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Original Article

Efficacy of peripheral blood stem cell transplantation versus conventional chemotherapy on anaplastic large-cell lymphoma: a retrospective study of 64 patients from a single center

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Abstract

Anaplastic large-cell lymphoma (ALCL) is characterized by frequently presenting adverse factors at diagnosis. Many groups believed aggressive treatment strategies such as autologous stem cell transplantation brought survival benefit for ALCL patients. However, few compared these approaches with conventional chemotherapy to validate their superiority. Here, we report a study comparing the efficacy of peripheral blood stem cell transplantation (PBSCT) and conventional chemotherapy on ALCL. A total of 64 patients with primary systemic ALCL were studied retrospectively. The median follow-up period was 51 months (range, 1–167 months). For 48 patients undergoing conventional chemotherapy only, the 4-year event-free survival (EFS) and overall survival (OS) rates were 70.7% and 88.3%, respectively. Altogether, 16 patients underwent PBSCT, including 11 at first remission (CR1/PR1), 3 at second remission, and 2 with disease progression during first-line chemotherapy. The 4-year EFS and OS rates for patients underwent PBSCT at first remission were 81.8% and 90.9%, respectively. Compared with conventional chemotherapy, PBSCT did not show superiority either in EFS (P = 0.240) or in OS (P = 0.580) when applied at first remission. Univariate analysis showed that patients with B symptoms (P = 0.001), stage III/IV disease (P = 0.008), bulky disease (P = 0.075), negative anaplastic lymphoma kinase (ALK) expression (P = 0.059), and age ⩽ 60 years (P = 0.054) had lower EFS. Furthermore, PBSCT significantly improved EFS in patients with B symptoms (100% vs. 50.8%, P = 0.027) or bulky disease (100% vs. 52.8%, P = 0.045) when applied as an up-front strategy. Based on these results, we conclude that, for patients with specific adverse factors such as B symptoms and bulky disease, PBSCT was superior to conventional chemotherapy in terms of EFS.

Key words Anaplastic large-cell lymphoma, peripheral blood stem cell transplantation, chemotherapy, anaplastic lymphoma kinase (ALK)

Anaplastic large-cell lymphoma (ALCL), a distinct entity of non-Hodgkin's lymphoma (NHL) originally described by Stein *et al.*[1] in 1985, is characterized by large anaplastic cells expressing CD30 (Ki-1 antigen). Although several ALCL cases have been reported to express antigens of T-cell or B-cell lineage, many cases may lack lymphoid antigens (null type), and rare cases may express both markers[2].

Clinically, primary ALCL is divided into three subtypes: primary systemic anaplastic lymphoma kinase (ALK)-positive ALCL, primary systemic ALK-negative ALCL, and primary cutaneous ALCL. Many studies have described the clinicopathologic features of ALCL and explored different treatment strategies, especially for

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systemic ALCL. By far, no standard chemotherapy regimen has been established for systemic ALCL patients. At diagnosis, ALCL frequently present with many adverse factors, including advanced disease, B symptoms, and extranodal involvement. Thus, many groups have employed aggressive treatment strategies such as third-generation regimens, hybrid regimens, or autologous stem cell transplantation (ASCT) [3-6]. Prospective studies indicated that third-generation regimens were not superior to first-line regimens in terms of response rate or long-term survival[7]. Studies of transplantation showed that, whenever it is administrated as an up-front therapy or salvage therapy, 60%–90% of patients survived after ASCT [8-16]. Although high-dose chemotherapy with autologous stem cell support can effectively induce long-term remission and survival in ALCL patients, few studies compared this approach with conventional chemotherapy to validate its superiority. Hence, the role of aggressive treatment strategies in treating ALCL should be reconsidered.

This study aimed to explore the role of ASCT in treating ALCL by comparing its efficacy with conventional chemotherapy. Thus, we retrospectively reviewed the clinical data of 64 patients with systemic ALCL who were diagnosed and treated with conventional chemotherapy or ASCT in our hospital. Here we present the results.

