Characteristic patterns of relapse after allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma: a comparative study of recurrent lesions after transplantation and chemotherapy by the Nagasaki Transplant Group

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is a promising therapy that may provide long-term durable remission for adult T cell leukemia-lymphoma (ATL) patients; however, the incidence of relapse associated with ATL remains high. To

determine the clinical features of these patients at relapse, we retrospectively analyzed tumor lesions in 30 or 49 patients who relapsed following allo-SCT or chemotherapy (CHT), respectively, at 3 institutions in Nagasaki prefecture between 1997 and 2011. A multivariate analysis revealed that the development of abnormal lymphocytes in the peripheral blood of patients at relapse was less frequent after allo-SCT than after CHT (P<.001). Furthermore, relapse with a new lesion only in the absence of the primary lesion was more frequent in allo-SCT (P=.014). Lesions were more frequently observed in the central nervous systems of patients who relapsed with new lesions only (P=.005). Thus, the clinical manifestation of relapsed ATL was slightly complex, especially in post-transplant patients. Our results emphasized the need to develop adoptive modalities for early and accurate diagnoses of relapsed ATL.

Introduction

Adult T-cell leukemia-lymphoma (ATL) is a peripheral T-lymphocytic neoplasm that is caused by human T-cell lymphotropic virus type I (HTLV-1) [1]. One of the characteristic features of ATL is its frequent multi-organ involvement, which has been implicated in the poor prognosis of patients with ATL. Lymphadenopathy, hepatomegaly, splenomegaly, as well as skin, pulmonary, and central nervous system (CNS) lesions,

and 5% or more abnormal T-lymphocytes in the peripheral blood have been reported in most cases of ATL. The clinical manifestation of ATL is heterogeneous and is characterized by this organ involvement, which has been used to classify the disease into 4 subtypes: acute, lymphoma, chronic, and smoldering [2].

ATL is resistant to various cytotoxic agents and has a poor prognosis [3, 4]. Allogeneic hematopoietic stem cell transplantation (allo-SCT) for patients with aggressive ATL (acute, lymphoma, and the unfavorable chronic type) is considered to be a therapeutic option that can provide apparent durable remission along with graft-versus-ATL effects [5-18]. However, both the relapse rate and transplantation-related mortality after allo-SCT were previously shown to be high, and are urgent issues that need to be addressed [9, 19, 20]. Previous studies, including ours, raised the possibility that patients with local relapse may achieve long-term remission by local cytoreductive therapy alone, and that those with skin recurrence (i.e. non-aggressive disease) could benefit from donor lymphocyte infusion [21, 22]. These findings implied that an intervention for the residual disease at the early phase may improve the outcomes of ATL patients; however, a standard method to monitor the residual disease after remission has not yet been established. Moreover, very few studies have examined the clinical manifestation of relapsed ATL by carefully analyzing an adequate number of

cases. Identifying the clinical characteristics of ATL at relapse is important for establishing an adoptive monitoring strategy. In the present study, we retrospectively analyzed 30 and 49 ATL patients who relapsed after allo-SCT and chemotherapy (CHT), respectively, at three institutes in Nagasaki prefecture.

Patients and Methods

Patient population

We conducted a retrospective survey of patients diagnosed with aggressive ATL [2] who received initial systemic CHT at 3 hospitals in Nagasaki prefecture between April 1, 1997 and March 31, 2011. The unfavorable chronic type of ATL was defined according to previous criteria [4]. The diagnosis of ATL was based on clinical features, histologically and/or cytologically proven mature T-cell malignancy, the presence of the anti-HTLV-1 antibody, and the monoclonal integration of HTLV-1 original DNA into tumor cells, as described previously [2, 23, 24]. A total of 336 patients were excluded from the 497 patients whose data were available because they did not achieve complete remission (CR) after CHT or allo-SCT (Figure 1). Chemotherapy and transplant procedures were performed according to the decision of the clinicians at each center. The intrathecal administration of chemotherapy as prophylaxis for CNS relapse was

performed based on the decision of clinicians before 2007, and was then routinely performed after 2007 as described previously in a phase III clinical trial for aggressive ATL [4]. No patient received mogamulizumab before achieving the first CR. Relapse after the first CR was observed in 79 of the remaining 161 patients, and these patients were included in this analysis. Data on the 79 patients were collected and updated as of July 2013. This study was approved by the Ethical Committee of each participating hospital.

