PERGAMON

European Journal of Cancer 38 (2002) 75–81

European Journal of Cancer

www.ejconline.com

Clinical features of peripheral T-cell lymphomas in 78 patients diagnosed according to the Revised European-American lymphoma (REAL) classification

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Received 29 May 2001; received in revised form 16 August 2001; accepted 27 September 2001

Abstract

The aim of this study was to analyse the clinical characteristics and prognostic factors of peripheral T-cell lymphomas (PTCLs) according to the Revised European-American Lymphoma (REAL) classification. From 1994 to 1999, 78 patients were diagnosed with PTCLs, excluding cutaneous T-cell lymphomas and T-cell chronic lymphocytic leukaemia. The distribution of the histological subgroups were: PTCL unspecified (PTCL-U), 40%; angiocentric lymphoma, 32%; anaplastic large cell lymphoma (ALCL), 17%; angioimmunoblastic T-cell lymphoma (AILD), 6%; intestinal T-cell lymphoma, 3%; and panniculitic T-cell lymphoma, 3%. Patients with angiocentric lymphoma presented with favourable prognostic factors, whereas those with AILD presented with unfavourable prognostic factors. Most patients were treated with doxorubicin-containing combination chemotherapy (with or without radiation therapy). The overall complete remission rate was 61.2% (95% Confidence Interval (CI): 48.5–72.8%) and the 5-year probability of failure-free survival was 33.5%. Median survival of all patients was 45 months (range 0–64+ months) and the 5-year probability of survival was 36.2%. In the multivariate analysis, only the International Prognosis Index (IPI) was an independent prognostic factor for overall survival ($P<0.01$). Taken together, the proportion of angiocentric lymphoma in this study was higher than that in the studies of Western countries. PTCL responds poorly to treatment with low survival rates and the IPI is a useful prognostic factor for PTCL.

Keywords: Peripheral T-cell lymphoma; International Prognosis Index; CHOP

1. Introduction

Peripheral T-cell lymphomas (PTCLs) are neoplasia from post-thymic T-cells at different stages of differentiation and are a heterogeneous group of malignancies which present with different morphological patterns, phenotypes and clinical presentations [1–8]. Recent reports suggest that Epstein–Barr virus (EBV) may play an important role in the lymphomagenesis of PTCLs [9]. These tumours have a striking epidemiological distribution with a lower incidence in Western countries than in Asia [2–8,13], are common in Japan and Taiwan and are frequently associated with human T-lymphotropic virus (HTLV-1) [8,21]. In Korea, PTCLs including T- or natural killer (NK)-cell lymphomas constitute approximately 25 to 35% of all non-Hodgkin's lymphomas [2,18,19].

Cytological features alone are not sufficient to distinguish between PTCL disease entities. Clinical presentation is very important in the classification of PTCLs [4,11]. Although a few studies about the clinical features of PTCLs according to the Revised European-American Lymphoma (REAL) classification have been reported recently [1], the clinical features of each entity are not fully understood because of their rarity and broad cytomorphological spectrum [1–7,11]. There is substantial

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0959-8049/02/$ - see front matter
PII: S0959-8049(01)00344-6

disagreement in the literature concerning the prognostic parameters to be applied to the study of PTCLs [3,6,14]. Recent studies suggest that the T-cell phenotype is an independent significant prognostic factor, with PTCLs having one of the lowest overall survival and failure-free survival rates [3,8,10,22].

Following publication of the REAL classification [1], we retrospectively analysed the clinical features of PTCL in 78 patients diagnosed according to the REAL classification to assess the clinical and pathological relevance.

2. Patients and methods

2.1. Patient selection

Between October 1994 and March 1999, 78 patients with PTCLs were analysed. In all cases, Haematoxylin and Eosin (H&E) slides and immunostains for CD20 and CD3 (and CD30, CD56, etc., if needed), were performed and the diagnosis for subtype was made according to the REAL classification. For staging, bone marrow biopsy was immunostained with anti-CD3 and anti-CD20 antibodies. Mycosis fungoides, T-cell chronic lymphocytic leukaemia/prolymphocytic leukaemia, large granular lymphocytic leukaemia, and adult T-cell lymphoma/leukaemia were excluded.

