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Prognostic factors of peripheral T-cell lymphoma (PTL): statistical analysis on 30 patients.

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Abstract

Peripheral T-cell lymphoma (PTL) is a distinctive clinical entity, albeit it comprises several diseases with histologically heterogeneous diagnoses. We studied prognostic factors on 30 patients diagnosed and treated at Shikoku Cancer Center Hospital. Clinical findings and laboratory data were evaluated by statistical analysis to investigate the important factors influencing survival duration. Variables influencing survival were stage, leukemic change, bone marrow infiltration (BMI), anti-human T-lymphocyte virus-type I antibody, white blood cell count, and lactate dehydrogenase (LDH). Multivariate analysis revealed high level of LDH and positive BMI as the important factors for short survival. Histological classifications of the Working Formulation and the T-lymphoma classification by Suchi et al. were also evaluated whether these were related with prognosis. Our data revealed that there was no significant relationship between histological subtype and survival duration. The study of prognostic factors provides valuable aids for us to understand the clinical characteristics of PTL patients with various backgrounds.

KEYWORDS: non-Hodgkin's lymphoma, peripheral T-cell lymphoma, prognostic factors, histological classification

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Prognostic Factors of Peripheral T-Cell Lymphoma (PTL): Statistical Analysis on 30 Patients

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Peripheral T-cell lymphoma (PTL) is a distinctive clinical entity, albeit it comprises several diseases with histologically heterogeneous diagnoses. We studied prognostic factors on 30 patients diagnosed and treated at Shikoku Cancer Center Hospital. Clinical findings and laboratory data were evaluated by statistical analysis to investigate the important factors influencing survival duration. Variables influencing survival were stage, leukemic change, bone marrow infiltration (BMI), anti-human T-lymphocyte virus-type I antybody, white blood cell count, and lactate dehydrogenase (LDH). Multivariate analysis revealed high level of LDH and positive BMI as the important factors for short survival. Histological classifications of the Working Formulation and the T-lymphoma classification by Suchi *et al.* were also evaluated whether these were related with prognosis. Our data revealed that there was no significant relationship between histological subtype and survival duration. The study of prognostic factors provides valuable aids for us to understand the clinical characteristics of PTL patients with various backgrounds.

Key words : **non-Hodgkin's lymphoma, peripheral T-cell lymphoma, prognostic factors, histological classification**

PTL is a rather rare disease among Europeans and Americans compared with the occurrence among Japanese (1). Although PTL is a distinctive clinical entity with a common feature of T-cell phenotype of non-Hodgkin's lymphoma (NHL), clinical characteristics on each patient are widely variable and their histological patterns are heterogeneous as well (2, 3). Furthermore, an intervention of human T-cell leukemia virus (HTLV)-type I may be related with the complexity of clinical characteristics of PTL patients.

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Several reports have been published regarding to the clinical characteristics and prognosis of T-cell lymphoma (2-13), and the results of these studies were variable on these problems because of different backgrounds of their patients. There were only a few reports discussing the prognostic factors of PTL patients (11, 12). The clinical research evaluating prognostic factors is important to know the details of the patients' backgrounds and also to develop a new treatment strategy on this rare disease.

The Working Formulation (14) has been appraised as a standard classification of his-

tological subtyping of NHL internationally, as it has an advantage of close relevance with clinical prognosis. However, the merit of this classification has been applied mostly on the cases of NHL in the European countries and the United States where the majority of NHL are B-cell lymphomas (1). For the purpose of defining various diseases included in a category of T-cell lymphoma with a reference to clinical prognosis, Suchi *et al.* have recently proposed a new classification (2).

In order to clarify the characteristics of PTL in Japan, especially emphasizing HTLV-I and histological classification, we have studied the prognostic factors of PTL patients in our hospital.

Materials and Methods

We studied on 30 patients who had been diagnosed and treated at Shikoku Cancer Center Hospital during the period from 1976 to 1989. Histological classification was done according to the Working Formulation (14) and also to the classification by Suchi *et al.* (2).

