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ARTICLE

Prognostic importance of pretransplant disease status for posttransplant outcomes in patients with adult T cell leukemia/lymphoma

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Abstract

Adult T cell leukemia/lymphoma (ATL) is an aggressive T cell lymphoma with a poor prognosis. Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) can be a curative treatment for ATL, a significant proportion of allo-HSCT recipients suffer from relapse/progression of ATL. Here we aimed to clarify the risk factors for and outcomes after posttransplant relapse/progression. We retrospectively reviewed 76 patients with ATL who received allo-HSCT at our institute. At the time of allo-HSCT, disease status was complete response in 17 patients, partial response in 29, stable disease (SD) in 18, and progressive disease (PD) in 12. In multivariate analysis, SD/PD at allo-HSCT, lymphoma subtype, reduced-intensity conditioning regimen, and time from diagnosis to allo-HSCT were associated with risk of relapse/progression. After allo-HSCT, 26 patients had relapse/progression at a median of 66 days (range, 13–2064 days). The 2-year overall survival rate after relapse/progression was only 19%. Compared with acute-type, lymphoma-type experienced local recurrence more frequently (1/15 acute vs. 7/11 lymphoma, $P < 0.01$) and had a significantly longer OS after relapse/progression (median; 112 days in acute vs. 554 days in lymphoma, $P < 0.01$). Since the prognosis of patients with ATL who experienced relapse/progression after allo-HSCT was poor, strategies to reduce the risk of these outcomes are warranted.

Introduction

Adult T cell leukemia/lymphoma (ATL) is a peripheral T cell neoplasm that is associated with human T cell leukemia virus type I (HTLV-I) [1–4]. HTLV- I is endemic in southwestern Japan, sub-Saharan Africa, the Caribbean Basin, and South America [3, 4]. In Japan, more than one million people were estimated to be infected with HTLV-I and more than 1000 develop ATL every year [4–6]. For the first-line treatment of aggressive ATL (acute-type and lymphoma-type), which accounts for 80% of ATL, combination chemotherapies such as mLSG15 have been developed [7–9]. However, the median survival of aggressive ATL is approximately 12 months with conventional chemotherapy alone [7, 10]. Although the anti-CCR4 antibody mogamulizumab (Mog) was approved for ATL, the addition of Mog to conventional chemotherapy did not contribute to better overall survival (OS) [11].

Meanwhile, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been considered to be a curative treatment for aggressive ATL. Although early experience with myeloablative allo-HSCT was associated with an unacceptably high incidence of non-relapse mortality (NRM) (40–60%), the introduction of reduced-intensity conditioning (RIC) regimens has expanded the indication of allo-HSCT to elderly patients without compromising OS [12]. Currently, allo-HSCT is considered to be a standard

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treatment in transplant-eligible patients with aggressive ATL [13].

Detailed analyses of risk factors for and clinical outcomes after relapse/progression following allo-HSCT for aggressive ATL are still limited because the registry data of ATL in Japan are missing detailed information such as pretransplant disease status and treatment after relapse/progression. In this study, we evaluated risk factors for and outcomes after relapse/progression at our institute.

Patients and methods

Patients

This study included patients with ATL who underwent their first allo-HSCT between January 2001 and December 2012 at the National Cancer Center Hospital, Tokyo, Japan. Patients who died before graft infusion or who had a history of previous allo-HSCT were excluded.

Definition

Clinical subtypes of ATL were categorized according to Shimoyama's classification [14]. Disease status at allo-HSCT was categorized according to the Japan Clinical Oncology Group criteria [15]. Complete response (CR) was defined as the disappearance of all clinical, microscopic, and radiographic evidence of ATL. In addition, all lymph nodes must regress to normal size (≤1.5 cm in their greatest transverse diameter), and previously involved nodes that were 1.1 to 1.5 cm must decrease to <1.0 cm. The peripheral blood (PB) of HTLV-1 carriers often contains a small percentage of abnormal lymphocytes with polylobated nuclei, the so-called flower cells; provided that <5% of such cells remained, CR was judged to have been attained if the absolute lymphocyte count, including flower cells, was $<4 \times 10^9$/L. Partial response (PR) was defined as a ≥50% reduction in the sum of the products of the greatest diameters of measurable lesion without the appearance of new lesions. PR also required a ≥50% reduction in absolute abnormal lymphocyte counts in PB. Progressive disease (PD) in PB was defined by a ≥50% increase relative to the lowest count of flower cells, and an absolute lymphocyte count, including flower cells, of $\geq 4 \times 10^9$/L. Stable disease (SD) was defined as any other disease status. Progression after allo-HSCT was defined as a ≥50% increase from the smallest sum of the products of the greatest diameters of measurable disease or the increase in the number of abnormal lymphocytes in PB or the appearance of new lesions. Relapse after allo-HSCT was defined as progression after CR.