Patients were staged according to the Ann Arbor staging system, which included a thorough history taking, physical examination, routine blood and urine tests, simple chest X-rays, computer tomography (CT) scans of the abdomen and pelvis, and bilateral bone marrow aspiration and biopsy. Patients with localised (stage I/II), non-bulky disease received four cycles of cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP) followed by involved field radiation. Patients with stage III/IV disease received six cycles of (CHOP) [12]. Clinical tumour responses were assessed, using standard criteria, by a follow-up physical examination and Computed Tomography (CT) scans [15].

2.2. Statistical analyses

Remission rates were compared with Fisher's Exact test. The Kaplan–Meier product-limit method was used to estimate the failure-free survival and overall survival [16]. Failure-free survival was calculated from the date treatment began to the date when disease progression was recognised or the date of the last follow-up visit. Overall survival duration was measured from the date of diagnosis to the date of death or the last follow-up visit. Survival rates were compared for statistical differences by using the log-rank analysis. Prognostic factors including histological subtype, age, gender, performance status, the presence of B symptoms, serum lactate dehydrogenase (LDH) level, number of extranodal involvements, disease stage, bone marrow involvement, liver involvement, presence of bulky disease and International Prognosis Index (IPI) were analysed. Significant variables in the univariate analysis, except for variables included in IPI, were considered as variables for the multivariate analysis for survival. The latter was performed by Cox's proportional hazard regression model [17,18].

Table 1
Pretreatment characteristics of 78 patients

	Overall $n=78$	PTCL-U $n=31$ (40%)	Angiocentric $n=25$ (32%)	ALCL $n=13$ (17%)	AILD $n=5$ (6%)	Intestinal $n=2$ (23%)	Panniculitic $n=2$ (23%)
Age (years) median (range)	44 (15—77)	54 (18–77)	40 (15–66)	30 (16–71)	52 (36–77)	45 (42–57)	45 (41–58)
>60	18 (23%)	11 (35%)	3 (12%)	3 (23%)	1 (20%)	0	0
Male sex	46 (59%)	20 (65%)	14 (56%)	8 (62%)	2 (40%)	1 (50%)	1 (50%)
B symptoms	43 (55%)	16 (52%)	11 (44%)	8 (62%)	5 (100%)	1 (50%)	2 (100%)
Bone marrow	17 (22%)	10 (32%)	1 (4%)	3 (23%)	3 (60%)	0	0
Liver	17 (22%)	10 (32%)	2 (12%)	1 (8%)	3 (60%)	0	0
Extanodal $\geqslant 2$	23 (29%)	11 (35%)	6 (24%)	4 (31%)	2 (40%)	0	0
ECOG $\geqslant 2$	19 (24%)	10 (32%)	1 (4%)	4 (31%)	3 (60%)	1 (50%)	0
LDH > normal	31 (40%)	16 (52%)	5 (20%)	7 (54%)	3 (60%)	0	0
Ann Arbor stage							
I or II	34 (44%)	9 (29%)	18 (72%)	6 (46%)	0	0	1 (50%)
III or IV	44 (56%)	22 (71%)	7 (28%)	7 (54%)	5 (100%)	2 (100%)	1 (50%)
IPI							
Low	40 (51%)	10 (32%)	19 (76%)	7 (54%)	1 (20%)	1 (50%)	2 (100%)
Low-intermediate	15 (19%)	9 (29%)	4 (16%)	1 (78%)	0	1 (50%)	0
High-intermediate	11 (14%)	4 (13%)	2 (8%)	2 (15%)	3 (60%)	0	0
High	12 (15%)	8 (26%)	0	3 (23%)	1 (20%)	0	0

ECOG, Eastern Co-operative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognosis Index; PTCL-U, peripheral T-cell lymphoma—unspecified; ALCL, anaplastic large cell lymphoma; AILD, angioimmunoblastic T-cell lymphoma; Panniculitic, Subcutaneous panniculitic T-cell lymphoma.

3. Results

3.1. Patient characteristics

The clinical characteristics of the 78 patients are given in Table 1. The median age was 44 years with a range of 15–77 years. The study involved 46 males (59%) and 32 females (41%). B symptoms were noted in 43 patients (55%).

The most common histopathological type was PTCL unspecified (PTCL-U), followed by angiocentric lymphoma, anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AILD), intestinal T-cell lymphoma, and subcutaneous panniculitic T-cell lymphoma, in decreasing order of frequency (Table 1).