Materials and Methods

Patients and diagnosis

A total of 64 patients newly diagnosed with ALCL were studied retrospectively. All these patients were treated in the Department of Medical Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS & PUMC) between October 1992 and December 2006. The study protocol was approved by the institutional review board of CAMS & PUMC. Informed consent was obtained according to the Declaration of Helsinki. All specimens were reviewed separately by two experienced pathologists, and consensus was reached in all cases. The WHO diagnosis criteria for NHL were adopted for diagnosis. Antibodies against CD30, CD3, CD45RO, CD20, and CD79a were used for immunohistochemical analysis to determine diagnosis and cell origin. Furthermore, ALK and epithelial membrane antigen (EMA) staining were also performed. All antibodies were obtained from Dako Corporation (Denmark).

Staging

Staging was performed according to the Ann Arbor staging systems for Hodgkin disease. At the time of diagnosis, each patient underwent a physical examination, full blood count and biochemical profile, serum lactate dehydrogenase (LDH) determination, chest X-ray, bone marrow aspirate smears, ultrasonography, and computed tomography (CT) or magnetic resonance imaging (MRI) scan. B symptoms were defined as unknown fever (>38℃) for more than 3 days, weight loss of more than 10% within 6 months, and night sweat. Bulky disease was defined as tumor mass larger than 5 cm.

Treatment strategy and response criteria

Anthracycline-based chemotherapy (up to 6 cycles) was given to each patient, and locoregional radiotherapy was added for patients with stage I/II disease or bulky disease. CT scan of target sites was performed every two cycles for response evaluation according to the WHO criteria. Patients with adverse factors such as stage III/IV disease, bulky disease, elevated LDH, or negative ALK expression were candidates for peripheral blood stem cell transplantation (PBSCT). Refractory disease (progression during first-line chemotherapy) or sensitive relapse was also an indication for PBSCT.

Statistical analysis

SSPS 10.0 software was used for data analysis. The Kaplan-Meier method was used to estimate overall survival (OS), which were determined from the date of diagnosis to the date of death or the last follow-up visit. Event-free survival (EFS) was estimated from the date of diagnosis to the date of documented failure [date of the beginning of treatment for patients whose disease progressed while on chemotherapy before achieving complete response (CR), date of relapse, or date of death for any reason] or to the date of the last follow-up visit for those in first CR. The log-rank test was used to compare survival curves. For continuous variables, *t* test or Mann-Whitney *U* test was employed to analyze the difference between two groups. The Chi-square (χ^2) test was employed to analyze categorical variables. *P* values less than 0.05 were considered significant.

Results

Immunohistochemistry results

Of the 64 patients, 58 (90.6%) had tumors of T-cell lineage as indicated by positive staining for CD3 and CD45RO, 4 (7.8%) had tumors of B-cell lineage as indicated by positive staining for CD20 and CD79a, and 2 (1.6%) had tumors of null phenotype because cells did not express any lineage-specific antigens. Altogether, CD30 expression was examined in 60 patients, ALK expression

was examined in 35 patients, and EMA expression was examined in 29 patients; the positive rate for each marker was 96.7% (58/60), 60.0% (21/35), and 51.7% (15/29), respectively.

Patient characteristics

Of the 64 patients, 38 (59.4%) were males and 26 (40.6%) were females (male/female ratio, 1.46:1). The median age at diagnosis was 33 years (range, 8–74 years). Twenty-six (40.6%) patients had stage I disease, 18 (28.1%) had stage II, 9 (14.1%) had stage III, and 11 (17.2%) had stage IV. Fifty-three (82.8%) patients showed peripheral lymph node involvement, whereas mediastinal involvement was noted in 24(37.5%) patients. Extranodal disease was present in 16 (25.0%) patients. The skin and lung were the most frequently involved sites, and extranodal disease at these sites was observed in 3 patients each. Other extranodal involved sites included the liver (2 patients), bone (2 patients), bone marrow (2 patients), stomach (1 patient), muscle (1 patient), testis (1 patient), nasal cavity (1 patient), and soft tissue (1 patient). B symptoms were present in 28 (43.8%) patients, with fever being the most common. Bulky disease was seen in 25 (39.1%) patients, including 6 patients with tumor diameter larger than 10 cm. In total, 49 patients had complete clinical data for international prognostic index (IPI) scoring. Thirty-eight patients (77.6%) were in the low risk group, 10 (20.4%) were in the low/intermediate risk group, and 1 (2.0%) was in the high/intermediate risk group (Table 1).

