

Original Article

# Comparison of Long-Term Clinical Outcomes of CHOP Chemotherapy between Japanese Patients with Nodal Peripheral T-Cell Lymphomas and Those with Diffuse Large B-Cell Lymphoma in the Study Group of the Tohoku Hematology Forum

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To clarify the clinical outcome of peripheral T-cell lymphomas (PTCLs), we conducted a retrospective review comparing the outcomes of patients with PTCL (nodal peripheral T-cell lymphoma, unspecified, n = 34 ; angioimmunoblastic T-cell lymphoma, n = 12) to those with diffuse large B-cell lymphoma (DLBCL, n = 48). All patients received CHOP-based chemotherapy without rituximab. PTCL patients presented at a more advanced clinical stage (91% vs. 65%,  $P < 0.002$ ) with a poorer performance status (26% vs. 17%,  $P < 0.002$ ) than DLBCL patients. The complete response rate among PTCL patients was significantly lower than among DLBCL patients (39% vs. 67%,  $P < 0.008$ ), as was the 3-year overall survival rate (26% vs. 50%,  $P = 0.005$ ), and Cox multivariate analysis revealed immunophenotype, performance status, and extranodal site involved to be significantly associated with shorter overall survival ( $P = 0.045$ ,  $P = 0.007$ , and  $P = 0.034$ , respectively). Our findings suggest that PTCL patients tend to have a poor prognosis associated with several initial risk factors. Moreover, the T-cell phenotype itself appears to have a significant impact on overall survival. Thus, standard CHOP chemotherapy may be inadequate for PTCLs, especially in patients with high-risk factors. The development of newly stratified therapies for the treatment of PTCLs would be highly desirable. [*J Clin Exp Hematopathol* 51(1) : 29-35, 2011]

**Keywords:** peripheral T-cell lymphomas, diffuse large B-cell lymphoma, survival, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)

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## INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are relatively uncommon malignancies, accounting for only 10-15% of non-Hodgkin's lymphomas (NHLs) in large international studies.<sup>1,2</sup> However, their incidence shows significant geographical and racial variation, such that they are much more common in Asia, including Japan, than in North America or Europe.<sup>3,4</sup> The most common PTCL subtypes are peripheral T-cell lymphoma, unspecified (PTCL-u or PTCL, not otherwise specified) (25.9%), angioimmunoblastic T-cell lymphoma (AITL) (18.5%), and anaplastic large cell lymphoma (ALCL) [anaplastic lymphoma kinase (ALK)-positive ALCL, 6.6% ; ALK-negative ALCL, 5.5%].<sup>5</sup> Patients with PTCL usually present with systemic lymphadenopathy and frequent

involvement of extranodal tissues, including bone marrow, skin, and spleen, and a majority have advanced disease with B symptoms.<sup>6</sup> Moreover, PTCLs include primary extranodal T-cell lymphoma, especially cutaneous peripheral T-cell lymphomas. However, this subtype is a different entity from nodal PTCLs by clinical features or etiology.

PTCLs have an aggressive clinical course with a poor response to therapy. When stratified on the basis of international prognostic index (IPI), treatment of PTCLs using standard anthracycline-based regimens results in significantly poorer outcomes within each risk group than when the same regimens are used to treat diffuse large B-cell lymphoma (DLBCL).<sup>2,7,8</sup> Indeed, long-term disease-free survival (DFS) is achieved in only 20-30% of patients with PTCL.<sup>2,6-10</sup> However, these results showed substantial heterogeneity due to the inclusion in the PTCL group of patients with ALK-positive ALCL, which has a significantly better outcome than DLBCL.<sup>11-13</sup> To clarify the clinical outcome of PTCLs, we conducted a retrospective review of patients with PTCL, including nodal PTCL-u (n = 34) and AITL (n = 12), who were treated using a CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone). A cohort of consecutive patients with primary nodal DLBCL, which is the same aggressive lymphoma as PTCLs, also treated with a CHOP regimen (without rituximab) served as a reference group for comparison.