The patients with angiocentric lymphoma were presented with favourable prognostic features: good performance status (ECOG 0, 1, 96% versus 66% for the other subtypes; $P=0.004$), less frequent bone marrow involvement (4% versus 30%; $P=0.009$), normal serum LDH (80% versus 60%; $P=0.014$), early stage (I or II, 72% versus 30%; $P=0.001$), and low or low-intermediate risk by IPI (92% versus 60%; $P=0.004$).

However, the patients with AILD presented with poor prognostic features; more frequent bone marrow and liver involvement (60% versus 19%; $P=0.03$), more frequent B symptoms (100% versus 52%; $P=0.037$), advanced stage (III or VI, 100% versus 53%; $P=0.04$), and high or high-intermediate risk by IPI (80% versus 26%; $P=0.018$).

The most commonly involved extranodal sites were bone marrow, liver, nasal/paranasal sinus (PNS), and skin (Table 2). Angiocentric lymphomas presented with nasal/PNS in 68% of cases, while intestinal T-cell lymphoma showed no extranodal involvement other than intestine.

3.2. Radiotherapy in stage III–IV patients

Two patients received radiotherapy to residual mass after chemotherapy. In one patient, radiotherapy was given to residual bulky spleen after six cycles of CHOP. However, the disease recurred. In the other patient, RT was given to the residual mass in left arm (initally bulky site) after six cycles of CHOP resulting in a complete response.

3.3. Second-line treatment

Many kinds of different salvage chemotherapy regimens were given to the patients and we could not find any firm conclusions according to the second-line therapy.

Autologous stem cell transplantation (A-SCT) with BEAM CBCNU, etoposide, Ara-C, and Melphalan conditioning was tried in three out of 12 relapsed patients. In 2 patients, disease recurred after 4 and 14 months, respectively, after A-SCT. One patient experienced quadriplegia (cause unknown) after A-SCT. He was then lost to follow-up.

3.4. Treatment and response to the therapy

67 patients (86%) received CHOP therapy, or CHOP followed by radiation therapy as their initial treatment. Forty-one complete responses (61.2%, 95% Confidence Interval (CI): 48.5–72.8%) were observed from 67 patients. Other patients received only palliative chemotherapy due to either poor general condition or the advanced age of the patient. In the univariate analysis, the following parameters predicted a poor response to therapy; presence of B symptoms ($P<0.01$), bone marrow involvement ($P<0.01$), liver involvement ($P<0.01$), poor performance status ($P<0.01$), high LDH ($P<0.01$), advanced stage ($P=0.01$), and high-intermediate/

Table 2
Extranodal involvement in 78 patients according to the histological subtypes

	Overall $n=78$ (%)	PTCL $n=31$ (%)	Angiocentric $n=25$ (%)	ALCL $n=13$ (%)	AILD $n=5$ (%)	Intestinal $n=2$ (%)	Panniculitic $n=2$ (%)
Bone marrow	21.8	32.3	4.0	23.1	60	0	0
Liver	21.8	32.3	12.0	7.7	60	0	0
Nasal/PNS	21.8	0	68.0	0	0	0	0
Pharynx	12.8	3.2	32.0	7.7	0	0	0
Skin	16.7	16.1	4.0	38.5	20	0	50
Gastrointestinal	6.4	3.2	4.0	7.7	0	100	0
Subcutaneous	6.4	9.7	0	0	0	0	100
Effusion	6.4	12.9	0	7.7	0	0	0
Lung	3.8	6.5	0	7.7	0	0	0
Kidney	2.6	6.5	0	0	0	0	0
Bone	2.6	0	0	15.4	0	0	0
Testis	1.3	3.2	0	0	0	0	0
Urethra	1.3	0	0	7.7	0	0	0
Adrenal	1.3	3.2	0	0	0	0	0

PNS, paranasal sinus; ALCL, anaplastic large cell lymphoma; AILD, angioimmunoblastic T-cell lymphoma.

high-risk group by IPI ($P<0.01$) (Table 3). No significant difference was found according to the histological subtype. In the multivariate analysis, only the presence of B symptoms and high-intermediate/high-risk group of the IPI were significant in the risk of a lower complete remission (CR) rate (Table 4). Recurrance of disease occurred in 12 of 41 CR patients. The median failure-free survival was 16 months (range 0–64+ months), and the estimated 5-year failure-free survival rate was 33.5% (95% CI: 20–47.0%).

3.5. Survival and prognostic factors

The median overall survival of 78 patients in this study was 45 months (range 0–64+ months), and the estimated 5-year overall survival rate was 36.2% (95% CI: 16.2–56.2%) with median of 33 months follow-up (Fig. 1).