Determination of phenotype was performed by two methods, *i.e.* surface marker study on viable cells of biopsied specimens and immunohistologic staining on formalin-fixed, paraffin-embedded tissues. Surface markers were examined using monoclonal antibodies related with T-cell and B-cell. We used Leu-2a (CD8), Leu-3a (CD4), Leu-4 (CD3), OKT11 (CD2) for T-cell related monoclonal antibodies, and monoclonal antibodies B1 (CD20), B4 (CD19), J5 (CD10), HLA-DR as well as reactivities to surface immunoglobulins for defining B-cell phenotype (15). Immunological histochemistry was done using monoclonal antibodies of LCA, UCHL-1, MT-1, Mx-PanB, MB-1, Ig-kappa and Ig-lamda on the section specimens from paraffin-embedded tissues (16). The determination of T-cell origin was done with positive findings of T-cell related markers of surface phenotyping and immunological histochemistry, and this was confirmed with negative findings of B-cell related markers as well.

The patients were treated by us with chemotherapy and/or radiotherapy for remission induction followed by maintenance therapy and for reinduction therapy in relapse. Combination chemotherapy with multiple drugs was administered.

Statistical analysis was performed to evaluate the prognostic factors as variables related with survival duration. Survival duration was defined as a period from the beginning of treatment to the death or the censoring date. Univariate analysis was applied on various prognostic factors representing clinical features and laboratory data before therapy; *i.e.*, sex, age, performance status (PS), stage, anti-HTLV-I antibody, leukemic change, bone marrow infiltration (BMI), mass size, primary site, white blood cell count (WBC), lymphocyte count, albumin, alkaline phosphatase, glutamate pyruvate transaminase (GPT), lactate dehydrogenase (LDH), the Working Formulation, and classification by Suchi *et al.* In addition, multivariate analysis was performed on the selected variables which were considered important from the clinical standpoint.

Survival curves were drawn according to the Kaplan-Meier's method. The computer programs of STAX (medical statistical program, Nakayama Shoten) and SAS (statistical analysis system, SAS Institute Inc.) were used for data analysis. To determine the significant levels, logrank test were used for univariate analysis, and Cox's proportional hazard model was applied for multivariate analysis.

Results

Patient characteristics are shown in Table 1. On this table, the patients are listed in the groups according to the result of anti-HTLV-I reactivity. Fortunately, we had approximately equal numbers of the patients with positive and negative anti-HTLV-I antibody. More patients with leukemic change and stage IV disease were seen in the positive group. Sixteen patients out of 30 attained complete remission (CR) by remission induction therapy and 14 patients did not. The median suvival duration was 15 months in CR group and 5 months in non-CR group. In Table 2, patient numbers are shown according to the classifications by Suchi *et al.* and the Working Formulation. The analysis of prognosis due to the histological subtypes was done between the low grade and the high grade in the classification of Suchi *et al.*, and between the intermediate grade and the high grade in the Working Formu-

lation.

The results of univariate analysis by logrank test on each prognostic factor are indicated in the Tables 3 and 4. The significant factors influencing survival duration were stage, anti-HTLV-I antibody, leukemic change, BMI, WBC and LDH. Histological subclassification of both

Table 1 Patient characteristics

	Anti-HTLV-I Antibody		
	Positive (13)	Negative (15)	Unknown (2)
Sex			
Male	5	13	2
Female	8	2	0
Age			
Median	62	59	60, 70
(Range)	(41–80)	(14–80)	
Stage			
I	2	3	0
II, III	3	8	2
IV	8	4	0
Leukemic			
(−)	7	14	2
(+)	6	1	0
Therapy			
Chemotherapy	12	12	2
Radiotheraphy	1	3	0

Table 2 Patient numbers according to the pathological classification

	Anti-HTLV-I Antibody		
	Positive (13)	Negative (15)	Unknown (2)
The Classification by Suchi *et al.*			
Low grade:			
Lymphoepithelioid	1	2	0
Angioimmunoblastic	0	0	0
T-zone	0	1	0
Pleomorphic, small cell	0	0	1
High grade:			
Pleomorphic, medium and large cell	11	5	1
Immunoblastic	1	6	0
Large cell anaplastic	0	1	0
Working Formation			
Intermediate grade			
Diffuse, small cleaved	1	2	1
Diffuse, mixed, small and large	6	5	1
Diffuse, large	0	1	0
High grade			
Large, immunoblastic	6	7	0