The conditioning regimens were the same as those used in previous reports [16, 17]. The myeloablative conditioning (MAC) regimen included cyclophosphamide (Cy, 60 mg/kg for 2 days) plus busulfan (Bu, orally 4 mg/kg for 4 days or intravenously (i.v.) 3.2 mg/kg for 4 days), or Cy plus total body irradiation (TBI, 12 Gy), or fludarabine (Flu, 30 mg/m^2 for 6 days) plus Bu4 (orally 4 mg/kg for 4 days or i.v. 3.2 mg/kg for 4 days). The RIC regimen included Flu plus Bu2 (orally 4 mg/kg for 2 days or i.v. 3.2 mg/kg for 2 days) or Flu plus melphalan (Mel, 70 mg/m^2 for 2 days). GVHD prophylaxis included either cyclosporine (CSP) alone or CSP plus short-term methotrexate (MTX) in patients who received stem cells from a related donor, and tacrolimus (TAC) plus short-term MTX in those whose stem cells were derived from an unrelated donor. Neutrophil recovery was defined as an absolute neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days. Acute and chronic GVHD were diagnosed and graded according to standard criteria [18, 19].

Statistical analysis

The endpoints of this study included the incidence of relapse/progression, GVHD, NRM, and the probability of OS after allo-HSCT. We used Fisher's exact test to compare categorical variables and the Mann–Whitney *U* test to compare continuous variables. OS was estimated by the Kaplan–Meier method, and differences between groups were evaluated by the log-rank test. Relapse/progression and NRM were considered to be competing risk events. GVHD and NRM from any cause other than GVHD were considered as competing risk events. The probabilities of relapse/progression, NRM, and GVHD were estimated by the cumulative incidence function, and differences between groups were evaluated by the Gray test. The Cox proportional-hazards regression model was used for the analysis of OS, and Fine and Grey's regression was used for the analysis of relapse/progression and NRM in univariate and multivariate analyses. In multivariate analyses, we included the following factors as covariates: patient age (<55 years vs. ≥55 years), patient gender (male vs. female), ATL clinical subtype (acute-type vs. lymphoma-type), disease status (CR/PR vs. SD/PD), time from diagnosis to allo-HSCT (<7 months vs. ≥7 months), donor type (related vs. unrelated), HLA compatibility (matched vs. mismatched), conditioning intensity (MAC vs. RIC), and GVHD prophylaxis (CSP-based vs. TAC-based). All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0) [20]. More precisely, it is a modified version of R commander (version 1.6–3) designed to add statistical functions frequently used in biostatistics.

Table 1 Patient characteristics

	Disease status			*P* value
	All	CR/PR	SD/PD	
	No. of patients			
	N = 76	*N* = 46 (60.5%)	*N* = 30 (39.5%)	
Age				
Median (range), years	56 (28–69)	56 (28–69)	53 (33–64)	0.15
≤55 years	36 (47.4%)	20 (43.5%)	16 (53.3%)	0.48
>55 years	40 (52.6%)	26 (56.5%)	14 (46.7%)	
Sex				
Male	35 (46.1%)	25 (54.3%)	10 (33.3%)	0.10
Female	41 (53.9%)	21 (45.7%)	20 (66.7%)	
ATL clinical subtype				
Acute	55 (72.4%)	30 (65.2%)	25 (83.3%)	0.12
Lymphoma	21 (27.6%)	16 (34.8%)	5 (16.7%)	
Disease status				
CR	17 (22.4%)	17 (37.0%)	—	—
PR	29 (38.2%)	29 (63.0%)	–	
SD	18 (23.7%)	—	18 (60.0%)	
PD	12 (15.8%)	—	12 (40.0%)	
Relapsed before allo-HCT	7 (9.2%)	3 (6.5%)	4 (13.3%)	0.42
Number of lines of therapy pre-allo-HSCT				
Median (range), lines	1 (1–6)	1 (1–4)	2 (1–6)	<0.01
1 line	41 (53.9%)	31 (67.4%)	10 (33.3%)	<0.01
≥2 lines	35 (46.1%)	15 (32.6%)	20 (66.7%)	
Time from diagnosis to transplantaion				
Median time (range), days	214 (67–881)	216 (67–736)	208 (88–881)	0.87
7 months or less	37 (48.7%)	22 (47.8%)	15 (50.0%)	1.00
More than 7 months	39 (51.3%)	24 (52.2%)	15 (50.0%)	
Donor				
Related	34 (44.7%)	22 (47.8%)	12 (40.0%)	0.64
Unrelated	42 (55.3%)	24 (52.2%)	18 (60.0%)	
Source of stem cells				
Peripheral blood stem cells	31 (40.8%)	20 (43.5%)	11 (36.7%)	0.78
Bone marrow	44 (57.9%)	25 (54.3%)	19 (63.3%)	
Cord blood	1 (1.3%)	1 (2.2%)	0 (0%)	
HLA compatibility				
Matched	49 (64.5%)	31 (67.4%)	18 (60.0%)	0.63
Mismatched	27 (35.5%)	15 (32.6%)	12 (40.0%)	
Conditioning regimen				
Myeloablative	14 (18.4%)	5 (10.9%)	9 (30.0%)	0.07
CY/TBI	4 (5.3%)	1 (2.2%)	3 (10.0%)	
Bu/CY	9 (11.8%)	3 (6.5%)	6 (20.0%)	
Flu/Bu4	1 (1.3%)	1 (2.2%)	0 (0%)	
Reduced-intensity	62 (81.6%)	41 (89.1%)	21 (70.0%)	
Flu/Bu2	59 (77.6%)	39 (84.8%)	20 (66.7%)	
Flu/Mel140	3 (3.9%)	2 (4.3%)	1 (3.3%)	
Use of TBI				