Definitions

Performance status was based on the 5-grade scale of the Eastern Cooperative Oncology Group (ECOG). Because HTLV-1 carriers frequently have a small percentage of abnormal lymphocytes with polylobated nuclei in their peripheral blood, and provided that less than 5% of such cells remained, peripheral blood involvement was confirmed if more than 5% of these abnormal lymphocytes were present in the peripheral blood [25]. The definition of extranodal lesions has been described previously [24]. Lymph nodes and extranodal tumor lesions were both determined according to the Ann Arbor classification [2].

CR was determined according to previously described criteria [25]. The diagnosis and

clinical grading of acute and chronic GVHD were performed using established criteria [26, 27].

Clinical data

We collected information regarding patient characteristics and underlying diseases (including a prognostic index for acute- and lymphoma-type ATL [ATL-PI] [28]). Factors used in analyses were listed in Table 1. The intensity of the conditioning regimen was classified as myeloablative and reduced-intensity [29]. An evaluation of the involved sites was based on the Shimoyama classification [2].

Statistics

Descriptive statistics were used to summarize variables related to patient demographic and transplant characteristics. Comparisons between the allo-SCT and CHT groups were performed using Fisher's exact test where appropriate for categorical variables and the Mann-Whitney U test for continuous variables. The Kaplan-Meier method was used to estimate overall survival (OS) after relapse. The log-rank test was used in the univariate analysis in order to compare OS. The impact of potential confounding factors on the appearance of involvement sites at relapse was evaluated using Fisher's exact test and

logistic regression analysis.

Leukocytosis was defined as a white blood cell count of 8.9×10^9/L or greater with the median value as the cut-off level. Lactate dehydrogenase (LDH) or blood urea nitrogen (BUN) concentrations were dichotomized into normal and elevated concentrations [30]. Serum albumin (ALB) was dichotomized into concentrations of 40.0 g/L (4.0g/dL) or greater and less than 40.0 g/L (4.0g/dL) [2]. Factors with at least borderline significance (P<.25) according to the univariate analysis were included in the multivariate analysis. All analyses were performed using SAS version 9.2 software (SAS Institute, Cary, NC). Values of P<.05 were considered significant in all analyses.

Results

Patient Characteristics and Transplant Procedures

Table 1 shows the patient characteristics of each group; 30 and 49 ATL patients relapsed after allo-SCT and CHT, respectively. In a total of 79 patients, the median intervals from CR to relapse and from the last treatment to relapse were 180 days (range, 28-3490) and 79 days (range, 9-3073), respectively. Intrathecal prophylaxis was not performed in 11 patients: 10 patients started the initial treatment before 2007 and 1 patients did not receive prophylaxis because of advanced age. Transplant procedures

were shown in Table 2. In the allo-SCT group, 9 patients achieved CR at the time of receiving allo-SCT, whereas 21 patients did not. One patient received a reduced-intensity conditioning regimen with antithymocyte globulin. No patients underwent *in vitro* T cell-depleted transplantation.

Comparison of involved sites at relapse between allo-SCT and CHT groups

The involvement sites at the initial diagnosis and relapse were shown in Table 3. At relapse, the frequency by which abnormal lymphocytes (≥5%) developed in the peripheral blood was significantly less in the allo-SCT group than in the CHT group (P<.001). This was maintained when the percentage of abnormal lymphocytes as the threshold of peripheral blood involvement was considered to be ≥2% or ≥10% (data not shown). A multivariate analysis showed that the likelihood of developing abnormal lymphocytes in the peripheral blood at relapse was significantly lower in the allo-SCT group than in the CHT group (P<.001) (Table 4). We performed a stratification analysis according to the Shimoyama classification. In patients with the acute plus unfavorable chronic type, the frequency by which the allo-SCT group developed abnormal lymphocytes in peripheral blood at relapse was lower (P=.001 by the multivariate analysis). However, this was not clear due to the small number of patients with the

lymphoma type; relapse in the peripheral blood was observed in 1 and 3 patients in the allo-SCT (n=4) and CHT (n=7) groups, respectively (data not shown).

Relationship between primary and relapsed lesions

We next evaluated the relationship between initially diagnosed and relapsed lesions. The most frequent lesion of relapse was the primary lesion (i.e. the lesion at the initial diagnosis); 19 (63.3%) and 43 (87.8%) patients in the allo-SCT and CHT groups had primary lesions (Figure 2). Among primary involved lesions, relapse significantly occurred at the same sites; lymph nodes (*P*=.018), spleen (*P*=.010), and gastrointestinal tract (*P*=.005) (see Table S1). Relapse was only observed in new lesions in 11 (36.7%) and 6 (12.2%) patients in the allo-SCT and CHT groups, respectively. Lesions were more frequently observed in the CNS of patients who relapsed with new lesions only (*P*=.005). The relapse pattern in which new lesions only occurred at relapse was more frequently observed in the allo-SCT group than in the CHT group (*P*=.022). The multivariate analysis showed that the likelihood of relapse only in a new lesion was significantly higher in the allo-SCT group (*P*=.014) (Table 5), and was also the case when patients with the acute plus unfavorable chronic type were analyzed (*P*=.048). We did not observe a similar result in patients with lymphoma type ATL because the

number of patients was small.