Treatment and outcome

Of the 64 patients, 51 underwent CHOP chemotherapy (cyclophosphamide, doxorubicin/epirubicin, vincristine, and prednisone), 9 underwent proMACE/cytaBOM chemotherapy (prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue), and the other 4 (with stage I/II disease) underwent localized radiotherapy followed by

Table 1. Characteristics of 64 patients with primary systemic anaplastic large-cell lymphoma

Characteristic	No. of patients	Percentage (%)
Gender		
Male	38	59.4
Female	26	40.6
Stage		
I	26	40.6
II	18	28.1
III	9	14.1
IV	11	17.2
With extranodal disease	16	25.0
B symptoms[a]	28	43.8
Fever	25	39.1
Weight loss	6	9.4
Night sweat	10	15.6
Bulky disease	25	39.1
LDH elevation[b]	14	28.6
IPI score[c]		
Low	38	77.6
Low-intermediate	10	20.4
High-intermediate	1	2.0
Immunology		
B cell	4	7.8
T cell	58	90.6
Null	2	1.6
ALK expression[d]	21	60.0

LDH, lactate dehydrogenase; IPI, international prognostic index; ALK, anaplastic lymphoma kinase. [a] One patient may have one or more B symptoms. [b] LDH was evaluable in 49 patients and elevated in 14. [c] A total of 49 patients had complete records for IPI scoring. [d] ALK expression was assayed in 35 patients.

CHEP chemotherapy (cyclophosphamide, doxorubicin/epirubicin, etoposide, and prednisone). Among 54 patients who had targets for response evaluation, CR was achieved in 25 (46.3%) patients, PR in 21 (38.9%) patients, stable disease (SD) in 6 (11.1%) patients, and progressive disease (PD) was observed in 2 (3.7%) patients. For the whole series, the median follow-up period was 51 months (range, 1–167 months). The 4-year EFS and OS rates were 66.6% and 89.6%, respectively. For patients treated with conventional chemotherapy only, the 4-year EFS and OS rates were 70.7% and 88.3%, respectively.

Altogether, 16 patients underwent PBSCT, which was conducted at first remission in 11 patients (6 with CR1 and 5 with PR1) and at second remission in 3 patients (all with CR2); the other 2 proceeded to PBSCT for disease progression during first-line chemotherapy. Conditioning regimens included E-TBI (etoposide, total body irradiation) in 2 patients, CE-TBI (cyclophosphamide, etoposide, total body irradiation) in 2 patients, CBV (cyclophosphamide, carmustine, etoposide) in 3 patients, and BEAM (carmustine, etoposide, cytarabine, melphalan) in 9 patients (Table 2). After a median follow-up of 86.5 months (range, 20–133 months), only 2 patients with negative ALK expression and bone marrow involvement relapsed. One patient (No. 3) relapsed 3 months after PBSCT and was successfully rescued by allogeneic transplantation, whereas the other (No. 2) relapsed 12 months after PBSCT and died 8 months later. The 4-year OS rates for patients treated with PBSCT was 93.3%.

Because EFS for patients undergoing PBSCT could be compromised by mixed population, we focused the analysis on patients underwent PBSCT at CR1/PR1. Due to inclusion criteria, more patients accompanied with adverse factors when compared with those treated with conventional chemotherapy (Table 3). The EFS and OS rates were 81.8% and 90.9%, respectively. Compared with conventional chemotherapy, PBSCT did not show significant advantages either in EFS (P = 0.240) or in OS (P = 0.580) when it was applied at first remission (CR1/PR1) (Figure 1).

