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ORIGINAL REPORT

International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes

International T-Cell Lymphoma Project

From The International T-Cell Lymphoma Project. The members and affiliations of the writing committee, as well as the participants, are listed in the Appendix (online only).

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ABSTRACT

Purpose
Peripheral T-cell lymphoma (PTCL) and natural killer/T-cell lymphoma (NKTCL) are rare and heterogeneous forms of non-Hodgkin's lymphoma (NHL) that, in general, are associated with a poor clinical outcome.

Patients and Methods
A cohort of 1,314 cases of PTCL and NKTCL was organized from 22 centers worldwide, consisting of patients with previously untreated PTCL or NKTCL who were diagnosed between 1990 and 2002. Tissue biopsies, immunophenotypic markers, molecular genetic studies, and clinical information from consecutive patients at each site were reviewed by panels of four expert hematopathologists and classified according to the WHO classification.

Results
A diagnosis of PTCL or NKTCL was confirmed in 1,153 (87.8%) of the cases. The most common subtypes were PTCL not otherwise specified (NOS; 25.9%), angioimmunoblastic type (18.5%), NKTCL (10.4%), and adult T-cell leukemia/lymphoma (ATLL; 9.6%). Misclassification occurred in 10.4% of the cases including Hodgkin's lymphoma (3%), B-cell lymphoma (1.4%), unclassifiable lymphoma (2.8%), or a diagnosis other than lymphoma (2.3%). We found marked variation in the frequency of the various subtypes by geographic region. The use of an anthracycline-containing regimen was not associated with an improved outcome in PTCL-NOS or angioimmunoblastic type, but was associated with an improved outcome in anaplastic large-cell lymphoma, ALK positive.

Conclusion
The WHO classification is useful for defining subtypes of PTCL and NKTCL. However, expert hematopathology review is important for accurate diagnosis. The clinical outcome for patients with most of these lymphoma subtypes is poor with standard therapies, and novel agents and new modalities are needed to improve survival.

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INTRODUCTION

The classification of non-Hodgkin's lymphoma (NHL) has evolved steadily during the last several decades. In the 1950s, Rappaport et al[1] recognized the importance of the growth pattern in NHL and used pattern, cell size, and shape as the basis of a classification. In the 1970s, recognition that NHL cells were derived from T or B cells led to the immunologically based classification of Lukes and Collins[2] and the Kiel classification of Lennert.[3] The Working Formulation was proposed in 1982 in an attempt to unify the various classifications.[4]

In 1994, a group of pathologists proposed a classification of lymphoid neoplasms on the basis of contemporary morphologic, immunologic, and genetic techniques.[5] This eventually formed the foundation for a new WHO classification of the hematopoietic and lymphoid neoplasms.[6] This new classification was tested on a cohort of 1,403 cases of NHL obtained worldwide in the International Non-Hodgkin's Lymphoma Classification Project.[7] Of these cases, only 7% represented a subtype of peripheral T-cell lymphoma (PTCL), and 2.4% were anaplastic large T/null-cell lymphoma (ALCL).

In Western countries, PTCL accounts for 15% to 20% of aggressive lymphomas and 5% to 10% of all NHL.[8,9] On the Asian continent, this number is higher, with approximately 15% to 20% of all lymphomas classified as PTCL or

NK/T-cell lymphoma (NKTCL).[9,10] Despite aggressive chemotherapy, the majority of patients with most subtypes of PTCL do not enjoy long-term disease-free survival.

The study presented in this article represents the largest clinicopathologic study of PTCL and NKTCL organized to date. Five goals were outlined for the study: (1) to evaluate the ability of hematopathologists to apply the WHO classification to a large group of cases; (2) to evaluate the role of clinical data in the diagnosis of the lymphoma subtypes; (3) to determine the relative frequencies and geographic variation of the subtypes; (4) to determine clinical correlations, including clinical features, treatment, and survival outcomes; and (5) to evaluate the percentage of transformed cells, Ki-67 proliferation, Epstein-Barr virus (EBV) status, and phenotypic markers. This article will discuss our overall findings from the international study and additional articles with more detail on specific subtypes of lymphoma will be published separately.

