and NR disease status at transplantation represented significant risk factors for OS. The multivariate analyses were limited by the small number of patients in each subgroup; however, patients displaying these risk factors tended to have a higher rate of treatment-related mortality than patients without these factors, and it can be assumed that these risk factors have a significant relationship with outcome clinically. In this study, mostly myeloablative conditioning regimens were used before transplantation. Given that conventional allo-HSCT is designed to eradicate tumor cells with myeloablative intensity using maximally tolerated doses of high-dose chemotherapy and radiotherapy, the desirable effects often may be offset by overwhelming toxicity in patients age ≥50 years. Moreover, the number of patients with ATLL who are eligible for allo-HSCT with myeloablative conditioning is limited, because the typical patient with ATLL has a relatively advanced age at presentation (about 60 years). To reduce treatment-related mortality, allo-HSCT with reduced-intensity conditioning offers a new treatment option for patients with ATLL who are ineligible for allo-HSCT with myeloablative conditioning due to advanced age or medical infirmity. [30,31] Okamura et al [32] reported on 16 patients age > 50 years with ATLL who underwent allo-HSCT with reduced-intensity conditioning from HLA-matched related donors and found that treatment-related mortality was acceptable and that allo-HSCT with reduced-intensity conditioning was a feasible treatment for ATLL. Given these findings, UBMT

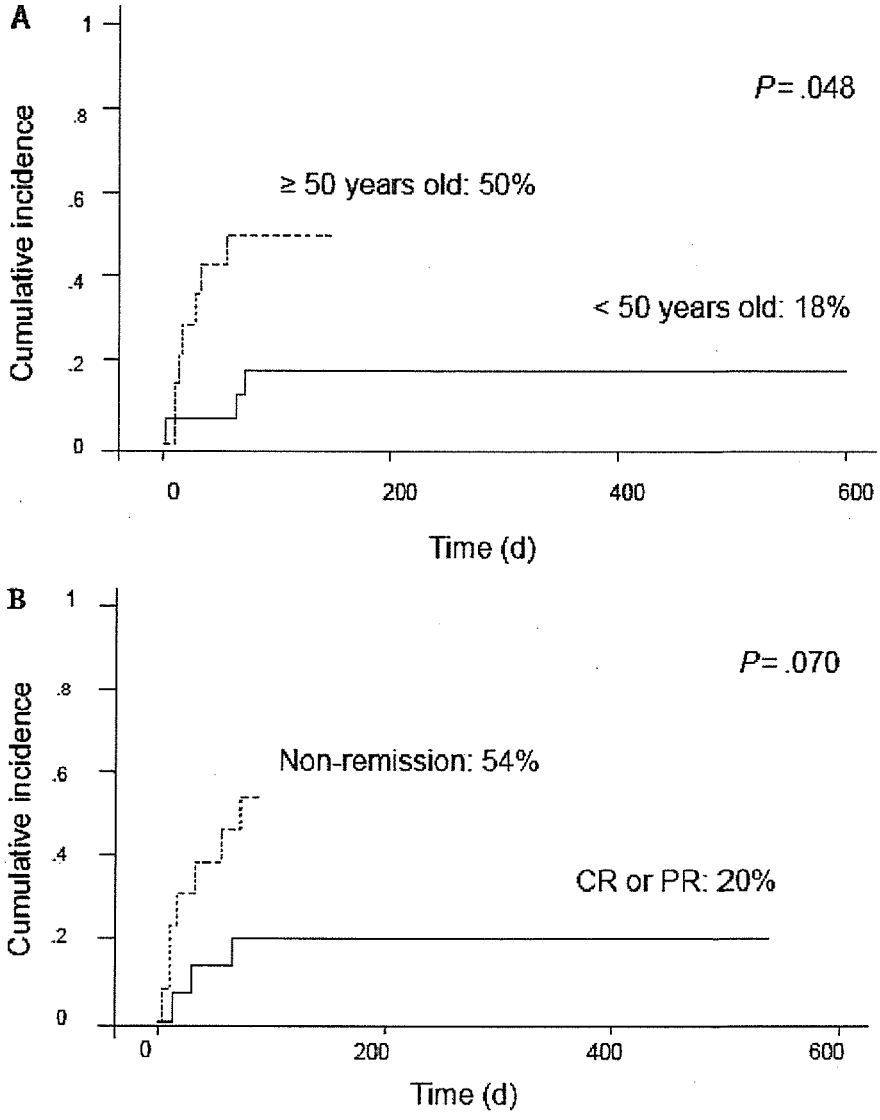

Figure 5. Cumulative incidence of progression-free mortality grouped according to pretransplantation factors, age (A) and disease status at transplantation (B).

with reduced-intensity conditioning should be considered for elderly patients with ATLL.