In the univariate analysis, the presence of B symptoms, bone marrow involvement, liver involvement, two or more sites of extranodal involvement, poor performance status (ECOG 2-4), extranodal involvement (≥ 2), elevated LDH

Table 3
Univariate prognostic factor analysis for complete response, failure-free survival and overall survival of 78 patients

	Complete response		Failure-free survival		Overall survival	
	%	*P* value	Months	*P* value	Months	P value
Age (years)						
60	56.7	0.43	29 (0–64+)	0.01	51 (0–64+)	0.14
>60	44.4		4 (0–42)		9 (0–45)	
Gender						
Male	50.0	0.49	8 (0–56+)	0.35	27 (0–56+)	0.46
Female	59.4		25 (0–64+)		NR (0–64+)	
B symptoms						
Absent	82.9	<0.01	42 (2–64+)	<0.01	51 (0–64+)	<0.01
Present	30.2		5 (0–56+)		9 (0–60+)	
BM involvement						
Absent	62.3	<0.01	32 (0–64+)	<0.01	51 (0-64+)	<0.01
Present	23.5		5 (0–42+)		5 (0–42+)	
Liver involvement						
Absent	62.3	<0.01	25 (2–64+)	<0.01	51 (2–64+)	<0.01
Present	23.5		2 (0–42+)		2 (0–60+)	
Extranodal involvement						
⩽1	70.9	<0.01	38 (0–64+)	<0.01	51 (0–64+)	<0.01
⩾2	13.0		4 (0–49+)		5 (0–30+)	
Performance status						
ECOG 0,1	64.4	<0.01	29 (1–64+)	<0.01	51 (2–64+)	<0.01
ECOG 2–4	21.1		4 (0–42+)		4 (0–42+)	
LDH						
Normal	68.1	<0.01	29 (0–60+)	0.02	51 (0–64+)	<0.01
>Normal	32.2		4 (0–56+)		6 (0–56+)	
Stage						
I or II	70.6	0.01	NR (2–64+)	<0.01	NR (2–64+)	<0.01
III or IV	40.9		6 (0–42+)		14 (0–60+)	
Pathology						
PTCL	51.6	0.82	12 (0–64+)	0.69	18 (0–64+)	0.32
Others	55.3		12 (0–56+)		51 (0–56)	
Angiocentric	52.0	1.00	29 (2–49+)	0.48	51 (2–51+)	0.41
Others	54.7		12 (0–64+)		26 (0–64+)	
ALCL	69.2	0.36	25 (0–56+)	0.66	NR (0–56+)	0.26
Others	50.8		12 (0–64+)		27 (0–64+)	
AILD	40.0	0.66	4 (0–42+)	0.27	4 (0–42+)	0.04
Others	54.8		12 (0–64+)		45 (0–64+)	
IPI						
Low	77.5	<0.01	NR (2–64+)	<0.01	NR (3–64+)	<0.01
Low-Intermediate	53.3		12 (2–42+)		36 (2–46+)	
High- Intermediate	9.1		3 (0–17+)		5 (0–17+)	
High	17.7		2 (0–42+)		2 (0–42+)	

NR, not reached; BM, bone marrow; AILD, angioimmunoblastic T-cell lymphoma; IPI, international prognosis index; Low, low risk group; Low intermediate, low intermediate risk group; high intermediate; high intermediate risk group; High, high risk group; ECOG, European Cooperative Oncology Group; LDH, lactate dehydrogenase; PTCL, peripheral T-cell lymphoma; ALCL, anaplastic large cell lymphoma.

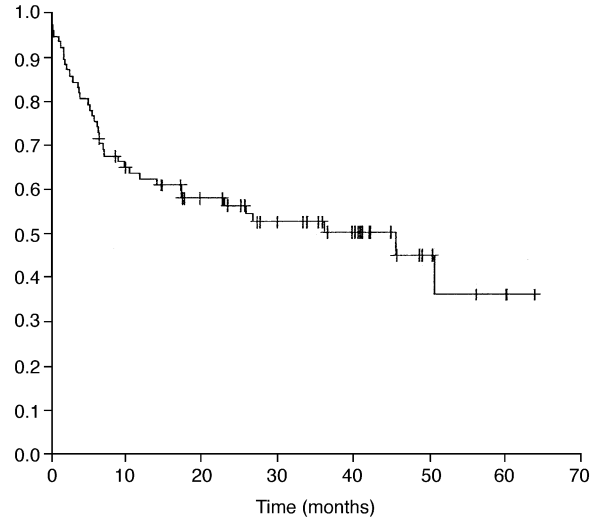

Fig. 1. Overall survival curve of 78 patients.