Table 1 (continued)

	Disease status			*P* value
	All	CR/PR	SD/PD	
	No. of patients			
	N = 76	*N* = 46 (60.5%)	*N* = 30 (39.5%)	
No	46 (60.5%)	27 (58.7%)	19 (63.3%)	0.81
Yes	30 (39.5%)	19 (41.3%)	11 (36.7%)	
Use of ATG				
No	67 (88.2%)	41 (89.1%)	26 (86.7%)	0.73
Yes	9 (11.8%)	5 (10.9%)	4 (13.3%)	
GVHD prophylaxis				
Cyclosporine-based	37 (48.7%)	23 (50.0%)	14 (46.7%)	0.82
Tacrolimus-based	39 (51.3%)	23 (50.0%)	16 (53.3%)	

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CY* cyclophosphamide, *ATL* adult T cell leukemia/lymphoma, *allo-HCT* allogeneic stem cell transplantation, *allo-HSCT* allogeneic hematopoietic stem cell transplantation, *TBI* total body irradiation, *Bu* busulfan, *Flu* fludarabine, *Mel* melphalan, *ATG* anti-human thymocyte immunoglobulin, GVHD graft-versus-host disease

Results

Patient characteristics

This study included 76 patients. The patient and transplantation characteristics are listed in Table 1. The median age was 56 years (range, 28–69 years), and the median follow-up of the surviving patients was 51.8 months (range, 3.3–138.3 months) after allo-HSCT.

Disease status at the time of allo-HSCT was CR in 17 patients (22.4%), PR in 29 (38.2%), SD in 18 (23.7%), and PD in 12 (15.8%). Relapsed ATL patients after objective response before allo-HSCT were three in the CR/PR group and four in the SD/PD group ($P = 0.42$). Two or more lines of chemotherapy before allo-HSCT were more frequently used in patients in the SD/PD group than in the CR/PR group ($P < 0.01$). The common first-line chemotherapy regimen before allo-HSCT was mLSG15 or LSG15 ($n = 48$) and CHOP ($n = 22$). Only two patients in this cohort received Mog before allo-HSCT. In the majority of cases, the MAC regimen consisted of Bu/Cy ($n = 9$, 64.3%), and almost all patients who received a RIC regimen received Flu/Bu2 ($n = 59$, 95.2%). A MAC regimen was administered to more patients in the SD/PD group than in the CR/PR group, but this difference was not significant ($P = 0.07$). There were no significant differences in other patient and transplant characteristics.

Relapse/progression

Overall, 26 of the 76 patients (34.2%) relapsed or progressed at a median of 66 days (range, 13–2064 days) after allo-HSCT, and the majority within 1 year ($n = 23$, 88.5%). The cumulative incidence of relapse/progression at 2 years after allo-HSCT was 33.2%. Stratified according to pre-transplant disease status, the cumulative incidence of relapse/progression were 23.5% in CR, 24.5% in PR, 33.3% in SD, and 66.7% in PD (Fig. 1a). The SD/PD group had a significantly higher incidence of relapse/progression than the CR/PR group (24.2 vs. 47.2%, $P = 0.01$, Fig. 1b). In a multivariate analysis (Table 2), covariates that were associated with a higher risk of relapse/progression were SD/PD (vs. CR/PR; HR 6.41, 95% confidence interval (CI): 2.68–15.31, $P < 0.01$), lymphoma-type (vs. acute-type; HR 6.18, 95% CI: 2.55–15.02, $P < 0.01$), RIC (vs. MAC; HR 5.72, 95% CI: 1.29–25.42, $P = 0.02$), and time from diagnosis to allo-HSCT (more than 7 months; HR 2.60, 95% CI: 1.25–5.42, $P = 0.01$).

GVHD, non-relapse mortality, and OS

The cumulative incidences of grade II–IV, grade III–IV acute GVHD and chronic GVHD were 49.3, 18.8, and 47.5%, respectively. There was no significant difference between the CR/PR and SD/PD groups with regard to the incidences of acute and chronic GVHD. In multivariate analysis that treated acute or chronic GVHD as a time-dependent covariate, neither grade II–IV acute nor extensive chronic GVHD was an independent risk factor for relapse/progression, NRM, or OS.

The cumulative incidences of 2-year NRM were 11.8% in CR, 17.6% in PR, 17.3% in SD, and 25.0% in PD (Fig. 1c). There was no significant difference between the CR/PR group and the SD/PD group ($P = 0.49$, Fig. 1d). In a multivariate analysis, MAC was associated with a higher risk of NRM (vs. RIC; HR 3.84, 95% CI: 1.39–10.60, $P = 0.01$).