Table 3 Univariate analysis on clinical data influencing survival duration

Prognostic factor	(Total cases)	Comparable group	No. of cases	Survival (Median mo.)	Logrank p value
Sex	(30)	Male	20	12.5	0.067
		Female	10	7.5	
Age	(30)	≦60	16	11.5	0.767
		>60	14	13	
PS	(30)	0, 1	25	12	0.240
		2, 3, 4	5	4	
Stage	(30)	I, II, III	18	14	0.006
		IV	12	4	
HTLV-I Antibody	(28)	(−)	15	12	0.022
		(+)	13	7	
Leukemic	(30)	(−)	23	13	0.001
		(+)	7	4	
BMI	(30)	(−)	19	13	0.005
		(+)	11	4	
Mass size	(29)	<5 cm	19	13	0.517
		≧5 cm	10	8	
Primary	(27)	W + GI	4	45.1	0.086
		LN	23	10	

Abbreviations: PS, performance status; BMI, bone marrow infiltration; W, Waldeyer's ring; GI, gastrointestinal tract; LN, lymph node

Table 4 Univariate analysis on laboratory data influencing survival duration

Prognostic factor	(Total cases)	Comparable group	No. of cases	Survival (Median mo.)	Logrank p value
WBC	(29)	3,500–10,000/mm^3	22	12	0.033
		< 3,500 or > 10,000	7	7	
Lymphocyte	(29)	≧ 1,000/mm^3	19	12	0.649
		< 1,000	10	11	
Albumin	(29)	≧ 3.5 g/dl	24	11.5	0.348
		< 3.5	5	12	
ALP	(29)	≦ 100 U/ml	23	12	0.823
		> 100	6	13.5	
GPT	(29)	≦ 50 U/ml	19	11	0.537
		> 50	10	12.5	
LDH	(29)	≦ 250 U/ml	10	17.5	0.000
		> 250	19	7	
W-F	(30)	intermediate	17	11	0.567
		high grade	13	12	
Suchi *et al*	(30)	low grade	6	6.5	0.369
		high grade	24	14	

abbreviations: WBC, white blood cell count; ALP, alkaline phosphatase; GPT, glutamate pyruvate transaminase; LDH, lactate dehydrogenase; W-F, Working Formulation; Suchi *et al.*, classification by Suchi *et al.*

the classification by Suchi *et al.* and the Working Formulation was not significant as a risk factor.

To find the important prognostic factors, 14 variables were selected for multivariate analysis in considering the result of significant levels by univariate analysis and the relationship among the variables in the clinical setting. These variables were sex, age, PS, anti-HTLV-I antibody, BMI, mass size, primary site, WBC, lymphocyte count, albumin, alkaline phosphatase, GPT, LDH and the classification by Suchi *et al.*. The result of chi-square value calculated by Cox's proportional hazard model is shown in Table 5. Significant variables at less than 5 % level were BMI and LDH. Furthermore, more important factors were calculated by the stepwise method on the selected variables. The variables were selected from those with significant level more than 10 % by a regression coefficient. LDH (estimated value 1.87 ± 0.66, chi-square value 7.97) and BMI (estimated value 1.13 ± 0.46, chi-square value 6.10) were finally chosen as the most important variables. This result suggests that the patients with high LDH level or positive BMI have short survival duration compared with those with nomal LDH or negative BMI.