Prognostic factors

In patients undergoing conventional chemotherapy, univariate analysis showed that B symptoms (P = 0.001) and stage III/IV (P = 0.008) indicated significantly lower EFS, whereas bulky disease (P = 0.075), negative ALK expression (P = 0.059), and age ⩽ 60 years (P = 0.054) showed a tendency towards lower EFS. Compared with conventional chemotherapy, PBSCT significantly improved the EFS of patients with B symptoms (100% vs. 50.8%, P = 0.027) or with bulky disease (100% vs. 52.8%, P = 0.045) when it was applied as an up-front strategy (Figures 2 and 3). However, PBSCT did not provide any additional survival benefit compared with conventional chemotherapy in patients with stage III/IV disease (75% vs. 43.8%, P =

Table 2. Characteristics of patients in the peripheral blood stem cell transplantation (PBSCT) group

No.	Age/gender	Cell origin	ALK	Stage	Visceral involvement	LDH	Bulk (cm)	Status before PBSCT	Conditioning regimen	Follow-up (months)	Outcome
1	34/M	T	NA	2	None	Normal	5	CR1	E-TBI	106	Alive
2	22/M	T	Negative	4	Skin	Normal	0	CR1	E-TBI	24	Died
3	37/M	B	Negative	4	None	Normal	0	CR1	CE-TBI	70	Alive
4	18/M	T	NA	3	Spleen	Normal	0	PR1	CE-TBI	133	Alive
5	45/M	T	Positive	1	Spleen, liver	Normal	6	PR1	BEAM	120	Alive
6	41/M	T	NA	2	None	Normal	6	RD	BEAM	117	Alive
7	11/M	T	NA	4	Spleen	NA	5	RD	CBV	76	Alive
8	26/F	T	Negative	1	None	Normal	7	PR1	BEAM	60	Alive
9	27/F	T	NA	3	None	Normal	0	CR1	CBV	112	Alive
10	15/M	T	Positive	4	None	NA	0	CR1	CBV	109	Alive
11	22/M	T	Positive	2	None	Elevated	0	CR2	BEAM	103	Alive
12	32/M	T	NA	3	None	NA	0	CR2	BEAM	52	Alive
13	23/F	T	Positive	4	Lung	NA	5	PR1	BEAM	97	Alive
14	46/F	B	Negative	4	Skin	NA	0	CR2	BEAM	20	Alive
15	21/F	T	Positive	4	Lung	Elevated	11	PR1	BEAM	56	Alive
16	12/M	Null	Positive	3	None	Elevated	0	CR1	BEAM	48	Alive

M, male; F, female; NA, not available; RD, refractory disease; E-TBI, etoposide and total body irradiation; BEAM, carmustine, etoposide, cytarabine, and melphalan; CBV, cyclophosphamide, carmustine, and etoposide. Other abbreviations as in Table 1.

Table 3. Comparison of patient characteristics between the conventional chemotherapy group and the transplantation group

Characteristic	Conventional chemotherapy group (n = 39)	Transplantation group (n = 11)	P
Median age (years, range)	34 (8–68)	23 (12–45)	0.002
Sex			0.77
Male	24 (61.5)	7 (63.6)	
Stage			<0.001
I	18 (46.2)	2 (18.2)	
II	12 (30.8)	1 (9.1)	
III	5 (12.8)	3 (27.3)	
IV	4 (10.2)	5 (45.4)	
With extranodal disease	7 (17.9)	5 (45.5)	<0.001
B symptoms	17 (43.6)	6 (54.5)	0.16
Bulky disease	17 (43.6)	5 (45.5)	0.89
LDH elevation	9 (30.0)	2 (22.2)	0.26
IPI score			<0.001
Low	24 (80.0)	5 (55.6)	
Low-intermediate	5 (16.7)	4 (44.4)	
High-intermediate	1 (3.3)	0	
Immunology			0.031
B cell	1 (2.6)	1 (9.1)	
T cell	37 (94.8)	9 (81.8)	
Null	1 (2.6)	1 (9.1)	
ALK expression	10 (52.6)	5 (62.5)	0.2

Except median age, the values are presented as numbers of patients with percentages in parenthesis.
Abbreviations as in Table 1.

