Clinical Relevance of Immunophenotype in a Retrospective Comparative Study of 297 Peripheral T-Cell Lymphomas, Unspecified, and 496 Diffuse Large B-Cell Lymphomas

Experience of the Intergruppo Italiano Linfomi

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BACKGROUND. To assess the impact of T-cell/B-cell phenotype on clinical outcome, the authors retrospectively compared patients who had peripheral T-cell lymphoma, unspecified (PTCL-U), with patients who had diffuse large B-cell lymphoma (DLBCL).

METHODS. Two hundred ninety-seven cases of PTCL-U and 496 cases of DLBCL that had been transferred from the files of the Intergruppo Italiano Linfomi or the Gruppo Italiano Linfomi were integrated into a unique working file and reviewed by the authors.

RESULTS. The PTCL-U group and the DLBCL group had significantly different distribution patterns with respect to patient age, gender, disease stage, performance status (PS), the presence or absence of systemic "B" symptoms, the presence or absence of bulky disease, lactic acid dehydrogenase (LDH) levels, and number of extranodal sites (ENS). A significantly greater number of patients in the DLBCL group experienced complete remission ($P < 0.0001$). Multinomial logistic regression analysis confirmed that immunophenotype, PS, LDH concentration, and number of ENS were independent predictors of response. At a median follow-

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up duration of 43 months, there was no observable difference in disease-free survival (DFS) between patients with DLBCL and patients with PTCL-U; however, multivariate analysis did reveal that poorer PS and bone marrow involvement were significantly associated with shorter DFS. Furthermore, although the overall survival (OS) curves associated with the T-cell and B-cell immunophenotypes were significantly different from each other at a median follow-up duration of 37 months ($P = 0.0012$), Cox multivariate analysis excluded immunophenotype from the final OS model.

CONCLUSIONS. The findings made in the current study indicate that the natural history of PTCL-U may differ from that of DLBCL. Patients with PTCL-U tended to have less favorable clinical outcomes, although the observed difference in outcome was only partially attributable to immunophenotype, which was independently associated with response, but not with survival. Differences in prognostic factor distributions between patients with PTCL-U and patients with DLBCL may account for some portion of the expected phenotype-associated risk. ***Cancer* 2004; 101:1601–8.** © *2004 American Cancer Society.*

KEYWORDS: peripheral T-cell lymphoma, unspecified; diffuse large B-cell lymphoma; immunophenotype; prognosis; clinical outcome.

T/natural killer (T/NK)-cell lymphomas are relatively rare, accounting for only approximately 5–15% of all non-Hodgkin lymphomas encountered in the Western world.[1–4] Analysis of differentiation marker expression has revealed that the majority of T/NK-cell lymphomas arise due to the malignant transformation of postthymic T cells and mature NK cells[5,6]; consequently, such malignancies are known generically as *peripheral T-cell lymphomas* (*PTCLs*). In the updated Kiel classification system,[7] PTCLs are categorized into various subtypes and are also stratified into two major prognostic groups (*high-grade* and *low-grade*) on the basis of cell size–related criteria. Although the Kiel classification system is based on clinicopathologic parameters, the prognostic significance of cell size has been questioned due to concerns regarding reproducibility. Because of these concerns, cell size is no longer considered a prognostic tool by the World Health Organization (WHO) International Classification Project.[8]

From a clinical point of view, PTCL is considered an aggressive malignancy, and in agreement with this characterization, many investigators have found the T-cell phenotype to be an independent adverse prognostic factor[2,3,9]; others, however, have been unable to confirm this finding.[10–13] PTCL is no longer included in the WHO classification system, and the significant clinical heterogeneity of malignancies that fall under the umbrella of PTCL has been emphasized. In fact, a number of well defined clinicopathologic entities, such as anaplastic large cell T-cell lymphoma, enteropathy-associated T-cell lymphoma, nasal-type T/NK-cell lymphoma, angioimmunoblasticlike T-cell lymphoma, and hepatosplenic $\gamma\delta$ T-cell lymphoma, have