Survival curves of the patients according to LDH factor or BMI status are illustrated in Figs. 1 and 2. The variable of anti-HTLV-I antibody was not significant according to the result of

Table 5 Multivariate analysis by Cox's proportional hazard model

Variable	Estimated value ± SE	χ_0^2 value	p value
Sex	1.05 ± 1.13	0.86	0.355
Age	2.11 ± 1.32	2.58	0.108
PS	−1.44 ± 2.14	0.46	0.500
HTLV-I	−1.77 ± 1.44	1.50	0.221
BMI	4.64 ± 1.74	7.08	0.008
Mass size	1.48 ± 0.83	3.21	0.073
Primary	0.20 ± 0.80	0.07	0.799
WBC	−0.93 ± 1.16	0.65	0.421
Lymphocyte	0.03 ± 0.99	0.00	0.978
Albumin	−1.53 ± 1.28	1.42	0.233
ALP	1.19 ± 1.49	0.64	0.424
GPT	−0.46 ± 0.86	0.27	0.603
LDH	3.82 ± 1.37	7.82	0.005
Suchi	−1.66 ± 1.36	1.48	0.224

Abbreviations are refered to those in Tables 3 and 4. SE; standard error

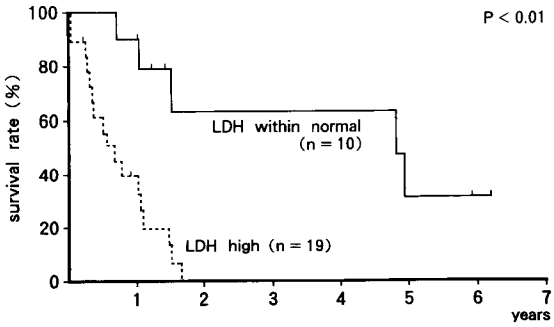

Fig. 1 Survival curves of patients with LDH ≦ 250 U/ml and those with LDH > 250 by Kaplan-Meier's method.

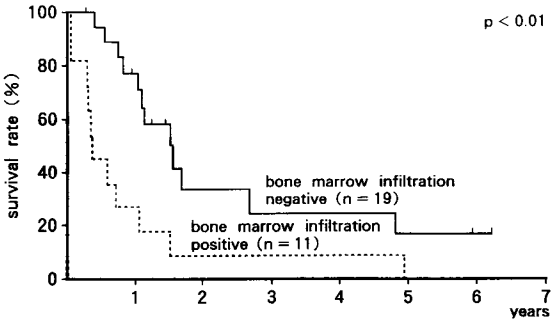

Fig. 2 Survival curves of patients with negative bone marrow infiltration and those with positive bone marroe infiltration.

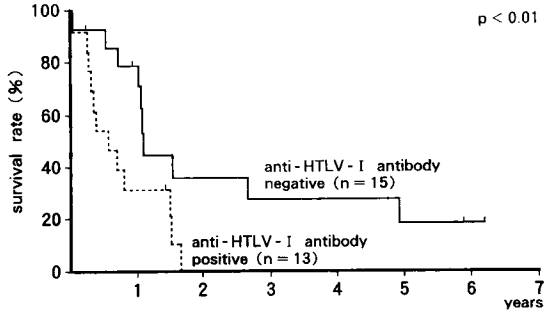

Fig. 3 Survival curves of patients with negative anti-HTLV-I antibody and those with positive anti-HTLV-I antibody.

multivariate analysis, although the patients with positive antibody had poor prognosis (Fig.3). Survival curves according to the histological subclassifications are also shown in Fig. 4.

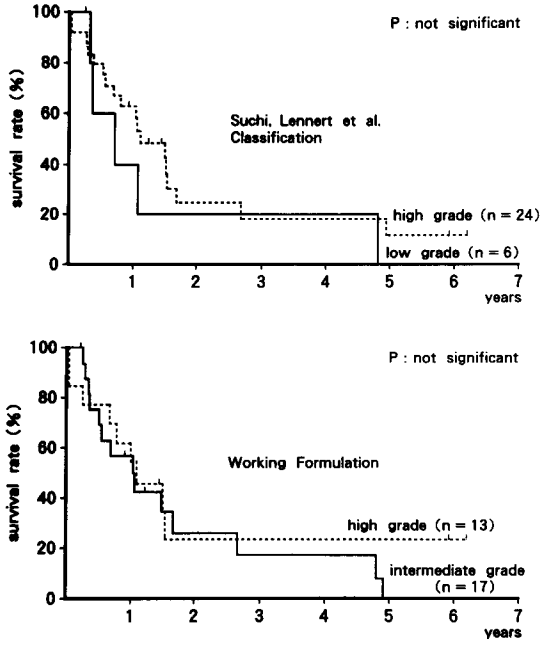

Fig. 4 Survival curves of patients according to the histological subclassification by Suchi *et al.* and that of the Working Formulation.