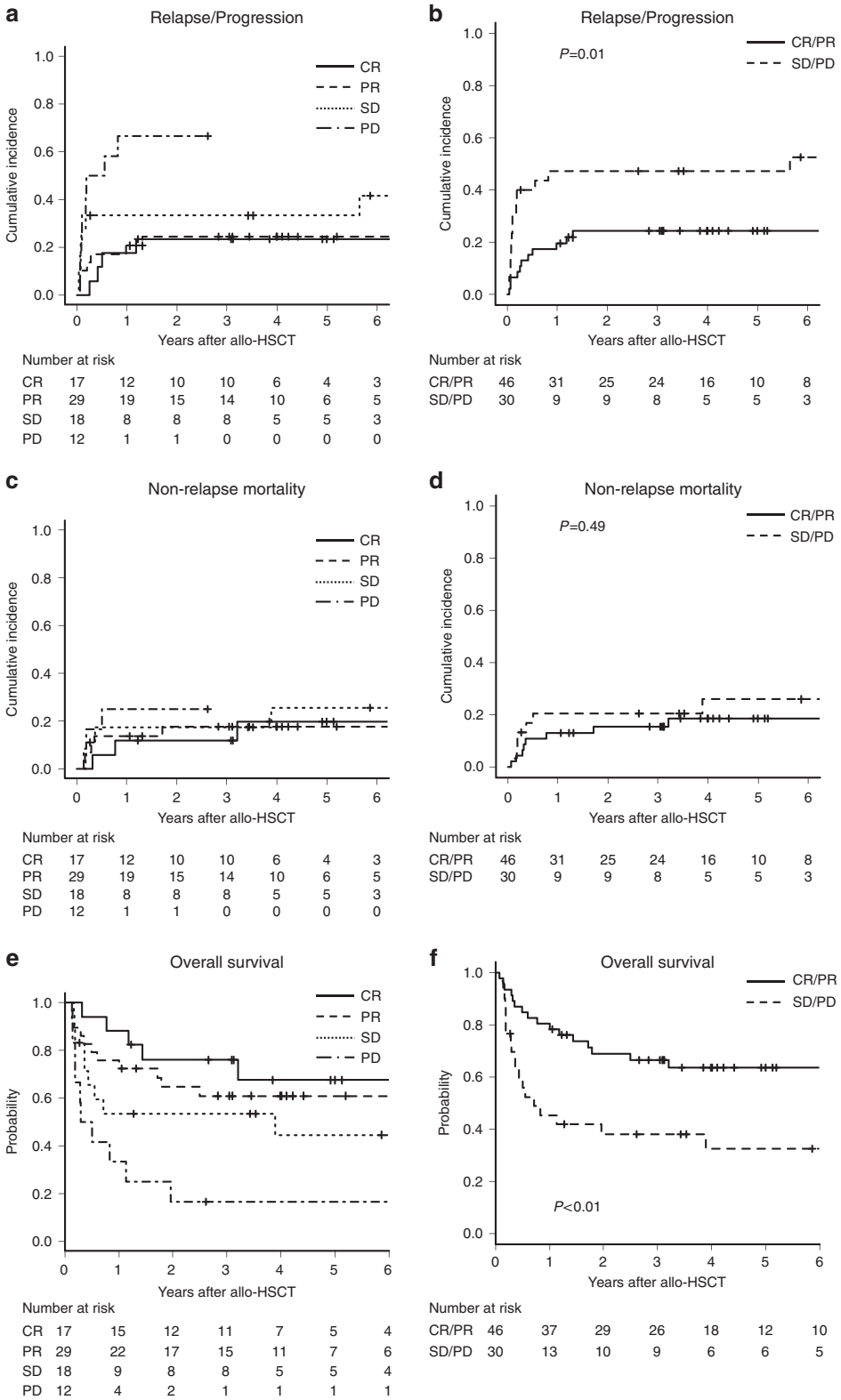

Fig. 1 The cumulative incidence of relapse/progression grouped according to disease status at the time of allo-HSCT: **a** CR, PR, SD, and PD; **b** CR/PR and SD/PD. The cumulative incidence of non-relapse mortality grouped according to disease status at the time of allo-HSCT: **c** CR, PR, SD, and PD; **d** CR/PR and SD/PD. The probability of overall survival grouped according to disease status at the time of allo-HSCT: **e** CR, PR, SD, and PD; **f** CR/PR and SD/PD

Table 2 Multivariate analysis of factors predicting relapse/progression, non-relapse mortality, and overall mortality after allo-HSCT

Outcome and significant factor	Hazard ratio	95% CI	*P* value
Relapse/progression			
Disease status			
CR/PR	1.00		
SD/PD	6.41	2.68–15.31	<0.01
ATL clinical subtype			
Acute	1.00		
Lymphoma	6.18	2.55–15.02	<0.01
Conditioning regimen			
Myeloablative	1.00		
Reduced-intensity	5.72	1.29–25.42	0.02
Time from diagnosis to transplantaion			
7 months or less	1.00		
More than 7 months	2.60	1.25–5.42	0.01
Non-relapse mortality			
Conditioning regimen			
Reduced-intensity	1.00		
Myeloablative	3.84	1.39–10.60	0.01
Overall survival			
Disease status			
CR/PR	1.00		
SD/PD	2.73	1.41–5.29	<0.01