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been identified within the PTCL category and are now classified as separate malignancies. In addition, a new subclass of PTCL has been identified and appropriately termed *peripheral T-cell lymphoma, unspecified* (*PTCL-U*); however, this is a blanket term that is used to describe a heterogeneous array of lymphomas with differing clinical features, histologic characteristics, genetic alterations, responses to treatment, and associated prognoses. The complex nature of PTCL is evident,[2,3,9–24] but various indicators can assist in the prediction of a given PTCL's clinical course. In this context, the International Prognostic Index (IPI),[25] which was developed for the assessment of aggressive lymphomas, represents a possible foundation on which to base a more appropriate clinical definition of PTCL-U.[26] Most previous studies comparing outcomes between patients with PTCL and patients with diffuse large B-cell lymphoma (DLBCL),[2,3,9,11–13] another classification that encompasses a variety of distinct entities,[27] have suffered from major limitations related to the heterogeneity encountered within each disease category. As a result, the findings of these studies are no longer considered a suitable framework for defining prognosis-based subclasses of T-cell lymphoma. Both the Revised European–American Lymphoma (REAL) Classification System[6] and the WHO system[8] define specific PTCL subtypes (e.g., PTCL-U) as being unique on the basis of clinical outcome; thus, a major limitation of past studies is that in most instances, all patients with PTCL have been grouped together.

Recently, the Intergruppo Italiano Linfomi conducted a retrospective study with the goals of more accurately defining the clinical and pathologic characteristics of PTCL-U and designing a prognostic model specifically for patients with this rare disease.[28] In the current investigation, to assess the possible independent prognostic role of immunophenotype, we compared a series of patients affected by PTCL-U with a series of patients affected by DLBCL, with all patients having been sequentially included in prospective trials involving anthracycline-containing chemotherapy regimens.

MATERIALS AND METHODS

Patient Population

The Intergruppo Italiano Linfomi recently reported on the construction of a prognostic model for patients with PTCL-U.[28] Using the working file employed in that study—a file that contained information on histologically confirmed cases of PTCL-U (according to the WHO criteria[8])—we assessed candidate patients' eligibility for the current study. Patients were required 1) to have complete clinical and hematologic data available; 2) to have a minimum follow-up duration of 1 year, with the most recent control recorded $\leq$ 6 months before data collection; and 3) to have received an anthracycline-based chemotherapy regimen.

A total of 297 cases of PTCL-U were included in the current retrospective study. In addition, 496 histologically confirmed DLBCL cases that had been transferred from the files of the Gruppo Italiano Linfomi were included in the final version of the working file for the current study.

Treatment

Ninety percent of patients in the PTCL-U group received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, a CHOP-like regimen, or a third-generation chemotherapy regimen (e.g., PROMACE-CytaBOM [methotrexate, prednisone, doxorubicin, cyclophosphamide, etoposide, cytosine arabinoside, bleomycin, and vincristine] or MACOP-B [doxorubicin, cyclophosphamide, vincristine, methotrexate, bleomycin, and prednisone]), whereas the remaining 10% were treated with a regimen that involved high-dose therapy and stem cell support. Most patients in the DLBCL group (89%) received PROMACE-CytaBOM chemotherapy, and all others received the MACOP-B regimen.

Disease Staging and Assessment of Response

All patients underwent clinical disease staging. The extent of disease was assessed using a procedure that involved computed tomographic scanning of the chest and abdomen as well as bone marrow (BM) biopsy. Response to treatment was evaluated 1 month after the end of induction therapy by performing all examinations necessary to reassess previously detected abnormal findings. Complete remission (CR) was defined as the disappearance of all initial clinical evidence of disease with accompanying normalization of all biochemical parameters and radiographic findings that were determined to be abnormal before the start of treatment; normalization of BM, if initially involved, was also required. Furthermore, patients who achieved CR during therapy but experienced disease recurrence within 30 days after the completion of treatment were classified as not having experienced a response. Partial remission (PR) was defined as a reduction of $\geq$ 50% in the largest tumor dimension at each anatomic site of measurable disease for $\geq$ 1 month. 'No response' (NR) was defined as stabilization or progression of disease or tumor regression by $<$ 50%. All evaluations of clinical stage and response to treatment were based on the original data recorded by local physicians.