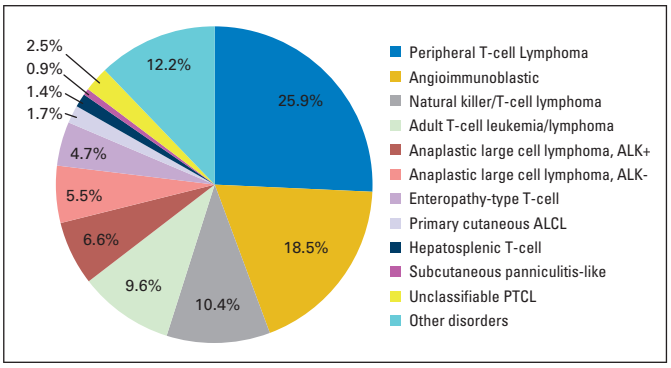

Fig 1. Distribution of 1,314 cases by consensus diagnosis. NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; PTCL, peripheral T-cell lymphoma.

PATIENTS AND METHODS

Pathology Review

Twenty-two institutions or groups in North America, Europe, and Asia participated in the study (Appendix Table A1, online only). Permission was obtained from the institutional review board and/or the scientific review committee as required by individual institutional policies. The cases selected for this study were previously untreated patients age 19 years or older with de novo PTCL or NKTCL. The initial presentation for the patients was between January 1, 1990, and December 31, 2002. The local pathologist selected consecutive cases with representative slides and a tissue block to submit for regional review and more detailed immunophenotyping. Clinical characteristics of the patients, including treatment data and follow-up information, were also required. The 22 local sites, which provided a total of 1314 cases, are shown in Appendix Table A2 (online only).

From each institution, the phenotype datasheets, diagnostic slides and tissue blocks were sent to a regional center. These centers included Omaha, NE (D.D. Weisenburger); Leeds, United Kingdom (K.A. MacLennan); Würzburg, Germany (T. Rüediger); Bologna, Italy (S. Pileri); and Nagoya, Japan (S. Nakamura); A standard panel of immunostains was performed on each case including CD20, CD2, CD3, CD4, CD5, CD8, CD30, CD56, TCR-β, TIA-1, Ki67, and in situ stains for EBV-encoded RNAs. Other immunostains, polymerase chain reaction analyses, and fluorescence in situ hybridization studies were performed as needed, and all cases were diagnosed according to criteria of the WHO classification.[6]

Panels of four expert hematopathologists, drawn from the contributing local sites and regional centers, then traveled to the regional centers to review the cases. The composition of the panels differed at the various regional centers. The initial diagnosis was classified by each pathologist on the basis of examination of the hematoxylin-eosin– and/or Giemsa-stained slides, the immunostains, and the phenotype data sheets, but with only limited clinical information (ie, diagnosis 1). Subsequently, the expert was presented with the entire clinical data sheet and a second diagnosis was rendered (ie, diagnosis 2). If a case was considered unclassifiable, the expert was required to give a reason (eg, inadequate material).

In addition to the independent diagnosis rendered by each of the four expert hematopathologists, a consensus diagnosis was also reached. A consensus was considered to have been reached if at least three of the four experts agreed on the second diagnosis (diagnosis 2). All cases without a consensus diagnosis and all unclassifiable cases were reviewed on a multiheaded microscope and discussed by the four experts in a conference. Approximately one half of the cases at each of the regional centers were reviewed and diagnosed twice by the respective regional expert hematopathologist (ie, at initial work-up of the case and later during the panel review [diagnosis 1]). This allowed for evaluation of the reproducibility of diagnosis on rereview for the regional experts.

Clinical Information

The clinical information included coded patient identifiers, patient sex, ethnic origin, date of birth, date and site of the diagnostic biopsy, sites of disease, and Ann Arbor stage at the time of diagnosis. Additional data recorded included symptoms at diagnosis, the site and diameter of the largest tumor, performance status, and immunosuppressive therapy, or immune system disorder. Laboratory data recorded included hemoglobin, platelet count, WBC and absolute lymphocyte counts, presence of circulating lymphoma cells, and serologies for human T-cell leukemia virus (HTLV-1) and HIV. The serum lactate dehydrogenase (LDH), β-2 microglobulin, and C-reactive protein levels, and the presence of hypercalcemia, hypogammaglobulinemia, hypergammaglobulinemia, monoclonal serum immunoglobulin, hemolytic anemia, and hemophagocytic syndrome were recorded. The initial therapy, response, details of remission, progression or relapse, and subsequent therapies, along with survival and cause of death, were recorded.