We assessed the risk factors associated with CNS lesions at relapse, which was significantly observed as relapse only in a new lesion. The univariate analysis revealed that the frequency of CNS lesions at relapse was higher when ascites was detected at the initial diagnosis (*P*=.006), with a short CR duration (*P*=.037), and with a high sIL-2R value (*P*=.024). In the multivariate analysis, the presence of ascites at the initial diagnosis and a short CR duration were also significant (*P*=.016 and *P*=.031, respectively), whereas a high sIL-2R value was not (*P*=.051) (see Table S2).

Survival by the relapse pattern of ATL

Median survival times after relapse were 176 days and 174 days in the allo-SCT and CHT groups, respectively (Figure 3). Estimated OS rates after relapse were 16.7% (95% CI: 6.1 to 31.8%) and 3.0% (95% CI: 0.2 to 12.9%) at 3 years in the allo-SCT and CHT groups, respectively. No significant differences were observed in the OS rates between the allo-SCT and CHT groups (*P*=.198). The OS rates were poor for patients who relapsed in pleural effusion (*P*<.001), ascites (*P*=.005), and splenomegaly (*P*=.002), but was better for those who relapsed in the skin (*P*=.031). The OS rates of the allo-SCT and CHT groups based on the involvement sites at relapse were shown in Table S2.

Relationship between GVHD and the involvement site

The timing of the relapse of ATL and GVHD was shown in Table S3. In the allo-SCT group, 11 and 13 patients relapsed after the improvement of GVHD, and without any episode of GVHD, respectively. Of the 24 patients who had no clinical symptoms of GVHD at relapse, the most frequent lesions of relapse were detected in the skin (n=8) and lymph nodes (n=10).

Relationship between transplant procedures and the involvement site

We evaluated the impact of conditioning regimens for the involved lesion. The univariate analysis revealed that the intensity of the conditioning regimen was not associated with any involved lesion at relapse, including the total body irradiation (TBI) 12Gy-based regimen, or the donor type (HLA-matched sibling vs alternative donor). The development of abnormal lymphocytes in the peripheral blood correlated with the use of an unrelated donor (P=.037); of the 4 patients who relapsed in the peripheral blood, 3 and 1 patients underwent transplantation from unrelated bone marrow and unrelated cord blood, respectively.

Discussion

We here observed significant differences in the lesions involved in relapse after allo-SCT and CHT. To the best of our knowledge, this is the first study to evaluate the clinical features of ATL at the first relapse. It should be noted that the clinical features at relapse in the allo-SCT group were slightly more complex than those in the CHT group.

Leukemic relapse was less frequent in the allo-SCT group. Previous studies suggested that differences in extramedullary and bone marrow relapse were attributed to the preferential occurrence of the graft-versus-leukemia effect after transplantation for acute myeloid leukemia (AML) with stronger graft-versus-leukemia effects in the blood system (i.e. bone marrow and peripheral blood) over extramedullary sites [31-34]. Although the underlying mechanism has not yet been elucidated in detail, an uneven graft-versus-ATL effect may explain, at least partly, the lower frequency of leukemic relapse following allo-SCT than CHT.

As we previously reported, chromosomal abnormalities and the overexpression of c-Met in ATL cells correlated with the type of involved sites at the initial diagnosis [35, 36]. Considering the chromosomal instability of ATL [37], it would be of interest to clarify the intrinsic characteristics of ATL cells that affect the pathogenesis of the involved sites at relapse.

Skin lesions are generally observed in 25.0-48.9% of ATL patients at the initial diagnosis [2, 38], which is consistent with the results obtained in the present study at the initial diagnosis. In the allo-SCT group, relapse with skin involvement was more likely to develop in the absence of GVHD. We previously reported that recurrent ATL with skin involvement represented a good target for donor-lymphocyte infusion [22]; therefore, skin involvement needs to be accurately diagnosed. Although it is often difficult to distinguish a cutaneous lesion of ATL from other causes (including GVHD and viral infection) [38], Southern blotting analysis or high-throughput DNA sequencing may be a promising tool for an accurate diagnosis by showing the clonal proliferation of HTLV-1-infected cells [39, 40].