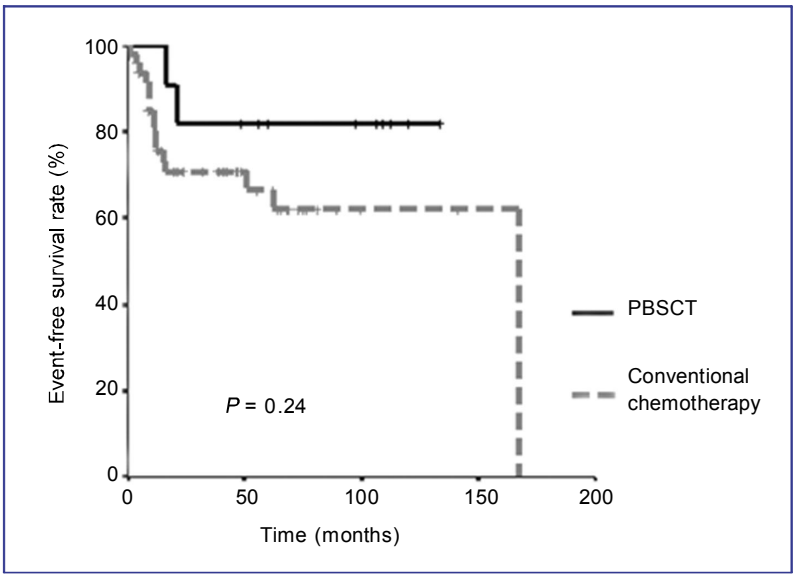

Figure 1. **Event-free survival (EFS) comparison according to the treatment modality.** The difference of EFS was not significant between patients treated with conventional chemotherapy and those treated with peripheral blood stem cell transplantation (PBSCT) at CR1/PR1.

0.130), negative ALK expression (33.3% vs. 50.0%, P = 0.900) or younger age (81.8% vs. 66.0%, P = 0.140). In terms of OS, only 8 patients died in this cohort (1 in the PBSCT group and 7 in the conventional chemotherapy

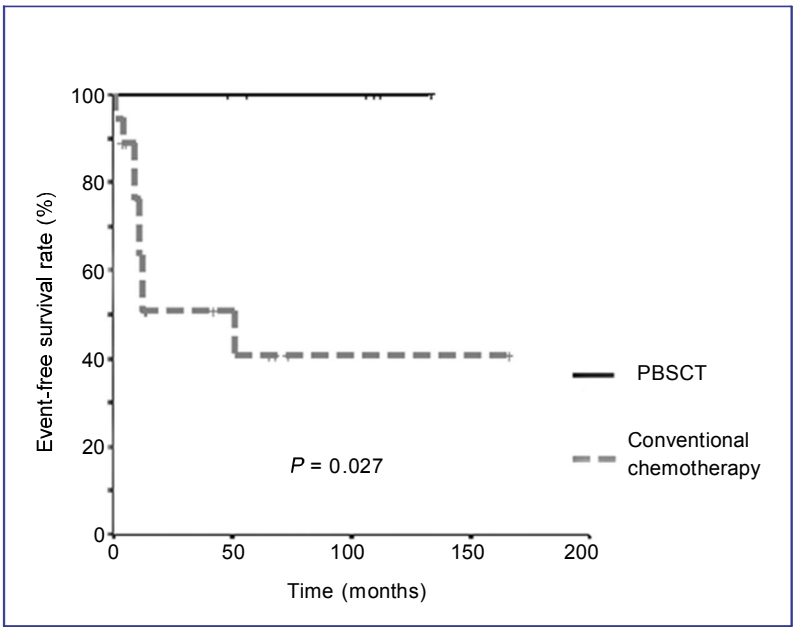

Figure 2. **EFS comparison according to the treatment modality in patients with B symptoms.** Patients treated with PBSCT had significantly higher EFS rate than those treated with conventional chemotherapy.