Discussion

Our data revealed that the important factors influencing survival were stage, leukemic change, BMI, anti-HTLV-I antibody, WBC, and LDH. The first three factors, *i.e.* stage, leukemic change, BMI, are apparently considered to be related each other by clinical standpoint. This was confirmed by statistic data regarding to the correlation coefficient. BMI was closely associated with leukemic change and stage IV status (correlation coefficient: BMI versus stage IV; 0.93, BMI versus leukemic change; 0.71). High LDH level means rapid proliferation of tumor cells, and this phenomenon is commonly seen in various malignancies. In our previous study of 102 NHL patients including both T-cell lymphomas and B-cell lymphomas, LDH was the main prognostic factor (17).

PTL associated with HTLV-I is considered as an equivalent of the lymphoma type of adult T-cell leukemia (ATL). The acute type of ATL

patients usually has very poor prognosis and some of them are complicated with hypercalcemia and severe infection resulting in rapid fatal outcome (18). In our series the prognosis of PTL patients with positive anti-HTLV-I antibody was worse compared 50 those with vegative anti-HTLV-I antibody.

Previously we reported that T-cell lymphomas had poorer prognosis compared with B-cell lymphomas (17). It is hard to explain the reasons why T-cell lymphomas have poorer prognosis. There are so many risk factors which are not categorized with variables such as immunological status that we can not investigate further by statistical analysis. Although the real cause is unknown, the intervention of HTLV-I virus induces lymphoma aggressive in disease progression and refractory to conventional chemotherapy. The presence of anti-HTLV-I antibody is considered to be one of the important factors.

There have been several reports concerning PTL, which mention the heterogeneity from histological aspects (3-9,12). Some reports concluded that NHL of T-cell phenotype had poorer prognosis compared with that of B-cell phenotype (19, 20), and on the other hand some studies reported that there was no difference between the prognosis of the two types (21, 22). In Japan, only one report regarding prognostic factors has been published (11). If we exclude PTL patients with anti-HTLV-I antibody, few patients with T-lymphoma would be reported in the statistics. Therefore, a bias concerning the number of PTL patients in each hospital is conceivable. The cooperative study of chemotherapy for advanced T-cell lymphomas was conducted previously in Japan. This result showed that PS and LDH levels were the most important prognotic factors for response rate and survival duration (11).

For clinicians the relationship between histological subtype and prognosis is an attractive question to be resolved. We used the Working Formulation and the classification by Suchi *et al.* for this analysis. There is a clear relationship between the prognosis and the classification by Suchi *et al.* according to Nakamura *et al.* (13). That our results differed from theirs was probably due to the difference of patients' background. The intensive treatment in our hospital might contribute to the prolongation of survival duration. The classification by Suchi *et al.* is acceptable for its reasonable explanation of histological subtyping. The clinical relevance should be investigated further.

Quality of therapy cannot be ignored when discussing clinical outcome. However, application of a standardized treatment with chemotherapy and radiotherapy was not possible on the PTL patients, because clinical problems of each PTL patient were variable through the entire clinical course, especially during the phase of relapse when several different treatments were usually applied.

Although we used multivariate analysis for additional data in this report, our results may have limitations for general application because of the small number of studied patients. When the number of patients evaluated is increased, more important factors by multivariate analysis can be elicited.

In conclusion, we found that stage, leukemic change, BMI, anti-HTLV-I antibody, WBC and LDH were the most useful prognostic factors influencing survival duration of PTL patients by statistical analysis using logrank test. In addition, LDH and BMI were found to be the important factors by multivariate analysis. The study of prognostic factors is useful for us to understand the clinical features of this kind of rare malignant disease.

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