An early and accurate diagnosis of relapse could be beneficial for selecting an appropriate treatment strategy (e.g. donor lymphocyte infusion, radiation, intrathecal administration of chemotherapy, and mogamulizumab) and improving the prognosis of patients [17, 21, 22, 41]. However, no standardized method has yet been established to detect the relapse of ATL after allo-SCT. In present clinical practices, symptoms are carefully monitored for the early detection of ATL relapse. Therefore, recognizing differences in relapse patterns between SCT and CHT, as well as in the sites of relapse likely to involve the primary lesion (i.e. lymph nodes, spleen, and gastrointestinal tract)

and CNS as relapse only with new lesions, will be important. Diagnostic modalities for CNS involvement, such as lumbar puncture and diagnostic imaging, should be considered as soon as possible when neurological symptoms are noted in ATL patients, especially those with high-risk factors.

The present study highlighted the clinical features of relapsed ATL in a retrospective cohort. However, the present study had several limitations. The number of patients in our study was relatively small and patient characteristics were highly heterogeneous. Moreover, selection bias was unavoidable in patients who underwent allo-SCT. Therefore, these factors may have affected the results obtained; therefore, the results presented here should be interpreted carefully and need to be confirmed in a larger study.

In conclusion, we here demonstrated a lower rate of relapse in the peripheral blood and a higher rate of recurrent disease in new lesions only in post-transplant patients than in those receiving CHT. The optimal salvage treatment may be more effective, even for post-transplant patients, when the relapse of ATL is detected early and accurately; therefore, further clinical and experimental studies are needed to establish monitoring systems for patients with ATL.

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Authorship

Contribution: H.I., J.T., and Y. Miyazaki conceived and designed the study; H.I., H. Taniguchi, J.M., and Y. Miyazaki collected the data; H.I. and Y. Miyazaki analyzed the data; H.I., S.H., and Y. Miyazaki performed the statistical analyses; H.I. and Y. Miyazaki wrote the manuscript, and created the figures and tables; and all authors critically reviewed the manuscript and read and approved the final version.

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

Supplementary information is available at BMT's website.

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Figure Legends

Figure 1. Patient flow diagram

We retrospectively analyzed patients who relapsed after the first complete remission at 3 institutions in Nagasaki prefecture between 1997 and 2011. Of these patients, 30 and 49 patients relapsed after allogeneic hematopoietic stem cell transplantation (allo-SCT) and chemotherapy (CHT), respectively.

Figure 2. Relapse pattern regarding primary and new lesions.

Relapse with a new lesion only was more likely to be observed in the allo-SCT group than in the CHT group (*P*=.022).

Figure 3. Overall survival rates after relapse.

The estimated overall survival rates after relapse were 16.7% and 3.0% at 3 years in

patients who relapsed after allo-SCT and CHT, respectively.