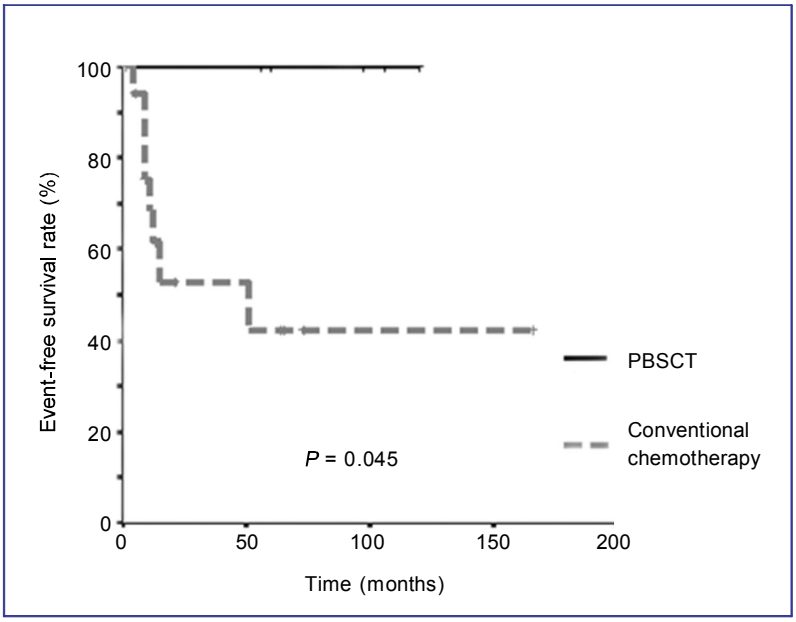

Figure 3. **EFS comparison according to the treatment modality in patients with bulky disease.** Patients treated with PBSCT had significantly higher EFS rate than those treated with conventional chemotherapy.

group). Thus, there were not enough censored events for statistical analysis to demonstrate the superiority of PBSCT in any stratified populations.

Discussion

ALCL is a rare disease, accounting for less than 5% of NHL[2,17,18]. Clinically, it is characterized by the frequent presence of adverse factors such as advanced disease, B symptoms, and extranodal involvement[4,19-22]. In terms of treatment, no standard strategy has been established for systemic ALCL patients. Because many adverse factors are present at diagnosis, more aggressive treatment modalities such as leukemia-like regimens or high-dose chemotherapy with stem cell support have been considered by many groups. Statistically, 60%–90% of ALCL patients, especially those with ALK-positive disease, achieved long-term survival after stem cell transplantation whenever it was administered as an

up-front or salvage therapy[8-16]. However, these studies were all single arm, which makes it difficult to draw a definitive conclusion about the superiority of transplantation. In addition, in many studies concerning conventional chemotherapy, the long-term OS rates ranged from 62% to 85% with a median follow-up time longer than 5 years, which was similar to the results of transplantation[3-5]. Therefore, it is necessary to compare conventional chemotherapy and transplantation in one setting to further evaluate the efficacy of transplantation on systemic ALCL. In our study, 64 patients underwent conventional chemotherapy and 16 proceeded to PBSCT thereafter. Because patient statuses at transplantation were not the same, we focused our analysis on 11 patients underwent PBSCT at CR1/PR1 to explore the efficacy of PBSCT as an up-front modality. Compared with conventional chemotherapy treatment in 48 patients, PBSCT did not show significant survival improvement either in EFS (P = 0.240) or in OS (P = 0.580).