CI confidence interval, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ATL* adult T cell leukemia/lymphoma, *allo-HSCT* allogeneic hematopoietic stem cell transplantation, *ATG* anti-human thymocyte immunoglobulin

The probability of 2-year OS in this cohort was 56.9%. Stratified according to the pretransplant disease status, the probabilities of 2-year OS were 76.0% in CR, 64.8% in PR, 53.6% in SD and 16.7% in PD (Fig. 1e). The probability of OS in the PD group was significantly lower than that in the CR group and the PR group (vs. CR, $P < 0.01$; vs. PR, $P = 0.02$), and the SD/PD group had a significantly worse OS than the CR/PR group (66.5 vs. 38.0%, $P < 0.01$, Fig. 1f). A multivariate analysis for OS showed that SD/PD was associated with an inferior OS (HR 2.73, 95% CI: 1.41–5.29, $P < 0.01$, Table 2).

Interventions and outcomes after relapse/progression

Various therapeutic options were used for the treatment of relapsed/progressed ATL after allo-HSCT. Clinical outcomes after the diagnosis of relapse/progression are summarized in Table 3 and Fig. 2. Among 26 patients with relapsed/progressed ATL, 18 had systemic relapse/progression (abnormal lymphocytes in PB, systemic lymph node lesions, or systemic skin lesions), 5 had focal lymph node lesions, 2 had relapse in the central nervous system (CNS) alone, and 1 had focal skin lesions. Among the 18 patients who relapsed or progressed systemically, 15 received intensive chemotherapy, 2 received donor lymphocyte infusions (DLIs), and 1 underwent only immunosuppression withdrawal. All of the patients with systemic relapse/progression died.

Five patients whose relapse/progression manifested as focal lymph node lesions received local radiotherapy, and three of them received DLI in combination with radiotherapy. In these five patients with relapse/progression of focal lymph node lesion, three patients achieved a long-term survival. Two patients with CNS relapse received intrathecal chemotherapy plus whole-brain radiation therapy, and one of them is currently alive. One patient who relapsed with focal skin lesions underwent only immunosuppression withdrawal and is currently alive.

Overall, 21 of the 26 patients died, at a median of 135 days (range, 17–691 days) after relapse/progression (Fig. 3a); more than half died within 6 months after relapse/progression. Eighteen died of disease progression and three died of transplant-related mortality (TRM). The causes of TRM were infection in two patients (one had *Pneumocystis jiroveci* pneumonia and one had bacterial infection) and non-infectious lung complications in one patient early after second allo-HSCT. Overall, five patients (19.2%) are currently alive with a median follow-up of 99.1 months (range, 14.3–132.5 months). Compared with acute-type patients, lymphoma-type patients had significantly more relapsed ATL patients after objective response before allo-HSCT (2 of 15 acute-type ATL vs. 5 of 11 lymphoma-type ATL, $P = 0.05$), whereas lymphoma-type patients experienced local recurrence more frequently (1 of 15 acute-type ATL vs. 7 of 11 lymphoma-type ATL, $P < 0.01$) and had a significantly longer OS (median OS after relapse/progression; 112 days in acute-type ATL vs. 554 days in lymphoma-type ATL, $P < 0.01$, Fig. 3b) than acute-type patients.

Discussion

Here, we retrospectively analyzed the clinical outcomes of allo-HSCT in patients with aggressive ATL at our institute. Our data clearly showed that pretransplant disease status was a significant risk factor for posttransplant clinical outcomes. Patients in CR at transplant had favorable outcomes, which is consistent with the findings of prior studies [12, 21–23]. These previous reports categorized pretransplant disease status into two groups, such as CR and non-CR. In contrast, our study grouped pretransplant disease status into four groups, and patients in PR and SD had favorable outcomes in addition to those in CR, compared with the dismal

Table 3 Patient characteristics and transplant outcomes in relapse/progression patients