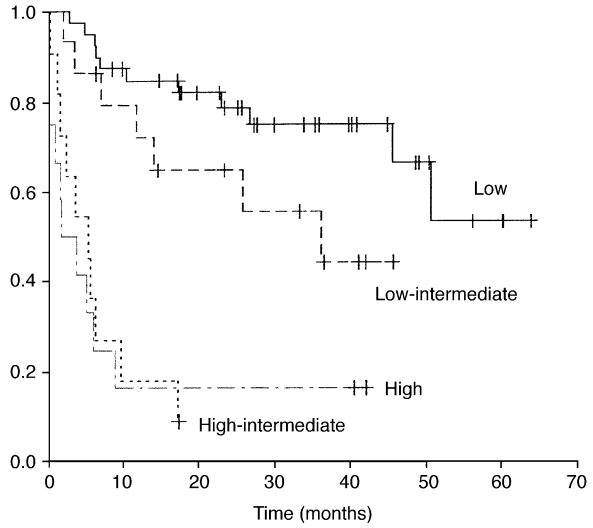

Fig. 2. Overall survival curve according to risk group by International Prognosis Index (IPI).

Table 4
Independent prognostic factor analysis for complete response, failure-free survival and overall survival of 78 patients

	Complete response		Failure-free survival		Overall survival	
	P value	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)
B symptoms	<0.01	7.50 (2.05–27.4)	0.03	2.20 (1.09–4.43)	0.07	2.50 (0.93–6.80)
BM involvement	0.82	1.21 (0.23–6.34)	0.64	1.21 (0.53–2.77)	0.87	1.08 (0.44–2.63)
Liver involvement	0.47	1.97 (0.31–12.57)	0.86	1.07 (0.48–2.38)	0.59	1.25 (0.55–2.82)
IPI						
Low	0.03	1	0.02	1	<0.01	1
L/I		2.90 (0.66–12.79)		1.59 (071–3.55)		1.89 (0.70–5.06)
H/I		22.23 (1.94–254-59)		4.45 (1.65–11.94)		6.66 (2.17–20.44)
High		13.88 (1.56–123.35)		4.60 (1.55–13.67)		6.75 (2.03–22.40)
Pathology						
AILD					0.59	1.03 (0.21–2.42)
Others						1

RR, relative risk; CI, confidential interval; BM, bone marrow; IPI, international prognosis index; Low, low risk group; L/I, low intermediate risk group; H/I, high-intermediate risk group; High, high-risk group AILD, angioimmunoblastic T-cell lymphoma.

(above normal), advanced disease stage (III or IV), AILD-type histology, and high-intermediate/high risk group by IPI were related to poor survival (Table 3). In the multivariate analysis, only high-intermediate/high risk by IPI was related to poor overall survival ($P < 0.01$, RR 6.7) (Table 4, Fig. 2). The presence of B symptoms was related to poor response to chemotherapy ($P < 0.01$, RR 7.5), poor failure-free survival ($P = 0.03$, RR 2.2), and marginal significance to overall survival ($P = 0.07$, RR 2.5).

Comparing the survival of low-risk patients, angiocentric lymphoma had a tendency towards poor prognosis (Fig. 3, $P = 0.07$).

4. Discussion

The histological categorisation of lymphoma has been a source of frustration for many years. Using morphology, immunology, and genetic techniques, the REAL classification was proposed by the International Lymphoma Study Group [1]. However, the classification of PTCLs is still difficult and includes entities which are heterogenous in both biological nature and clinical features [3,4,6,7,11].

PTCLs have a striking epidemiological distribution with a lower incidence in Western countries than in Asia [2–8,13], and the incidence of each histological subtype in Asia differs when compared with those of Western reports [3,6]. In this study, angiocentric lymphoma is the second most common subtype (32%), compared with less than 10% in Western reports [3,6]. The incidence is somewhat different from that of Japan. Human T-lymphotropic virus (HTLV-1)-associated PTCLs are common in Japan, especially in Kyushu [8,21]. In Korea, HTLV-1-associated PTCLs are very rare [2,5,19]. During the period of this study, no case of HTLV-1-associated lymphoma was identified.