Another concern related to allo-HSCT for ATLL involves the use of HTLV-1–positive carrier donors. About 2/3 of siblings of patients with ATLL are HTLV-I carriers. From the perspective of HTLV-I–positive donor risk, granulocyte colony–stimulating factor (G-CSF) can reportedly stimulate the proliferation of ATLL cells [33], and HTLV-I–positive donors may be at increased risk of developing ATLL due to the administration of G-CSF in the setting of allogeneic peripheral blood stem cell transplantation. From the perspective of patients with ATLL, allo-HSCT from an HTLV-I–positive donor may carry a risk of HTLV-I–associated disease after allo-HSCT [34] or a risk of promoting the future development of ATLL due to the new HTLV-I load on immunocompromised recipients [13,14]. On the other hand, to date there is no evidence in the JMDP or the literature that ATLL can develop from infected HTLV-I–negative donor cells due to the HTLV-I load of the recipient. The HTLV-I proviral load dramatically decreased to an undetectable level after transplantation, especially after transplantation from HTLV-I–negative donors. [18, 32] This decreased HTLV-I proviral load was observed after both myeloablative and reduced-intensity conditioning. Transplantation from an HTLV-I–positive donor is reportedly associated with a higher frequency of relapse compared with transplantation from an HTLV-I–negative donor. [11] Therefore, the uninfected normal donor T cells might overwhelm infected HTLV-I recipient T cells due to a GvATLL response and might act as an antiviral therapy. However, an HTLV-I–positive do-

nor might avoid clonal expansion of HTLV-I–infected T lymphocytes after allo-HSCT through the provision of cytotoxic T cells. Thus, it is currently difficult to determine whether an HTLV-I–positive or–negative donor should be selected. Longer follow-up is needed to resolve this issue. In the meantime, a prudent clinical attitude toward both HTLV-I–positive donors and recipients with ATLL is warranted.

In conclusion, allo-HSCT from an HTLV-I–negative unrelated donor appears to be an feasible alternative treatment for patients with ATLL for whom an HLA-matched related donor is unavailable. Further prospective controlled studies are needed to assess the efficacy of allo-HSCT for ATLL and to define the clinical indications of allo-HSCT for ATLL, taking into account donor selection, the conditioning regimen, and the prognostic factors identified in this study.

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APPENDIX: PARTICIPATING INSTITUTIONS

The following centers in Japan participated in this study: Hokkaido University Hospital, Sapporo University Hospital, Sapporo Hokuyu Hospital, Japanese Red Cross Asahikawa Hospital, Asahikawa Medical College Hospital, Hirosaki University Hospital, Tohoku University Hospital, Yamagata University Hospital, Akita University Hospital, Fukushima Medical College, National Cancer Center Central Hospital, Institute of Medical Science at the University of Tokyo, Toho University Hospital, Omori Hospital, Tokyo Metropolitan Komagome Hospital, Nihon University Hospital, Itabashi Hospital, Jikei University Hospital, Keio University Hospital, Tokyo Medical College Hospital, Tokyo Medical and Dental University Hospital, Tokyo University Hospital, Yokohama City University Hospital, Kanagawa Children's Medical Center, Kanagawa Cancer Center, Tokai University Hospital, St Marianna University Hospital, Chiba University Hospital, Chiba Children's Hospital, Matsudo Municipal Hospital, Kameda General Hospital, Saitama Children's Medical Center, Saitama Cancer Center Hospital, Saitama Medical School Hospital, Ibaraki Children's Hospital, Jichi Medical School Hospital, Dokkyo University Hospital, Fukaya Red Cross Hospital, Saiseikai Maebashi Hospital, Gunma University Hospital, Niigata University Hospital, Niigata Cancer Center Hospital, Shinshu University Hospital, Saku Central Hospital, Hamamatsu University Hospital, Hamamatsu Medical Center, Shizuoka General Hospital, Shizuoka Children's Hospital, Japanese Red Cross Nagoya First Hospital, Nagoya Daini Red Cross Hospital, Meitetsu Hospital, Nagoya University Hospital, Nagoya Ekisaikai Hospital, National Nagoya Hospital, Aichi Medical School Hospital, Nagoya City University Hospital, Showa Hospital, Anjo Kousei Hospital, Fujita Health University Hospital, Mie University Hospital, Kanazawa University Hospital, Kanazawa Medical University Hospital, Toyama Prefectural Central Hospital, Fukui Medical School Hospital, Shiga University of Medical Science, Center for Adult Disease in Osaka, Kinki University Hospital, Osaka University Hospital, Osaka Medical Center and Research Institute for Maternal and Child Health, Matsushita Memorial Hospital, Hyogo College of Medicine Hospital, Hyogo Medical Center for Adults, Kobe City General Hospital, Kobe University Hospital, Kyoto University Hospital, Kyoto Prefectural University of Medicine Hospital, Social Insurance Kyoto Hospital, Tottori Prefectural Central Hospital, Tottori University Hospital, Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, Yamaguchi University Hospital, Ehime Prefectural Central Hospital, Okayama National Hospital, Kurashiki Central Hospital, Kyushu University Hospital, Harasanshin General Hospital, Hamanomachi General Hospital, National Kyushu Cancer Center, St Mary's Hospital, Kokura Memorial Hospital, Saga Prefectural Hospital, Nagasaki University Hospital, Miyazaki Prefectural Hospital, Kumamoto National Hospital, Kumamoto University Hospital, Oita Medical University Hospital, Kagoshima University Hospital, and Imamura Bun-in Hospital.

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