Patient	Age/sex	ATL clinical subtype	Time from diagnosis to HSCT (days)	Disease status at HSCT	Donor type	Conditioning regimen	Acute GVHD grade	Chronic GVHD	Relapse after HSCT (days)	Type of relapse/ progression	Treatment of relapse/ progression after HSCT	Outcome	OS after relapse (days)	Cause of death
1	54/M	Lymphoma	536	CR1	R-PB	RIC Flu/Bu2/ATG	I		153	Focal Ly	DLI → RT	Alive	4185+	
2	45/F	Acute	156	PR1	R-PB	RIC Flu/Bu2	—		481	PB	EPOCH → DLI → C-MOPP	Dead	172	DP
3	50/M	Lymphoma	88	SD	R-PB	RIC Flu/Bu2	I		13	Systemic Ly	WIS → DLI → RT	Dead	144	DP
4	53/F	Lymphoma	125	PD	R-PB	RIC Flu/Bu2	I	Extensive	67	Focal Ly	WIS → RT → DLI	Alive	3661+	
5	51/F	Lymphoma	277	SD	R-PB	RIC Flu/Bu2/ATG	—		17	Systemic Ly, pleural effusion	WIS → etoposide → DLI	Dead	115	DP
6	51/M	Acute	204	PD	R-PB	RIC Flu/Bu2	IV	Extensive	202	Systemic Ly	WIS → DLI	Dead	102	DP
7	59/M	Lymphoma	198	PR1	R-BM	RIC Flu/Bu2	III	Extensive	76	Focal Ly	RT → Ope	Alive	3093+	
8	53/F	Acute	109	SD	R-BM	RIC Flu/Bu2	III		66	PB, systemic Ly	WIS → etoposide → EPOCH → DLI → RT + etoposide	Dead	135	DP
9	48/F	Acute	266	SD	UR-BM	MAC	Bu/CY	—	Extensive	2064	Systemic Ly			
		Etoposide → MPEC → RT → DLI	Dead	466	DP									
10	57/M	Lymphoma	244	CR2	UR-BM	RIC Flu/Bu2/TBI2 Gy	II	Extensive	93	PB, systemic Ly, skin	WIS → mLSG15 → C-MOPP + etoposide → 2nd HSCT	Dead	433	ARDS
11	54/M	Lymphoma	736	PR2	R-PB	RIC Flu/Bu2	I	Extensive	359	Focal Ly	RT → DLI → etoposide → VEP	Dead	554	DP
12	58/M	Lymphoma	244	PR2	R-PB	RIC Flu/Bu2	II	Extensive	15	Systemic Ly	WIS → etoposide RT	Dead	352	DP
13	65/F	Lymphoma	185	CR1	R-PB	RIC Flu/Bu2/ATG	II	Extensive	184	Focal Ly		Dead	246	DP
14	63/M	Acute	227	PR1	R-PB	RIC Flu/Bu2/ATG	II		22	Skin, lung	WIS → COP → EPOCH	Dead	160	DP
15	57/F	Acute	221	SD	UR-BM	RIC Flu/Bu2/TBI2 Gy	—		31	PB, lung	WIS alone	Dead	28	DP
16	55/M	Acute	407	PD	UR-BM	RIC Flu/Bu2/TBI2 Gy	II		69	Systemic Ly	WIS → etoposide → mLSG15	Dead	37	DP
17	69/F	Acute	263	PR1	UR-BM	RIC Flu/Bu2/TBI2 Gy	I	Extensive	101	PB	WIS → DLI	Dead	119	Infection (PCP)
18	59/F	Acute	254	PD	UR-BM	RIC Flu/Bu2	—		38	PB, systemic Ly, CNS	WIS → etoposide	Dead	32	DP
19	60/F	Acute	174	PD	UR-BM	RIC Flu/Bu2/TBI2 Gy	—		32	PB, skin	WIS → etoposide	Dead	17	DP

Table 3 (continued)

Patient	Age/sex	ATL clinical subtype	Time from diagnosis to HSCT (days)	Disease status at HSCT	Donor type	Conditioning regimen	Acute GVHD grade	Chronic GVHD	Relapse after HSCT (days)	Type of relapse/ progression	Treatment of relapse/ progression after HSCT	Outcome	OS after relapse (days)	Cause of death
20	60/M	Acute	216	PD	UR-BM RIC	Flu/Mel140	I	Extensive	301	Systemic Ly	WIS → CHOP → etoposide → DLI → pentostatin	Dead	112	DP
21	62/F	Lymphoma	147	PD	UR-BM RIC	Flu/Bu2/TBI2 Gy	—		26	CNS	IT → WBRT	Dead	691	Infection (bacterial)
22	63/F	Lymphoma	182	CR1	R-PB RIC	Flu/Bu2	III		433	CNS	IT → WBRT	Alive	971+	
23	43/M	Acute	514	SD	UR-BM	MAC	Bu/CY	II		38	Skin	WIS →	CHOP → RT →	EPOCH → MPEC → MOG → mESHAP
Dead	225	DP												
24	62/M	Acute	331	PR1	UR-BM RIC	Flu/Bu2	—		22	PB	WIS → VCAP	Dead	30	DP
25	51/M	Acute	365	PD	UR-BM	MAC	Bu/CY	II		24	Systemic Ly	WIS →		
						chemotherapy	Dead	81	DP					
26	64/F	Acute	301	SD	UR-BM RIC	Flu/Bu2	I	Extensive	29	Skin	WIS alone	Alive	464+	