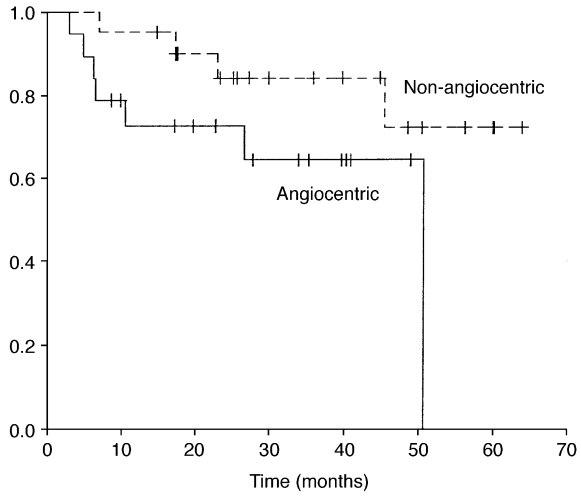

Fig. 3. Survival curve of low-risk patients.

The outcome of PTCLs is unfavourable compared with that of B-cell lymphoma [3,6,8,10,14], with some controversy about the prognostic factors [3,6,8,14]. Ansell and colleagues reported only the IPI as significant in the multivariate analysis [14]. Lopez-Guillermo and colleagues reported the presence of B symptoms, histological subgroup (ALCL versus other PTCL), and the IPI (low versus high) maintained independent predictive value in the multivariate analysis [3]. In this study, only the IPI maintained independent predictive value in the multivariate analysis. In previous reports, ALCL has a good prognosis compared with other subtypes [3,6,8]. However, in this study, there was no difference between the survival of ALCL and those of others. To clarify whether ALCL in Korean patients has a different natural history, we would need to study greater numbers of these patients.

The clinical presentation of angiocentric lymphoma and AILD were different from those of the other subtypes. Patients with angiocentric lymphoma presented with good prognostic features, whilst those with AILD presented with poor prognostic features.

Angiocentric lymphoma is a distinct clinicopathological entity. The most common clinical presentation is with a destructive nasal or midline facial tumour [4,20]. The optimal treatment is not yet defined [23]. In this study, most (72%) presented with localised, stage I/II disease. Over 90% of them had low/low-intermediate risk by IPI. Comparing the survival of low-risk patients, angiocentric lymphoma had a tendency towards poor prognosis ($P = 0.07$).

Most patients with AILD have generalised lymphadenopathy and prominent systemic symptoms with fever, weight loss, and skin rash [4], with most of them having stage IV disease. The clinical course appears to correlate with extent of systemic symptoms [4]. In our study, 5 AILD patients were included. All of them had stage IV disease, and systemic symptoms. 4 of 5 had high-intermediate/high risk by IPI. This may explain why the survival of AILD is significantly poorer than those of the other subtypes in the univariate analysis although this became insignificant in the multivariate analysis ($P = 0.04$).

Complete remission was observed in approximately 50% of the patients with PTCLs and approximately 70% in ALCL patients, after chemotherapy [3,6]. The complete response rate in this study was 61% and this is comparable to other studies. Ascani reported the risk of a lower complete response rate was related to the histological group (non-ALCL) [6]. However, Lopea-Guillermo and colleagues reported that there was no significant difference according to the histological subtype [3]. In this study, the presence of B symptoms and the IPI (low versus high) maintained the independent predictive value for the complete response rate in the multivariate analysis.

The optimal therapy for PTCLs remains to be defined. Some previous studies have shown better results using combined chemotherapy regimens compared with regimens with low dose intensity [24–26]. Randomised trials would be needed to confirm the superiority of an intensive chemotherapeutic regimen to standard CHOP therapy.

In conclusion, AILD and angiocentric lymphomas had a different clinical presentation from the other histological subtypes. The proportion of angiocentric lymphoma in PTCL of this study was higher than that in the studies of Western countries. PTCLs have a poor prognosis, with the IPI being the most important variable predicting survival.