Figure 1

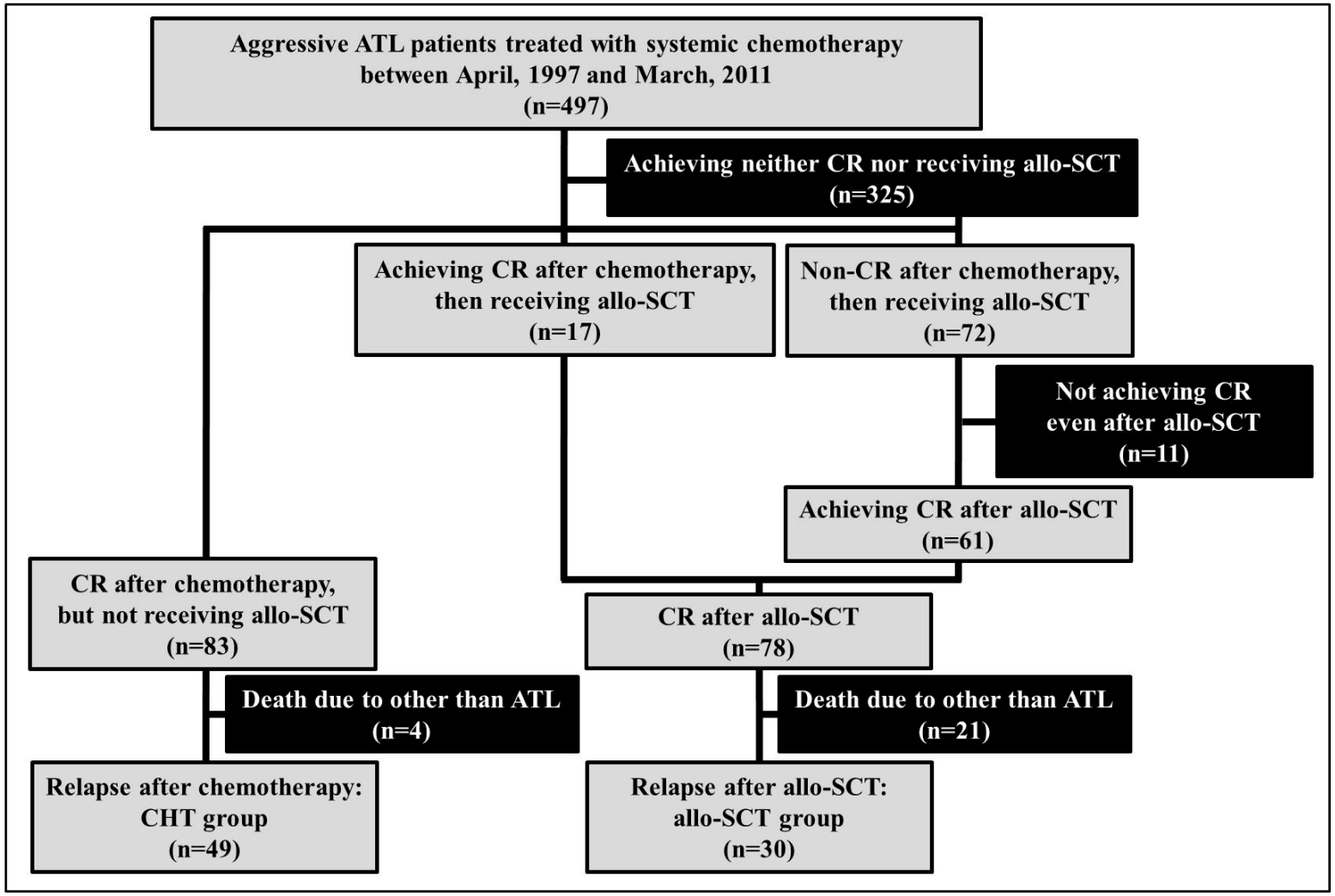
Aggressive ATL patients treated with systemic chemotherapy between April, 1997 and March, 2011 (n=497)
Achieving neither CR nor receiving allo-SCT (n=325)
Achieving CR after chemotherapy, then receiving allo-SCT (n=17)
Non-CR after chemotherapy, then receiving allo-SCT (n=72)
Not achieving CR even after allo-SCT (n=11)
Achieving CR after allo-SCT (n=61)
CR after chemotherapy, but not receiving allo-SCT (n=83)
CR after allo-SCT (n=78)
Death due to other than ATL (n=4)
Death due to other than ATL (n=21)
Relapse after chemotherapy: CHT group (n=49)
Relapse after allo-SCT: allo-SCT group (n=30)