Progressive disease (PD) was defined as an increase of $>$ 25% in tumor size or the appearance of any new neoplastic lesion. All patients who died pre-

maturely due to disease progression or treatment-related toxicity were considered to have experienced treatment failure and were included in the NR/PD group for the purposes of the current analysis.

Statistical Analysis

All calculations were performed using the SPSS statistical software package (Version 11.0; SPSS Inc., Chicago, IL). Along with immunophenotype, the following clinical features were analyzed as potential prognostic factors: age, gender, performance status (PS), symptoms, disease stage, lactic acid dehydrogenase (LDH) concentration, hemoglobin (Hb) concentration, number of extranodal disease sites (ENS), erythrocyte sedimentation rate (ESR), presence or absence of bulky disease, and presence or absence of BM involvement. Age, Hb and LDH concentrations, ESR, and number of ENS were transformed into binary variables as appropriate. Statistical comparisons involving binary variables were performed using two-way tables for the Fisher exact test and multiway tables for the Pearson chi-square test. Multivariate analysis was performed via multinomial logistic regression, because the dependent variable was restricted to three possible values (*CR*, *PR*, and *NR/PD*). Because the response evaluation date was not available in all cases, disease-free survival (DFS) for patients who achieved CR was calculated from the time of diagnosis to the time of recurrence or death using the Kaplan–Meier method. Overall survival (OS) was calculated as the interval between diagnosis and death due to any cause or, for surviving patients, as the interval between diagnosis and the most recent follow-up assessment. Prognostic groups were evaluated on univariate analysis (log-rank test), and the effects of potential prognostic variables on survival (significance threshold, $P = 0.1$) were assessed in a stepwise fashion according to the Cox regression method. $P \leq 0.05$ was considered indicative of significance in all statistical calculations.

RESULTS

Patient Characteristics

Table 1 compares the clinical and hematologic characteristics of patients with PTCL-U and patients with DLBCL. Distribution patterns with respect to patient age, gender, disease stage, PS, the presence of systemic symptoms, the presence of bulky disease, LDH concentration, and number of ENS were significantly different between these two groups. Specifically, male patients ($P < 0.0001$), patients with advanced-stage disease ($P < 0.0001$), patients presenting with poor PS ($P < 0.0001$), patients with > 2 ENS ($P < 0.0001$), patients with systemic symptoms ($P < 0.0001$), and patients with abnormal LDH levels ($P < 0.0005$) were significantly more common in the PTCL-U group. In contrast, older patients ($P = 0.015$) and patients with bulky disease ($P = 0.005$) were significantly more common in the DLBCL group. The two patient groups also differed significantly with respect to IPI, with a greater percentage of patients in the DLBCL group having favorable IPI scores ($P < 0.0001$). No other significant differences were noted.

TABLE 1
Comparison of the Primary Clinical Characteristics of Patients with PTCL-U and Patients with DLBCL at the Time of Disease Onset

	% of patients		
Characteristic	PTCL-U	DLBCL	P[a]
Age ≥ 60 yrs	27	36	0.015
Female gender	32	45	< 0.0001
Stage III–IV disease[b]	78	65	< 0.0001
WHO PS ≥ 2	29	10	< 0.0001
B symptoms present	49	32	< 0.0001
Bulky disease present	17	26	0.005
Abnormal LDH levels	47	35	0.005
Abnormal Hb levels	24	23	ns
BM involvement present	32	27	ns
> 2 extranodal sites involved	41	31	0.003
IPI score			
0–1	32	43	
2	26	29	< 0.0001[c]
3	25	20	
> 3	17	8	
ESR ≥ 15 mm/hr	69	69	ns

PTCL-U: peripheral T-cell lymphoma, unspecified; DLBCL: diffuse large B-cell lymphoma; WHO: World Health Organization; PS: performance status; LDH: lactic acid dehydrogenase; Hb: hemoglobin; ns: not significant; BM: bone marrow; IPI: International Prognostic Index; ESR: erythrocyte sedimentation rate.
[a] Fisher exact test.
[b] Ann Arbor staging system.
[c] Chi-square test.