M male, *F*female, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ATL* adult T cell leukemia/lymphoma, *R-PB* related donor, peripheral blood, *UR-BM* unrelated donor, bone marrow, *RIC* reduced-intensity conditioning, *MAC* myeloablative conditioning, *CY* cyclophosphamide, *TBI* total body irradiation, *Bu* busulfan, *Flu* fludarabine, *Mel* melphalan, *ATG* anti-human thymocyte immunoglobulin, *CSP* cyclosporine, *TAC* tacrolimus, *MTX* methotrexate, *Ly* lymph node lesion, *PB* abnormal cells in PB, *CNS* central nervous system, *DLI* donor lymphocyte infusion, *RT* radiotherapy, *EPOCH* etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin, *C-MOPP* cyclophosphamide, vincristine, procarbazine, and prednisolone, *WIS* withdrawal of immunosuppression, *Ope* operation, *MPEC* methotrexate, prednisolone, etoposide, and cyclophosphamide, *mLSG15*VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisolone)-AMP (doxorubicin, ranimustine, and prednisolone)-VECP (vindesine, etoposide, carboplatin, and prednisolone), *HSCT* hematopoietic stem cell transplantation, *VEP* vindesine, etoposide, and prednisolone, *COP* cyclophosphamide, vincristine, and prednisolone, *CHOP* cyclophosphamide, vincristine, doxorubicin, and prednisolone, *IT* intrathecal chemotherapy, *WBRT* whole-brain radiation therapy, *MOG* mogamulizumab, *mESHAP* etoposide, methylprednisolone, high-dose cytarabine, and carboplatin, *VCAP* vincristine, cyclophosphamide, doxorubicin, and prednisolone, *ARDS* acute respiratory distress syndrome, *PCP Pneumocystis jiroveci* pneumonia, *DP* disease progression

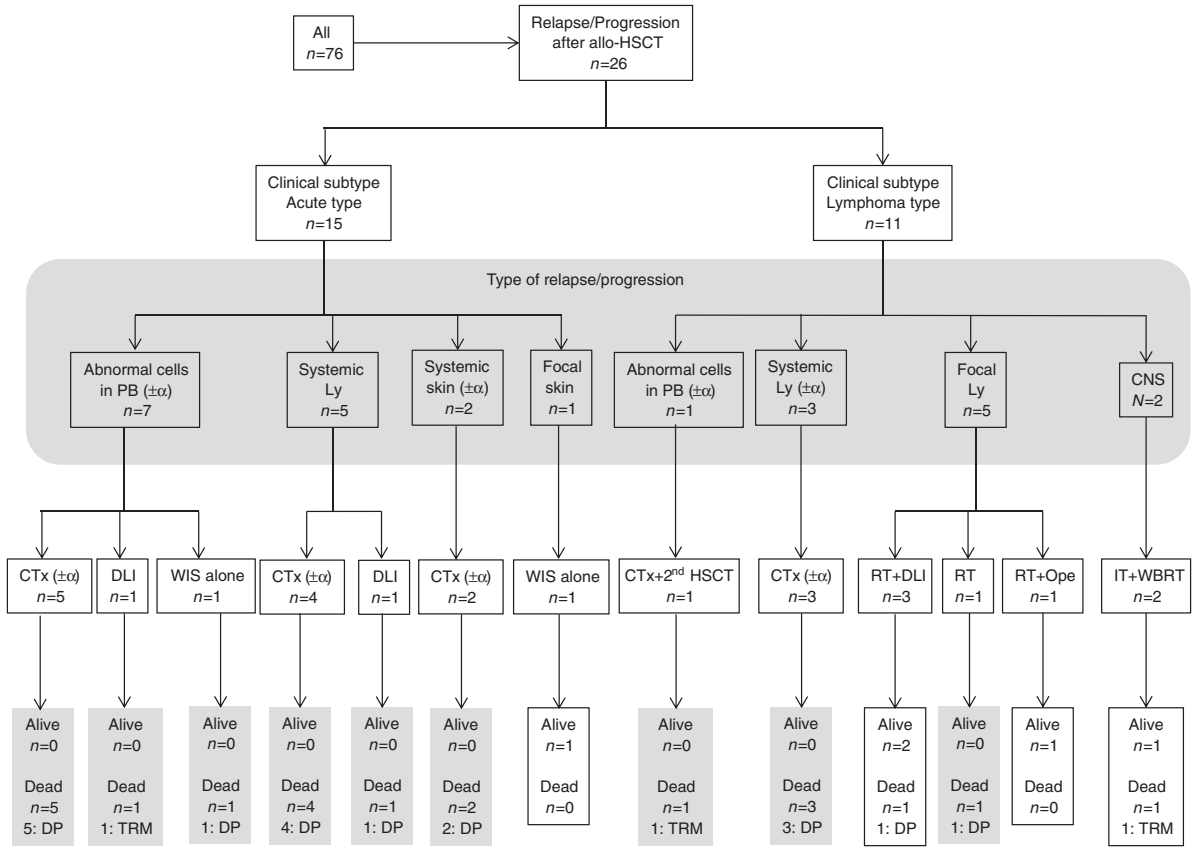

Fig. 2 Summary of interventions after relapse/progression. HSCT hematopoietic stem cell transplantation, Ly lymph node lesion, CNS central nervous system, CTx chemotherapy, DLI donor lymphocyte infusion, WIS withdrawal of immunosuppression, RT radiotherapy, Ope operation, IT intrathecal chemotherapy, WBRT whole-brain radiation therapy, DP disease progression, TRM transplant-related mortality

outcome with chemotherapy alone. As demonstrated in this study, chemosensitivity before allo-HSCT could be a more important predictive factor for posttransplant outcomes than the achievement of CR.