References

1. Harris NL, Jaffe ES, Stein H, *et al*. A revised European-American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. *Blood* 1994, **84**, 1361–1392.
2. Ko Y-H, Kim C-W, Park C-S, *et al*. and the Hematolymphoreticular Study Group of the Korean Society of Pathologists. REAL classification of malignant lymphomas in the Republic of Korea. *Cancer* 1998, **83**, 806–812.
3. López-Guillermo A, Cid J, Salar A, *et al*. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the REAL classification. *Ann Oncol* 1998, **9**, 849–855.
4. Jaffe ES, Krenacs L, Raffeld M. Classification of T-cell and NK-cell neoplasms based on the REAL classification. *Ann Oncol* 1997, **8**(Suppl. 2), 17–24.
5. Lee SS, Cho KJ, Kim CW, Kang YK. Clinicopathological analysis of 501 non-Hodgkin's lymphomas in Korea according to the revised European-American classification of lymphoid neoplasms. *Histopathology* 1999, **35**, 345–354.
6. Ascani S, Zinani PL, Gherlinzoni F, *et al*. Peripheral T-cell lymphomas. Clinico-pathologic study of 168 cases diagnosed according to the REAL classification. *Ann Oncol* 1997, **8**, 583–592.
7. Campo E, Gaulard P, Zucca E, *et al*. Report of the European Task Force on Lymphomas: workshop on peripheral T-cell lymphomas. *Ann Oncol* 1998, **9**, 835–843.

8. Gisselbrecht C, Gaulard P, Lepage E, *et al*. Prognostic significance of T-Cell phenotype in aggressive non-Hodgkin's lymphomas. *Blood* 1998, **92**, 76–82.
9. Huh J, Cho K, Heo DS, Kim JE, Kim CW. Detection of Epstein–Barr virus in Korean peripheral T-cell lymphoma. *Am J Hematol* 1999, **60**, 205–214.
10. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol* 1998, **16**, 2780–2795.
11. Chan JK. Peripheral T-cell and NK-cell neoplasms: an integrated approach to diagnosis. *Mod Pathol* 1999, **12**, 177–199.
12. Miller TP, Dahlberg S, Cassady R, *et al*. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med* 1998, **339**, 21–26.
13. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol* 1998, **9**, 717–720.
14. Ansell SM, Habermann TM, Kurtin P, *et al*. Predictive capacity of the International Prognostic Factor Index in patients with peripheral T-cell lymphoma. *J Clin Oncol* 1997, **15**, 296–2301.
15. Hoogstraten B. Reporting treatment results in solid tumours. In Byse ME, Staquet MJ, Sylvester RJ, eds. *Cancer Clinical Trials, Method and Practice*. Oxford, Oxford University Press, 1984, 139–152.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
17. Cox DR. *Analysis of Binary Data*. London, Methuen, 1970.
18. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc B* 1972, **34**, 457–481.
19. Kang Y-K, Kim B-S, Kim TW, *et al*. Clinicopathologic characteristics of Korean Non-Hodgkin's lymphomas based on REAL classification. *J Korean Cancer Assoc* 1999, **31**, 641–652.
20. Jaffe ES, Krenacs L, Kumar S, Kingma DW, Raffeld M. Extranodal peripheral T-cell and NK-cell neoplasms. *Am J Clin Pathol* 1999, **11**(Suppl. 1), S46–s55.
21. Lymphoma Study Group of Japanese Pathologists. The World Health Organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. *Pathol Int* 2000, **50**, 696–702.
22. Melnyk A, Rodriguez A, Pugh WC, Cabannillas F. Evaluation of the Revised European-American Lymphoma classification confirms the clinical relevance of immunophenotype in 560 cases of aggressive non-Hodgkin's lymphoma. *Blood* 1997, **89**, 4514–4520.
23. Kim WS, Song S-Y, Ahn YC, *et al*. CHOP followed by involved field radiation: is it optimal for localized nasal natural killer/T-cell lymphoma? *Ann Oncol* 2001, **12**, 349–352.
24. Karakas T, Bergmann L, Stutte H, *et al*. Peripheral T-cell lymphomas respond well to vincristine, adriamycin, cyclophosphamide, prednisone and etoposide (VACPE) and have a similar outcome as high-grade B-cell lymphomas. *Leuk Lymphoma* 1996, **24**, 121–129.
25. Liang R, Todd D, Chan TK, *et al*. Intensive chemotherapy for peripheral T-cell lymphomas. *Hematol Oncol* 1992, **10**, 155–161.
26. Coiffier B, Berger F, Bryon PA, Magaud JP. T-cell lymphomas: immunologic, histologic, clinical, and therapeutic analysis of 63 cases. *J Clin Oncol* 1988, **6**, 1584–1589.