Analysis of Response and Response Duration

Response to therapy was assessable in 95.6% of all patients (758 of 793). Overall, 544 of these patients (72%) experienced CR, 96 (13%) experienced PR, and 118 (13%) had NR/PD. Analysis of responses according to B-cell/T-cell phenotype revealed a significantly greater number of cases of CR in the DLBCL group ($P < 0.0001$) (Table 2). Furthermore, univariate analysis revealed highly significant correlations between CR and favorable PS, the absence of systemic symptoms, early-stage disease, normal LDH levels, normal Hb levels, the presence of ≤ 1 ENS, ESR < 15 mm/hr, and the absence of BM involvement. Multinomial logistic regression analysis identified immunophenotype ($P < 0.0001$), PS ($P < 0.0001$), LDH concentration ($P =$

TABLE 2
Univariate and Multivariate Logistic Regression Analyses of Potential Predictors of Response

Variable	% of patients			Univariate P^a	Multivariate P^b
	CR	PR	NR/PD		
Histology: DLBCL vs. PTCL-U	82 vs. 56	8 vs. 20	10 vs. 24	< 0.0001	< 0.0001
Age (yrs): < 60 vs. ≥ 60	73 vs. 70	14 vs. 10	13 vs. 20	0.059	ns
Gender: male vs. female	69 vs. 76	14 vs. 10	17 vs. 14	0.061	ns
WHO PS: ≤ 1 vs. > 2	78 vs. 47	10 vs. 23	12 vs. 30	< 0.0001	< 0.0001
B symptoms: yes vs. no	62 vs. 78	17 vs. 10	21 vs. 12	< 0.0001	ns
Disease stage: I–II vs. III–IV[c]	83 vs. 67	7 vs. 15	10 vs. 18	< 0.0001	ns
LDH levels: normal vs. abnormal	80 vs. 60	10 vs. 17	10 vs. 23	< 0.0001	0.004
Bulky disease: no vs. yes	72 vs. 71	13 vs. 12	15 vs. 17	ns	—
BM involvement: yes vs. no	65 vs. 74	17 vs. 11	18 vs. 15	0.027	ns
No. of extranodal sites: ≤ 1 vs. > 2	78 vs. 61	10 vs. 16	12 vs. 23	< 0.0001	0.040
ESR (mm/hr): < 15 vs. ≥ 15	81 vs. 70	10 vs. 13	9 vs. 17	0.007	ns
Hb levels: normal vs. abnormal	76 vs. 62	11 vs. 15	13 vs. 23	0.001	ns

CR: complete remission; PR: partial remission; NR/PD: no response/progressive disease; DLBCL: diffuse large B-cell lymphoma; PTCL-U: peripheral T-cell lymphoma, unspecified; ns: not significant; WHO: World Health Organization; PS: performance status; LDH: lactic acid dehydrogenase; BM: bone marrow; ESR: erythrocyte sedimentation rate; Hb: hemoglobin.

[a] Pearson chi-square test.

[b] Multinomial logistic regression.

[c] Ann Arbor staging system.

0.004), and number of ENS ($P = 0.04$) as independent predictors of response.

Of the 544 patients who experienced CR, 469 (including 159 with PTCL-U) were evaluable for disease recurrence; 249 of these patients (including 91 with PTCL-U) experienced recurrence or died during CR. After a median follow-up duration of 43 months, there was no difference in DFS between patients with DLBCL and patients with PTCL-U (Fig. 1). Furthermore, no significant difference in DFS was observed in association with age < 60 years, the absence of systemic symptoms, or the presence of ≤ 1 ENS and ESR < 15 mm/hr (Table 3). In contrast, advanced-stage disease, abnormal serum LDH levels, poor PS, and BM involvement all were associated with significantly reduced DFS; however, only poor PS ($P = 0.025$) and BM involvement ($P = 0.025$) remained significantly correlated with DFS on multivariate analysis (Table 3).