Although the overall outcomes in this study were favorable in comparison to previous reports [12, 21–23], relapse/progression was still a major cause of treatment failure after allo-HSCT. In particular, systemic relapse/progression occurred in many patients with acute-type ATL, and was associated with dismal clinical outcomes. On the other hand, local relapse/progression was common in patients with lymphoma-type ATL, and a significant proportion of these cases were successfully salvaged by DLI in combination with radiation. Itonaga et al. [24] reported the effectiveness of DLI in patients with relapse/progression after allo-HSCT. Our data support their findings; however, their study did not compare acute and lymphoma-type patients in terms of recurrence patterns or prognoses. Further, detailed analyses of relapse patterns and treatment could not be conducted in previous studies that used registry databases. To better prevent systemic relapse/progression, efficient monitoring methods and interventional strategies must be developed.

Our study cohort included only patients who received allo-HSCT, which made it difficult to determine the optimal timing of this treatment strategy in patients with aggressive ATL. However, considering the dismal outcomes with conventional chemotherapy and the favorable outcomes with allo-HSCT for patients in CR or PR, it would be reasonable to consider up-front allo-HSCT in patients with aggressive ATL when the disease is chemosensitive. Our group previously reported that in the setting of related HSCT, early allo-HSCT (<100 days after diagnosis) was associated with a favorable outcome compared with late allo-HSCT [25]. In addition, the patients who relapsed during chemotherapy had poor outcomes even if they received allo-HSCT [26]. In our current study, an interval longer than 7 months from diagnosis to allo-HSCT was associated with an increased risk of relapse/progression. This and other finding also support the idea of early up-front allo-HSCT in patients with aggressive ATL. In order to increase the proportion of patients who receive allo-HSCT when the disease is chemosensitive, alternative donors such

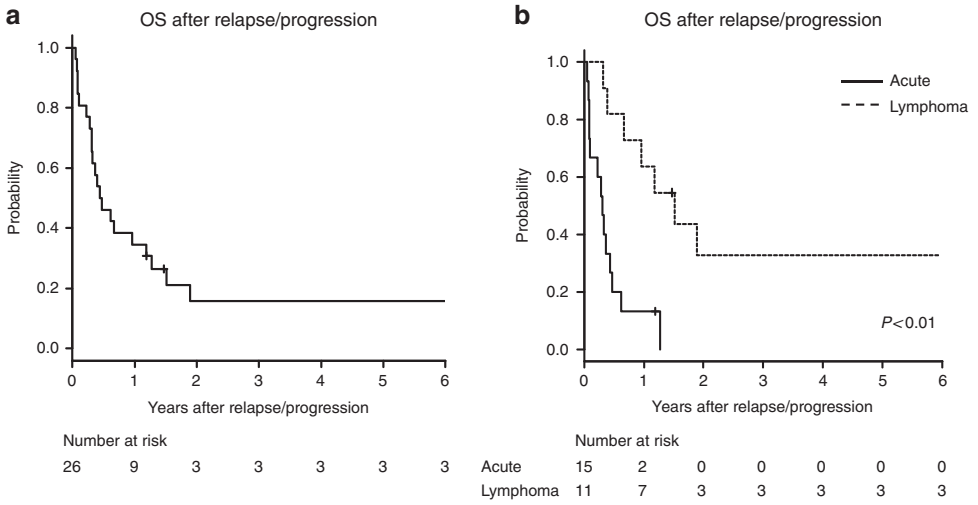

Fig. 3 The probability of overall survival after relapse/progression in all patients (**a**). The probability of overall survival after relapse/progression grouped according to clinical subtypes (**b**)

as cord blood or haploidentical related HSCT could be considered in the treatment strategy for aggressive ATL. Prospective studies are needed to confirm the benefits of these approaches. Recently, our group reported a new prognostic index in transplant-eligible patients with aggressive ATL [27]. This index might be useful to determine the appropriate timing of allo-HSCT in patients with this disease. In addition, further improvement is needed in the management of patients with chemorefractory ATL as this population is at high risk of relapse/progression after allo-HSCT. One option might be Mog, as it was reported to be effective in half of patients with relapsed/refractory ATL [8, 9]. However, significant attention would have to be paid to the interval between the last Mog treatment and the initiation of allo-HSCT, and it would be reasonable to consider strategies to mitigate the risk of severe GVHD [28, 29].

The limitations of this study should be clarified. We were not able to demonstrate a clinical benefit of acute/chronic GVHD in patients with ATL, which is inconsistent with a previous study [22]. This could be due to the small size of our cohort, although it is one of the largest thus far of ATL patients undergoing allo-HSCT. Another limitation was possible selection bias. Our data showed favorable clinical outs in patients who received allo-HSCT compared with previous nationwide studies [12, 21–23]. It is possible that only fit patients were referred to our institute and we conducted allo-HSCT in that select group. In this regard, relapsed ATL patients after objective response before allo-HSCT who was expected to have a dismal outcome after allo-HSCT as previously reported were only seven patients in our cohort [26]. To rule this out, we require a database that includes both transplanted and non-transplanted cases. Prospective cohort studies are also needed to determine the reasons why non-transplanted cases do not receive allo-HSCT.

In conclusion, we found that pretransplant disease status was the most important predictive factor for OS. Further studies including data of both transplanted and non-transplanted cases are needed to further clarify the benefits of up-front allo-HSCT in patients with aggressive ATL.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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