Figure 2

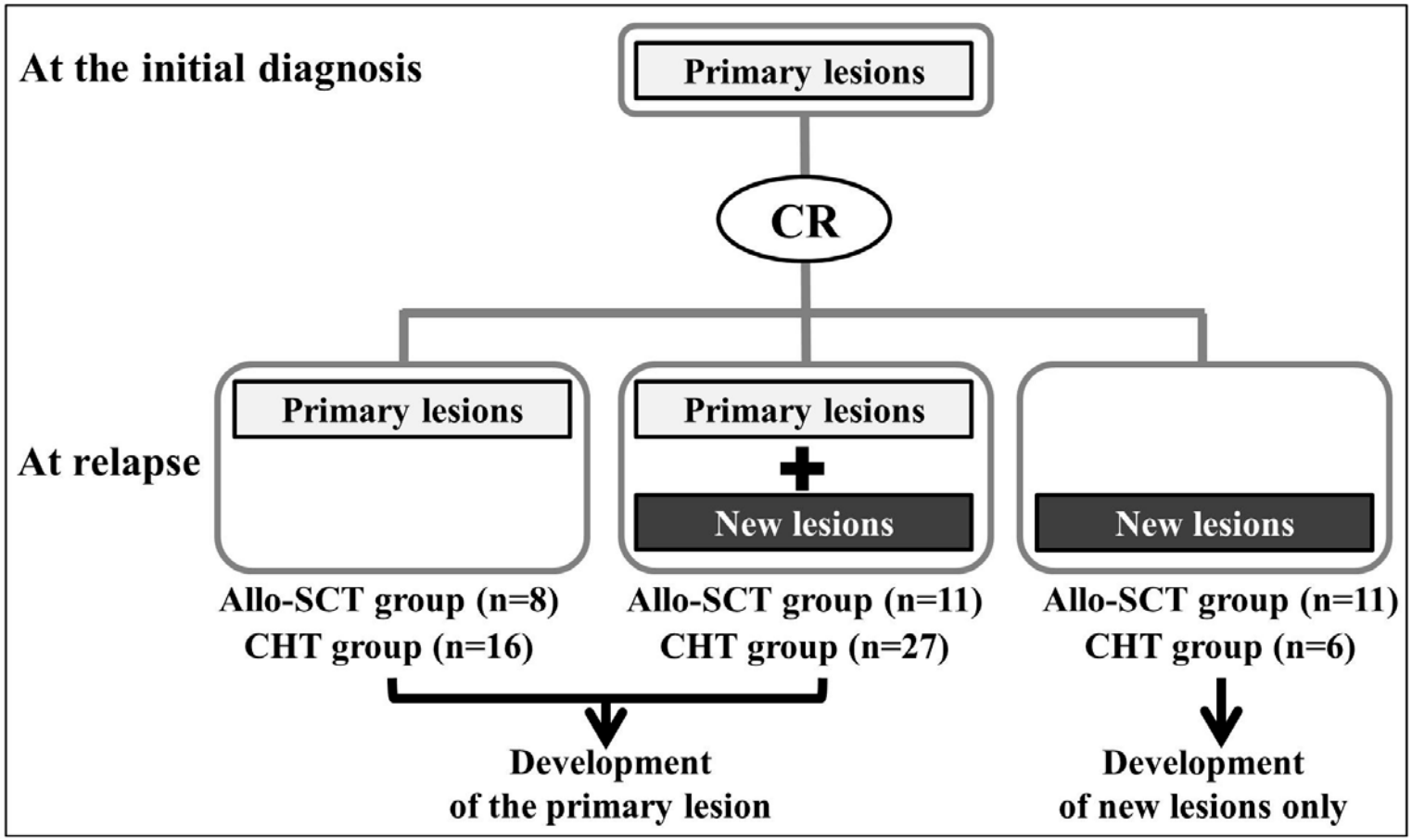
At the initial diagnosis
Primary lesions
CR
At relapse
Primary lesions
Primary lesions
New lesions
New lesions
Allo-SCT group (n=8)
CHT group (n=16)
Allo-SCT group (n=11)
CHT group (n=27)
Allo-SCT group (n=11)
CHT group (n=6)
Development
of the primary lesion
Development
of new lesions only

Figure 3

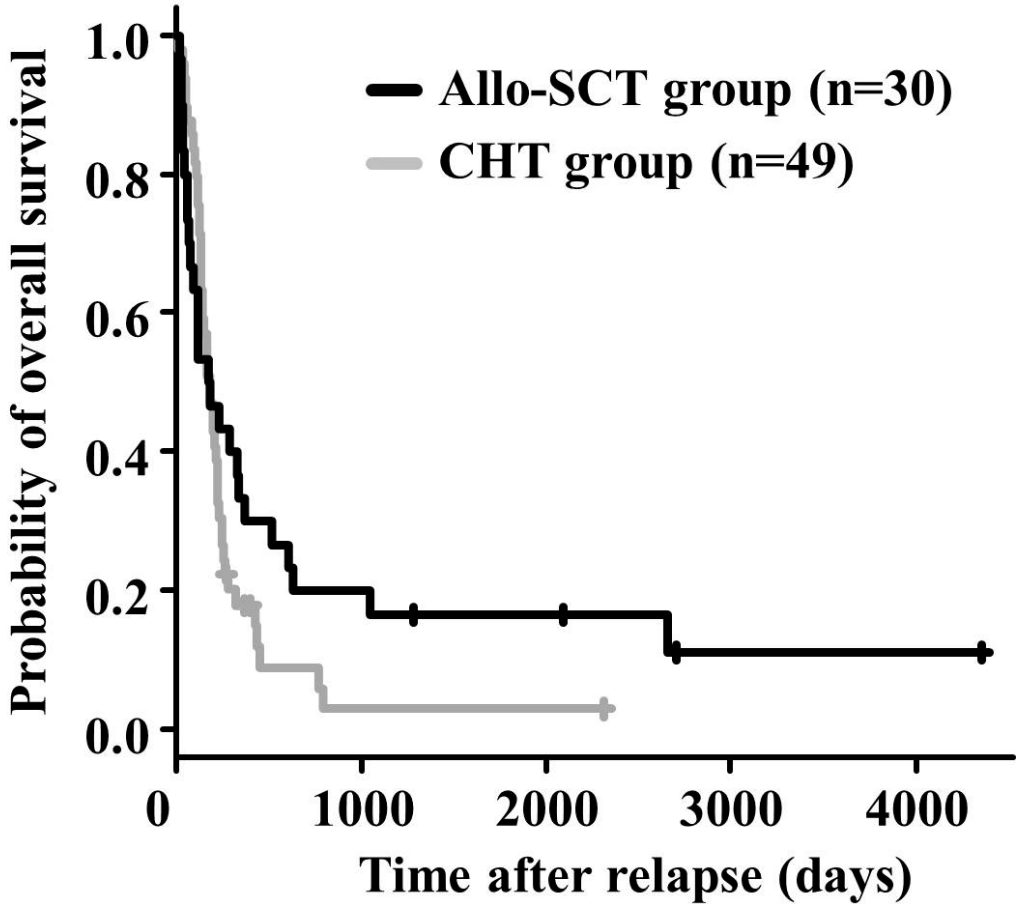
Probability of overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Time after relapse (days)
Allo-SCT group (n=30)
CHT group (n=49)