## PATIENTS AND METHODS

### *Patients*

A total of 46 Japanese patients with PTCL, including nodal PTCL-u (n = 34) and AITL (n = 12), were treated as members of the study group of the Tohoku Hematology Forum (THF) from April 1998 to December 2005. A consensus diagnosis for each patient was obtained using the World Health Organization (WHO) classification (2001).<sup>14</sup> A diagnosis was confirmed hematopathologically by pathologists at each institute and R.I. We specifically excluded from the study patients with extranodal PTCL-u, ALK-positive ALCL, HTLV-1-positive T cell lymphoma, extranodal NK/T-cell lymphoma, and the other subtypes of mature T-cell lymphoma. Clinical stage was defined according to the Ann Arbor classification. The IPI was calculated on the basis of age, performance status (PS), serum lactate dehydrogenase (LDH) value, number of involved extranodal sites, and clinical stage. The treatment response was assessed according to the WHO response criteria. A complete response (CR) was defined as no evidence of residual disease. All patients were newly diagnosed, were previously untreated, and were treated using a CHOP regimen. The median follow-up period was 11.5 months (range, 3-60 months). Consecutive patients with primary nodal DLBCL that received the aforementioned CHOP

regimen without rituximab were identified from the database of Aomori Prefectural Hospital and were selected as a control group. Patients with extranodal DLBCL (n = 7), who had been treated using high-dose chemotherapy following auto stem cell transplantation (n = 2) or who had been treated using chemotherapy without anthracycline because of old age (more than eighty years old ; n = 3) were excluded from the control group. Given these considerations, the control group was composed of 48 patients who received the CHOP regimen between April 1998 and December 2005, which was before we started routinely using rituximab as first-line therapy. The median follow-up period of the control group was 15.0 months (range, 6-60 months). The present study was conducted under approval of the institutional review board of Akita University Hospital in accordance with the Declaration of Helsinki.

### *Statistical Analyses*

All statistical analyses were performed using SPSS statistical software (SPSS Japan Inc., Tokyo, Japan, version 17.0). Data are presented as means  $\pm$  SD, unless indicated otherwise. Differences between two groups were evaluated using Student's t-test (parametric analysis). The  $\chi^2$  test or Fisher's exact test was used to compare the proportions of patients. Disease-free survival (DFS) for patients who achieved CR was calculated from the date of the first documentation of response to the date of recurrence or death. Overall survival (OS) was calculated from the date chemotherapy was initiated to the date of death from any cause or to the date of last contact. DFS and OS were analyzed using the Kaplan-Meier method. The statistical significance of differences in survival was assessed using the Log-rank test. The effects of potential prognostic variables on survival (significance threshold,  $P = 0.1$ ) were assessed in stepwise fashion according to the Cox regression method. Values of  $P$  less than 0.05 were considered significant.

## RESULTS

### *Patient Characteristics*

The main clinical characteristics of the 46 patients with PTCL and 48 with DLBCL (control) are shown in Table 1. As was carried out previously,<sup>2</sup> we evaluated age, PS, clinical stage, serum LDH values, and the number of involved extranodal sites as prognostic factors. The median age of the PTCL patients was 65 years (range 35-89 years), while that of the DLBCL patients was also 65 years (range 17-83 years). There was no significant difference between the two groups with respect to age, gender, serum LDH values, or the number of involved extranodal sites. On the other hand, more PTCL patients presented at an advanced clinical stage (91% vs.

**Table 1.** Patient characteristics and prognostic factors

Characteristics	PTCLs (n = 46)	DLBCL (n = 48)	P
Age (years)	64.9±11.1 65y (35-89)	63.6±11.0 65y (17-83)	0.549 <sup>a</sup> 0.555 <sup>b</sup>
Sex (male/female)	24/22	22/26	0.539
Performance status (2-4)	12	8	<0.002
Clinical stage (III + IV)	42	31	<0.002
Serum LDH (<UNL)	33	32	0.595
Extranodal sites (>2)	11	7	0.251
IPI (HI + H)	30	20	0.022

PTCLs, peripheral T-cell lymphomas ; DLBCL, diffuse large B-cell lymphoma ; LDH, lactate dehydrogenase ; UNL, upper normal limit ; IPI, international prognostic index ; HI, high-intermediate ; H, high ; <sup>a</sup>, Student's t-test ; <sup>b</sup>, Mann-Whitney test