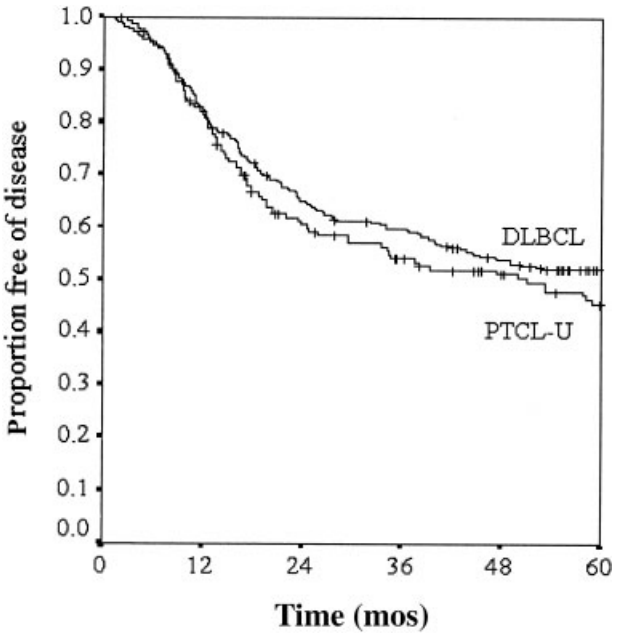

FIGURE 1. Kaplan–Meier analysis of disease-free survival according to histologic subtype. No difference was found between the two patient groups ($P = 0.1$). DLBCL: diffuse large B-cell lymphoma; PTCL-U: peripheral T-cell lymphoma, unspecified.

Analysis of Survival

After a median follow-up duration of 37 months (67 months for surviving patients), 392 patients had died. As expected, the survival curves associated with the T-cell and B-cell immunophenotypes were statistically different from each other (Fig. 2). Fifty-six percent of all patients with DLBCL were projected to be alive at 5 years, compared with 42% of all patients with PTCL-U ($P = 0.0012$). Univariate analysis revealed that age > 60 years ($P = 0.0051$), poor PS ($P < 0.00001$), the presence of systemic symptoms ($P < 0.00001$), advanced disease stage ($P < 0.00001$), elevated serum LDH levels ($P < 0.00001$), the presence of bulky disease ($P = 0.0425$), BM involvement ($P < 0.00001$), involvement at > 2 ENS ($P < 0.00001$), ESR > 15 mm/hr ($P < 0.00001$), and abnormally low Hb levels ($P < 0.00001$) also were significantly predictive of re-

TABLE 3
Univariate and Multivariate Analyses of Potential Predictors of Disease-Free Survival

Variable	Median DFS (mos)	Univariate P[a]	Multivariate P[b]	RR (95% CI)
Histology: DLBCL vs. PTCL-U	81 vs. 51	0.1	ns	—
Age (yrs): < 60 vs. ≥ 60	91 vs. 47	0.0837	ns	—
Gender: male vs. female	71 vs. 51	ns	—	
WHO PS: ≤ 1 vs. > 2	74 vs. 27	0.0228	0.025	1.6 (1.1–2.4)
B symptoms: yes vs. no	89 vs. 49	0.1	ns	—
Disease stage: I–II vs. III–IV[c]	Not reached vs. 39	0.0002	ns	—
LDH levels: normal vs. abnormal	90 vs. 28	0.0037	ns	—
Bulky disease: no vs. yes	73 vs. 47	ns	—	
BM involvement: yes vs. no	94 vs. 33	0.0005	0.025	1.5 (1.0–2.3)
No. of extranodal sites: ≤ 1 vs. > 2	81 vs. 38	0.1	ns	—
ESR (mm/hr): < 15 vs. ≥ 15	96 vs. 50	0.0889	ns	
Hb levels: normal vs. abnormal	59 vs. 72	ns	—	

DFS: disease-free survival; RR: risk ratio; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; PTCL-U: peripheral T-cell lymphoma, unspecified; ns: not significant; WHO: World Health Organization; PS: performance status; LDH: lactic acid dehydrogenase; BM: bone marrow; ESR: erythrocyte sedimentation rate; Hb: hemoglobin.

[a] Log-rank test.

[b] Cox regression analysis.

[c] Ann Arbor staging system.