Table 1. Patient characteristics

Characteristics	Allo-SCT group	CHT group	P-value
No. of patients	30	49	
Median age at diagnosis, y	51 (range, 33-65)	64 (range, 40-83)	<0.001
Sex, n			0.163
Male	13	30	
Female	17	19	
Subtype of ATL at diagnosis, n			0.935
Acute type	25	41	
Lymphoma type	4	7	
Unfavorable chronic type	1	1	
WBC, $\times 10^9$/L	9,800 (range, 4,000-80,000)	8,500 (range, 4,400-179,500)	0.959
Abnormal lymphocyte count, %	11 (range, 0-94)	4 (range, 0-91)	0.953
Serum ALB, g/dL	3.9 (range, 2.6-5.4)	4.0 (range, 2-4.6)	0.346
BUN, mg/dL	13 (range, 7-30)	14 (range, 5-47)	0.377
LDH, IU/mL	593 (range, 119-1561)	451 (range, 161-3309)	0.473
sIL-2R, U/mL	14300 (range, 1823-128000)	9730 (range, 397-114000)	0.396
Presence of hypercalcemia, n			0.802
Yes	10	14	
No	20	35	
Ann Arbor stage, n			0.644
I - II	1	4	
III - IV	29	45	
ECOG PS, n			0.643
0 - 1	17	24	
2 - 4	13	25	
ATL-PI, n			0.273
Low score	12	10	
Intermediate score	11	26	
High score	2	5	
Unknown	5	8	
Year of initial chemotherapy, n			0.609
1997 - 2003	9	12	
2004 - 2010	21	37	
Initial chemotherapy, n			0.316
VCAP-AMP-VECP-based	24	44	
CHOP-based	6	5	
IT before CR, n			0.519
Yes	27	41	
No	3	8	
Interval from last treatment to relapse, day	130 (range, 31-3073)	49 (range, 9-2060)	0.009
Interval from CR to relapse, day	135 (range, 31-3490)	238 (range, 28-2060)	0.235

Abbreviations: allo-SCT indicates allogeneic hematopoietic stem cell transplantation; CHT, chemotherapy; ATL, adult T-cell leukemia-lymphoma; WBC, white blood cell; ALB, albumin; BUN,

blood urea nitrogen; LDH, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor; PS, performance status; ATL-PI, a prognostic index for acute- and lymphoma-type ATL; VCAP, vincristine, cyclophosphamide, doxorubicin, and predonisone; AMP, doxorubicin, ranimustine, and predonisone; VECP, vindesine, etoposide, carboplatin, and predonisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and predonisone; IT, intrathecal administration of cytarabine, methotrexate, and predonisone; CR, complete remission.

Table 2. Transplant procedure

Characteristics	No. of patients in the allo-SCT group
Conditioning regimen	
Myeloablative	
TBI-regimen	11
Non TBI-regimen	4
Reduced intensity myeloablative	15
GVHD prophylaxis	
Cyclosporine A	4
Tacrolimus	4
Cyclosporine A + sMTX	13
Tacrolimus + sMTX	9
Donor type	
HLA-matched related donor	16
Alternative donor	14
HLA matching	
0 mismatched loci	22
1 mismatched locus	2
2 mismatched loci	6
Source of stem cells	
Bone marrow	16
Peripheral blood stem cell	7
Cord blood	7
Anti-HTLV-1 antibody of the donor	
Positive*	6
Negative	24
Disease status at allo-SCT	
CR	9
PR	8
Other	13
Acute GVHD	
Absent	15
Grade I	3
Grade II-IV	12
Chronic GVHD	
Absent	19
Limited type	1
Extensive type	5

* Peripheral blood mononuclear cells in these donors were subjected to Southern blot analysis to examine the monoclonal integration of the HTLV-1 provirus into the genome, and all 6 donors were

confirmed to be the carriers of HTLV-1.

Abbreviations: TBI indicates total body irradiation; GVHD, graft-versus-host disease; sMTX, short-term methotrexate; HTLV-1, human T-cell lymphotropic virus type I; PR, partial remission.