**Table 2.** Clinical response to CHOP regimen and survival

Outcomes	PTCLs (%)	DLBCL (%)	P
Complete response	18/46 (39%)	32/48 (67%)	<0.008
Relapse	10/18 (56%)	13/32 (41%)	0.309
3-year disease-free survival	40%	49%	0.253 <sup>a</sup>
3-year overall survival	26%	50%	0.005 <sup>a</sup>

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone ; PTCLs, peripheral T-cell lymphomas ; DLBCL, diffuse large B-cell lymphoma ; <sup>a</sup>, log-rank test

65%,  $P < 0.002$ ), with a poorer performance status (26% vs. 17%,  $P < 0.002$ ), and with a higher international prognostic index (IPI) (65% vs. 42%,  $P = 0.022$ ) than DLBCL patients.

### **Response to Treatment and Survival**

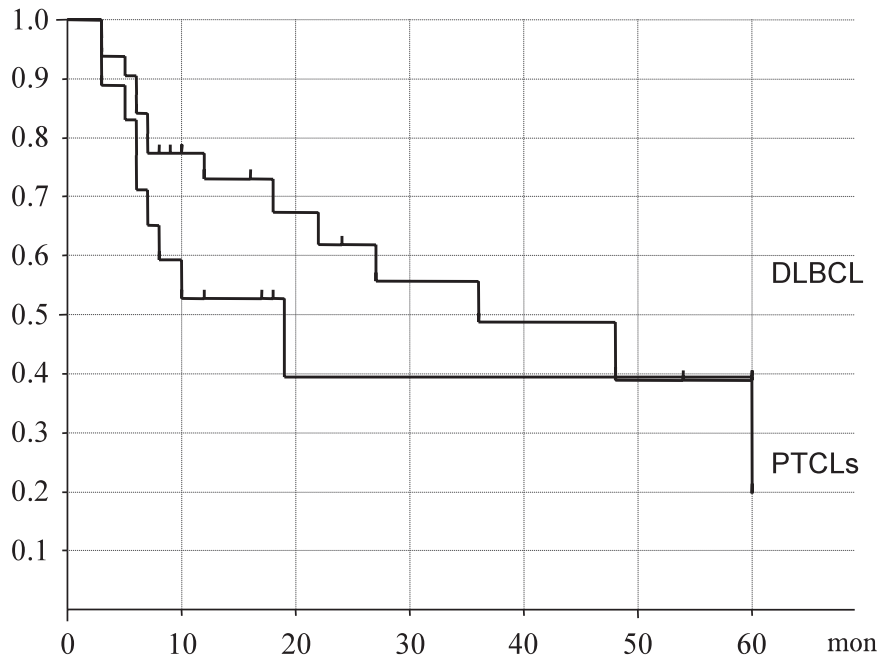
We assessed the impact of immunophenotype on clinical response and survival. A significantly lower CR rate was observed among the PTCL patients initially treated with the CHOP regimen than among the DLBCL patients (39% vs. 67%,  $P < 0.008$ , Table 2). As shown in Table 2, 10 of the 18 (56%) PTCL patients who achieved CR relapsed, whereas only 13 of 32 (41%) DLBCL patients relapsed. Thus, PTCLs appear to recur more frequently than DLBCL, although the difference was not significant ( $P = 0.309$ ).

When we then compared the DFS curves between PTCL and DLBCL patients (Fig. 1), we found that the frequency of 3-year DFS tended to be lower among PTCL patients than DLBCL patients (40% vs. 49%, Log-rank test :  $P = 0.253$ ). Similarly, comparison of the OS curves (Fig. 2) showed the 3-year OS rate to be significantly lower among PTCL patients than DLBCL patients (26% vs. 50%, Log-rank test :  $P = 0.005$ ). In addition, Cox multivariate analysis revealed that immunophenotype, performance status, and extranodal site involved were all significantly associated with shorter OS ( $P = 0.045$ ,  $P = 0.007$ , and  $P = 0.034$ , respectively ; Table 3).