For most study groups, the reason for employing aggressive modalities including PBSCT on ALCL has been adverse factors frequently present at diagnosis. However, factors indicating poor prognosis were mostly identified in other aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL)[23]. In ALCL, some studies failed to show that these aggressive factors had the same prognostic value as they did in other lymphoma subtypes[4,5]. Moreover, based on the findings of a study conducted in DLBCL, only patients with specific factors such as elevated LDH level or high IPI score benefit from PBSCT[24]. Hence, re-evaluation of these factors in ALCL patients is necessary.

Among patients undergoing conventional chemotherapy in our study, B symptoms (P = 0.001) and stage III/IV (P = 0.008) indicated significantly lower EFS rate, whereas the significance of bulky disease (P = 0.075), negative ALK expression (P = 0.059), and age $\leqslant$ 60 years (P = 0.054) was marginal. Other factors such as elevated LDH level, involvement of more than one extranodal site, and higher performance status, which were unanimously found to indicate poor prognosis in many studies on aggressive lymphoma, were not significant (data not shown). Thus, we confined our analysis to the five adverse factors that had an effect on survival. Our results showed that PBSCT could significantly improve the EFS of patients with B symptoms (100% vs. 50.8%, P = 0.027) or bulky disease (100% vs. 52.8%, P = 0.045) when it was applied as an up-front strategy. However, PBSCT yielded similar EFS as conventional chemotherapy for patients with stage III/IV disease (P = 0.130), negative ALK expression (P = 0.900), or younger age (P = 0.140).

ALK expression is an important prognostic factor that is used to evaluate the long-term survival of ALCL patients. For primary systemic ALCL patients, those without ALK expression have significantly lower 5-year survival rate than those with ALK expression[19,25,26]. However, in our study, negative ALK expression showed only marginal significance towards poor EFS for patients undergoing conventional chemotherapy. It should be noted, however, that some studies suggest that the significance of ALK expression differs in adult and child patients (<15 years). More specifically, the ALK expression rate in childhood patients was reported to be higher than that in adult patients[6,27-30]. Furthermore, ALK expression in younger patients did not have prognostic value in some studies[3,6]. Based on these results, patients younger than 15 in our study were ruled out from further analysis (n = 5, with ALK expression analyzed in 2 patients and identified as positive in both). Consequently, the difference of EFS between patients with ALK-negative and ALK-positive disease became significant (45.5% vs. 81.8%, P = 0.021). Although this result could not lead to the conclusion that there is indeed a difference in the significance of ALK expression in children and adults, the role of negative ALK expression in indicating poor survival seems more definite in adult ALCL patients.

In our series, PBSCT was conducted in 4 ALK-negative patients (3 at CR1/PR1, 1 at CR2). Two out of 3 patients who underwent PBSCT at CR1/PR1 relapsed. One was successfully rescued by allogeneic transplantation and the other died within 8 months after relapse. Consequently, compared with conventional chemotherapy, PBSCT at CR1/PR1 did not show superiority either in EFS or in OS. Another single-arm study conducted by Zamkoff *et al.*[31] explored the efficacy of ASCT in chemosensitive relapsed ALK-negative patients. Of 16 patients recruited, 9 died of disease, 4 relapsed, 1 succumbed to secondary acute myeloid leukemia, and 1 was lost to follow-up. Only 1 patient was alive free of disease at 6 years after transplantation. Therefore, for patients with ALK-negative ALCL, PBSCT showed unsatisfactory results when it was applied as first-line therapy or salvage therapy. Brand new treatment methods are needed to improve the dismal prognosis of these patients.

To our knowledge, our study is the first case-control study to explore the efficacy of PBSCT on ALCL. We show here that when compared with conventional chemotherapy, PBSCT improved the EFS of patients with specific adverse factors. In terms of OS, the improvement was not significant. Prolonged time of follow-up is needed because the long-term survival of ALCL seems longer than that of other subtypes of aggressive lymphoma[8,14,23]. Additionally, similar to other studies concerning ALCL, our study was limited by

relatively smaller samples and retrospective study design. Prospective study is necessary to further clarify the role of PBSCT in treating ALCL patients.

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