Table 3. Tumor lesion at the initial diagnosis and at relapse

Tumor lesion	At the initial diagnosis			At relapse		
	Allo-SCT group (n=30)	CHT group (n=49)	P-value	Allo-SCT group (n=30)	CHT group (n=49)	P-value
	No. of patients (%)	No. of patients (%)		No. of patients (%)	No. of patients (%)	
Abnormal lymphocytes (≥5%) in the peripheral blood	16 (53.3%)	22 (44.9%)	0.495	4 (13.3%)	25 (51.0%)	<0.001
Skin	13 (43.3%)	12 (24.5%)	0.138	9 (30.0%)	14 (28.6%)	1.000
Lung	3 (10.0%)	3 (6.1%)	0.668	3 (10.0%)	4 (8.2%)	1.000
Lymph node	21 (70.0%)	44 (89.7%)	0.035	11 (36.7%)	26 (53.1%)	0.172
Liver	6 (20.0%)	13 (26.5%)	0.595	2 (6.7%)	9 (18.7%)	0.191
Spleen	7 (23.3%)	11 (22.4%)	0.792	2 (6.7%)	10 (20.4%)	0.119
CNS	3 (10.0%)	3 (6.1%)	0.668	6 (20.0%)	7 (14.3%)	0.543
Bone	1 (3.3%)	3 (6.1%)	1.000	3 (10.0%)	3 (6.1%)	0.668
Ascites	2 (6.7%)	4 (8.2%)	1.000	1 (3.3%)	3 (6.1%)	1.000
Peripheral effusion	2 (6.7%)	5 (10.2%)	0.703	2 (6.7%)	5 (10.2%)	0.703
GI tract	3 (10.0%)	5 (10.2%)	1.000	1 (3.3%)	4 (8.2%)	0.644
Intestine	2 (6.7%)	0 (0.0%)	0.141	1 (3.3%)	0 (0.0%)	0.380

Abbreviations: CNS indicates the central nervous system; GI tract, the gastrointestinal tract.

Table 4. Factors affecting the development of abnormal lymphocytes in the peripheral blood at relapse

Factors		Univariate analysis			Multivariate analysis		
		Odds ratio	(95% CI)	P-value	Odds ratio	(95% CI)	P-value
Allo-SCT	Allo-SCT group *vs* CHT group	0.148	(0.045 - 0.487)	<0.001	0.095	(0.025 - 0.364)	<0.001
Age	≥60 yrs *vs* < 60 yrs	2.828	(1.078 - 7.423)	0.038	-	-	-
Hypercalcemia	Presence *vs* Absence	0.340	(0.111 - 1.042)	0.076	0.323	(0.094 - 1.114)	0.074
CNS lesion	Presence *vs* Absence	0.116	(0.006 - 2.140)	0.080	-	-	-
Sex	Male *vs* Female	0.433	(0.170 - 1.101)	0.102	0.236	(0.075 - 0.747)	0.014
Bulky mass	Presence *vs* Absence	0.140	(0.007 - 2.633)	0.152	-	-	-
Interval from CR to relapse	< 180 days *vs* ≥180 days	0.480	(0.188 - 1.223)	0.162	-	-	-
GI tract lesion	Presence *vs* Absence	0.219	(0.026 - 1.882)	0.246	-	-	-

The following factors were obtained at the initial diagnosis; age, hypercalcemia, CNS lesion, bulky mass, and GI tract lesion.

Factors with at least borderline significance (P<.25) according to Fisher's exact test were listed in the results of the univariate analysis.

Abbreviations: 95% CI indicates the 95% confidence interval.

Table 5. Factors affecting relapse only in new lesions

Factors		Univariate analysis			Multivariate analysis		
		Odds ratio	(95% CI)	P-value	Odds ratio	(95% CI)	P-value
Allo-SCT	Allo-SCT group *vs* CHT group	4.149	(1.338 - 12.870)	0.022	4.149	(1.338 - 12.867)	0.014
Lymph node lesion	Presence *vs* Absence	0.272	(0.078 - 0.940)	0.066	-	-	-
Interval from CR to relapse	< 180 days *vs* ≥180 days	2.226	(0.731 - 6.780)	0.18	-	-	-
WBC	$\geq 8.9 \times 10^9$/l *vs* $< 8.9 \times 10^9$/l	2.226	(0.731 - 6.780)	0.18	-	-	-

The following factors were obtained at the initial diagnosis; lymph node lesion and WBC.

Factors with at least borderline significance ($P<.25$) according to Fisher's exact test were listed in the results of the univariate analysis.