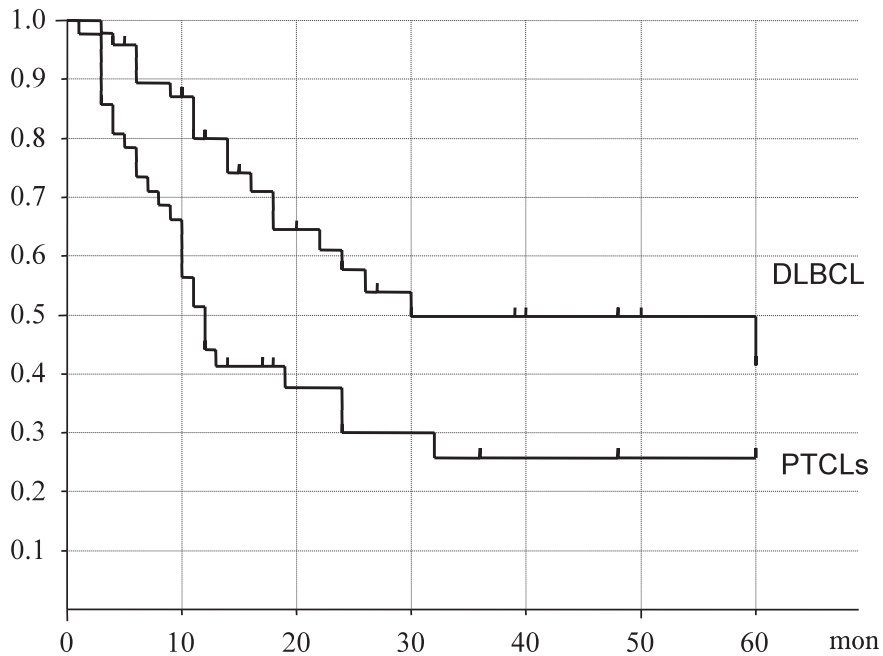
## **DISCUSSION**

We found that PTCL patients presented at a more advanced clinical stage and with poorer performance status than DLBCL patients. Consequently, the IPI among the patients was significantly higher than among DLBCL patients. This finding is consistent with earlier Japanese studies, which reported that high-risk groups (High + High-intermediate) accounted for 72.2% or 74% of Japanese patients with PTCL.<sup>15,16</sup> In Western countries, by contrast, high-risk groups account for only 42-46% of patients with PTCL.<sup>2,9,17</sup> Although the IPI for PTCLs appears to be higher in Japan than in Western countries, international studies with large patient populations will be required to confirm the racial differences in the clinical characteristics of PTCLs.

A significantly lower CR rate was observed among PTCL patients initially treated with a CHOP regimen than among DLBCL patients administered the same treatment. This finding was consistent with earlier reports in which CR rates for PTCLs ranged from 31% to 69%.<sup>2,6,7,9,15,16</sup> Furthermore, in the pre-rituximab era, the long-term remission rate was 50-60%, which is consistent with our result. If rituximab were combined with the CHOP regimen for CD20-positive DLBCL, the difference in CR rates between PTCLs and DLBCL would be expected to increase, as most studies have suggested that primary regimens containing rituximab improved the CR rate and long-term outcomes of DLBCL patients.<sup>18-21</sup>



**Fig. 1.** Disease-free survival curves for patients with nodal peripheral T-cell lymphoma, unspecified (n = 32), or diffuse large B-cell lymphoma (n = 18) were analyzed using Kaplan-Meier methods. The Log-rank test revealed no significant difference between the two groups ( $P=0.253$ ).



**Fig. 2.** Overall survival curves for patients with nodal peripheral T-cell lymphoma, unspecified (PTCL-u), or diffuse large B-cell lymphoma (DLBCL). Data from all patients with PTCL-u (n = 46) or DLBCL (n = 48) were analyzed using Kaplan-Meier methods. The Log-rank test revealed a statistically significant difference between the two groups ( $P=0.005$ ).