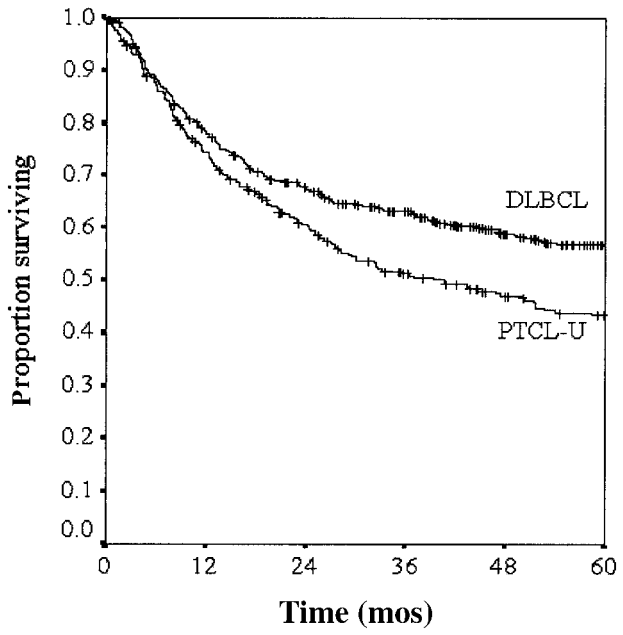

FIGURE 2. Overall survival of 793 patients according to histologic subtype. Projected survival was significantly longer ($P = 0.0012$) for patients who had diffuse large B-cell lymphoma (DLBCL) compared with patients who had peripheral T-cell lymphoma, unspecified (PTCL-U).

duced OS. Ultimately, Cox multivariate analysis excluded immunophenotype from the final OS model, which included age (risk ratio [RR], 1.3; $P = 0.023$), PS (RR, 1.9; $P < 0.0001$), LDH concentration (RR, 1.7; $P < 0.0001$), presence or absence of bulky disease (RR, 1.4; $P = 0.011$), and presence or absence of BM involvement (RR, 1.3; $P = 0.048$) (Table 4).

DISCUSSION

The efforts of the International Lymphoma Study Group and the diagnostic criteria set forth by the REAL and WHO classification systems have led to clarification of the definition of PTCL,[6,8] although characterization of the role of the T/NK-cell immunophenotype in prognostic workup remains a significant challenge. Montalban et al.[14] compared PTCL (which was limited to the prevalent lymph node subtype, as defined by the WHO International Classification Project,[8] due to the heterogeneity of PTCLs with respect to clinical presentation) with the equally aggressive DLBCL. Several studies have suggested that for patients with PTCL, outcome can be predicted on the basis of clinical parameters, and there is general agreement—with some exceptions[10–13]—that PTCL is associated with poorer survival compared with B-cell lymphoma[2,3,9]; however, comparisons of PTCL with DLBCL in these studies were inadequate, as individual REAL or WHO subtypes of PTCL were not considered separately from one another.

The current retrospective analysis, which involved 783 cases of malignant disease with either T-cell ($n = 297$) or B-cell phenotype ($n = 496$), is one of the largest comparison studies of PTCL-U and DLBCL performed to date. In this study, we assessed the impact of immunophenotype on clinical response and response duration. A significantly lower CR rate was observed in the PTCL-U group compared with the DLBCL group (56% vs. 82%), a finding that was consistent with previously reported CR rates (40–69%) in patients with

TABLE 4
Univariate and Multivariate Analyses of Potential Predictors of Overall Survival

Variable	Median OS (mos)	Univariate P^a	Multivariate P^b	RR (95% CI)
Histology, DLBCL vs. PTCL-U	94 vs. 39	0.0012	ns	—
Age (yrs): < 60 vs. ≥ 60	93 vs. 47	0.0051	0.023	1.3 (1.0–1.6)
Gender: male vs. female	52 vs. 89	0.1	ns	—
WHO PS: ≤ 1 vs. > 2	94 vs. 13	< 0.00001	< 0.0001	1.9 (1.4–2.5)
B symptoms: yes vs. no	95 vs. 30	< 0.00001	ns	—
Disease stage: I–II vs. III–IV[c]	Not reached vs. 45	< 0.00001	ns	—
LDH levels: normal vs. abnormal	117 vs. 23	< 0.00001	< 0.0001	1.7 (1.4–2.2)
Bulky disease: no vs. yes	81 vs. 33	0.0425	0.011	1.4 (1.0–1.8)
BM involvement: yes vs. no	95 vs. 38	0.0001	0.048	1.3 (1.0–1.7)
No. of extranodal sites: ≤ 1 vs. > 2	94 vs. 37	< 0.00001	ns	—
ESR (mm/hr): < 15 vs. ≥ 15	117 vs. 49	< 0.00001	ns	—
Hb levels: normal vs. abnormal	94 vs. 33	0.0001	ns	—