**Table 3.** Prognostic factors and overall survival

Variable	Median OS (mon)	Univariate <i>P</i> -value <sup>a</sup>	Multivariate <i>P</i> -value <sup>b</sup>	RP (95% CI)
Sex (male/female)	14/31	0.033	0.280	—
Age (<60/>60)	14/24	0.838	—	—
Immunophenotype (PTCLs/DLBCL)	12/30	0.005	0.045	0.53 (0.29-0.99)
Performance status (0-1/2-4)	32/6	<0.001	0.007	2.91 (1.34-6.33)
Clinical stage (I-II/ III-IV)	n.r./14	0.001	0.322	—
Serum LDH (<UNL/>UNL)	32/14	0.029	0.881	—
Extranodal sites (0-1/2-)	30/6	<0.001	0.034	2.30 (1.07-4.98)
IPI (L-LI/ HI-H)	12/60	<0.001	0.579	—

OS, overall survival; mon, months; <sup>a</sup>, Log-rank test; <sup>b</sup>, Cox regression analysis; RR, risk ratio; CI, confidence interval; PTCLs, peripheral T-cell lymphomas; DLBCL, diffuse large B-cell lymphoma; n.r., not reached; LDH, lactate dehydrogenase; UNL, upper normal limit; IPI, international prognostic index; L, low; LI, low-intermediate; HI, high-intermediate; H, high

Although the immunophenotype itself was an independent risk factor affecting OS in the present study, several earlier studies reported that there was no difference in OS between B-cell and T-cell lymphomas.<sup>22-24</sup> Moreover, Morabito *et al.* reported that, although the OS curves associated with the T-cell and B-cell immunophenotypes significantly differed from each other (5-year OS, 42% vs. 56%; median OS, 39 months vs. 94 months,  $P=0.0012$ ), multivariate analysis did not detect an association between OS and immunophenotype.<sup>17</sup> It seems likely that we were able to identify immunophenotype as an independent risk factor because we excluded patients with ALCL, which have more favorable outcomes than those with PTCL-u, and we compared nodal PTCLs with nodal DLBCL treated with the same standard CHOP regimen. Moreover, although they were small patient populations, we compared OS among patients with a high IPI index (14 of PTCLs, 10 of DLBCL). There was a significant difference between the two groups (50% OS, 4 months vs. 11 months; Log-rank test  $P=0.038$ ). This finding might be associated with three potential prognostic variables, including immunophenotype, performance status, and extranodal sites, which we analyzed by multivariate analysis.

Recently, the International T-Cell Project reported a cohort of 1,314 cases, including PTCLs, organized from 22 centers, worldwide. It was concluded that, unlike in DLBCL, the use of an anthracycline-containing regimen was not associated with improved outcomes in PTCLs.<sup>5</sup> On the other hand, the outcomes were equivalent in patients treated with high-dose sequential chemotherapy followed by autologous transplantation (ASCT).<sup>25-30</sup>

It has been reported that there is marked variability in the 5-year relative survival rate across PTCL subtypes, and that there has been no clear improvement in survival among PTCL patients over time.<sup>31</sup> This finding is in sharp contrast to the improvement in OS seen for B-cell NHLs over the same time

period,<sup>18-21</sup> which is due mainly to advances in therapy, particularly the addition of immunotherapy using anti-CD20 rituximab. CD52 antigen appears to be a suitable target for chemo-immunotherapy protocols for PTCLs, given the availability of anti-CD52 alemtuzumab. Prospective multicenter clinical trials have been designed to explore both the efficacy and the safety of a chemo-immunotherapeutic approach based on the combination of alemtuzumab and a standard-dose CHOP regimen as the first-line treatment for patients with PTCLs.<sup>32,33</sup> For patients who have high IPI score at the time of diagnosis, better therapeutic regimens are needed to improve the outcome of PTCLs.

Although this study was retrospective with only a small patient population, we found the prognosis of PTCL patients receiving the standard CHOP regimen to be poorer than that of DLBCL patients receiving the same therapy. This difference in clinical outcome seemed to depend on the phenotype itself, even in the era before rituximab, as well as on the more advanced clinical stage of the PTCL patients at the time of diagnosis. Thus, standard CHOP chemotherapy may be inadequate for PTCLs, especially in patients with high-risk factors. The development of new stratified therapies for the treatment of PTCLs would be highly desirable.

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