OS: overall survival; RR: risk ratio; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; PTCL-U: peripheral T-cell lymphoma, unspecified; ns: not significant; WHO: World Health Organization; PS: performance status; LDH: lactic acid dehydrogenase; BM: bone marrow; ESR: erythrocyte sedimentation rate; Hb: hemoglobin.

[a] Log-rank test.

[b] Cox regression analysis.

[c] Ann Arbor staging system.

PCTL-U.[3,16,18,24] Furthermore, T-cell immunophenotype, along with clinical parameters such as poor PS, abnormal LDH levels, and involvement of > 2 ENS, were identified as potential independent predictors of poor response. Notably, however, the significance of T-cell histology in predicting reduced DFS was lost on multivariate analysis, whereas poor PS and BM involvement maintained their prognostic significance. Thus, based on the first part of the current analysis, we can conclude that T-cell immunophenotype is associated with a higher risk of failure to achieve CR; however, if a CR is achieved, its duration is related primarily to specific clinical characteristics, rather than to disease immunophenotype. This unusual finding may represent a major problem for patients with PTCL-U, as Song et al.[29] have reported that the benefit associated with autologous BM transplantation for such patients is negligible.

As expected, the survival curves associated with the T-cell and B-cell immunophenotypes were statistically different from each other; the 5-year survival rate for patients with DLBCL was 56%, compared with 42% for patients with PTCL-U. The median OS duration for patients with PTCL-U was 39 months, greater than has been reported elsewhere.[3,16–18,23] This discrepancy may be attributable, at least in part, to the exclusion of patients who were not treated with anthracycline-based regimens from the current study. In addition to immunophenotype, various tumor-related and host-related characteristics were found to be significant predictors of reduced OS on univariate analysis. Further highlighting the significance of clinical presentation was the exclusion of disease histology from the final multivariate OS model; only age, performance status, LDH concentration, bulky disease (presence or absence), and BM involvement (presence or absence) remained significant following Cox multivariate analysis. This unexpected finding differs from those that have been reported by other investigators. For example, Gisselbrecht et al.[9] examined 288 cases of PTCL and 1595 cases of B-cell lymphoma and found that patients with T-anaplastic large cell lymphoma (n = 60) had a 5-year OS rate of 64%, superior to the corresponding rates for patients with other PTCL subtypes (35%) and patients with DLBCL (53%). In that study, nonanaplastic subtype (n = 228) remained significant on multivariate analysis (with IPI score included in the multivariate model) and therefore was deemed an independent adverse prognostic factor.

In conclusion, the results of the current study suggest that the natural history of PTCL-U may in fact be different from that of DLBCL. Overall, patients with PTCL-U had a less favorable clinical outcome, although this difference in outcome was only partially attributable to immunophenotype, which was independently associated with CR but not independently correlated with survival. The relative prevalence of adverse prognostic factors in the PTCL-U group has also been reported by Melnyk et al.[3] and Gisselbrecht et al.[9] and can account for some portion of the expected phenotype-associated risk.

An alternative and widely held belief is that the PTCL-U category encompasses a heterogeneous array of malignant subtypes that have not yet been fully

characterized. Lending support to this idea, Tsuchiya et al.[30] recently found that patients' prognoses varied according to the expression of certain Th1/Th2 cell–associated chemokine receptors and markers. This hypothesis could at least partially explain why the T-cell phenotype had differing effects on response and survival in the current study. Future genetic profiling studies involving large patient cohorts could lead to a biologic explanation for the observed association between PTCL-U and poor outcome.

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