Completed clinical and pathology data forms were reviewed and additional information was obtained. The International Prognostic Index (IPI)[11] and the new prognostic models for PTCL[12] and nasal NKTCL[13] were evaluated as appropriate for the histologic type. Treatment outcomes were measured by failure-free survival (FFS) and overall survival (OS). FFS

Table 1. Major Lymphoma Subtypes by Geographic Region

Subtype	%		
	North America	Europe	Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK positive	16.0	6.4	3.2
ALCL, ALK negative	7.8	9.4	2.6
NKTCL	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
Enteropathy-type	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Subcutaneous panniculitis-like	1.3	0.5	1.3
Unclassifiable T-cell	2.3	3.3	2.4

Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; NKTCL, natural killer/T-cell lymphoma.

was defined as the time from initial diagnosis to progression, relapse after response, or death resulting from any cause. Follow-up of patients not experiencing one of these events was censored at the date of last contact. OS was measured from initial diagnosis to death from any cause, with surviving patient follow-up censored at the last contact date. Estimates of FFS and OS distribution were calculated using the Kaplan-Meier method[14] and time-to-event distributions were compared using the log-rank test.[15]

RESULTS

A total of 1,320 cases were reviewed; however, six were found not to meet the entry criteria of age 19 years or older and were therefore excluded. The subtypes of lymphoma and other disorders found after review among the 1,314 cases are presented in Figure 1 and Table A3 (online only). A diagnosis of PTCL or NKTCL was confirmed in 1,153 of the cases (87.8%). The most common subtype identified was PTCL not otherwise specified (NOS; 25.9%), with the second most common subtype being angioimmunoblastic type (18.5%). NKTCL represented 10.4% and adult T-cell leukemia/lymphoma (ATLL) 9.6% of the cases. The next most common subtypes were anaplastic large-cell lymphoma (ALCL), ALK positive (6.6%); ALCL, ALK negative (5.5%); and enteropathy-type PTCL (4.7%). All of the other specific subtypes of PTCL represented less than 2% of the total. Some other T-cell disorders not specifically included in the study (1.8%) were also diagnosed, and 10.4% of the cases were misclassified and found to be other disorders including Hodgkin's lymphoma (3%), B-cell lymphoma (1.4%), or a diagnosis other than lymphoma (2.3%). Only 3.6% of the cases could not be adequately classified, usually because of inadequate material or technical factors.

Diagnostic Accuracy (agreement with consensus diagnosis)

Two diagnoses were made by each of the four expert pathologists in each case based mainly on histology, immunophenotype, and molecular genetic data (diagnosis 1) and with the clinical data (diagnosis 2). The agreement of diagnosis 2 from the experts with the consensus diagnosis was 97% for ALCL, ALK positive; 93% for ATLL; 92% for NKTCL; 81% for angioimmunoblastic type; 79% for enteropathy type; 75% for PTCL-NOS and subcutaneous panniculitis-like type; 74% for ALCL, ALK negative; 72% for hepatosplenic type; and only 66% for primary cutaneous ALCL. A change in diagnosis 1 with the addition of the clinical data occurred in 6.4% of the cases overall, and was the highest (38.7%) for a change from PTCL-NOS to ATLL resulting from clinical data on HTLV-1 status. The overall agreement on rereview (reproducibility) of a subset of the cases by the five regional experts was 81% (range, 67% to 95%), with the results by histology similar to those listed in the preceding description.

Variation by Geographic Region

The relative frequencies of the various lymphoma subtypes by geographic region are shown in Table 1. PTCL-NOS was the most common subtype in both North America and Europe, whereas NKTCL and ATLL were common in Asia. ATLL was frequent in Japan, but was not found in the other Asian countries, whereas NKTCL made up 44% of the cases in Asia excluding Japan. ALCL, ALK positive, was most common in North America, whereas enteropathy-type PTCL was most common in Europe (mainly Norway). Interestingly, angioimmunoblastic type was most common in Europe compared with the other regions. Primary cutaneous ALCL was higher in North America than in Europe, possibly because of referral of such cases to dermatologists in Europe, whereas systemic and cutaneous ALCL, enteropathy-type, and hepatosplenic PTCL were uncommon in Asia.

Clinical Characteristics

The clinical characteristics of the various subtypes of PTCL and NKTCL are presented in Table 2. All of the subtypes were found more commonly in male patients. The median age for all patients was 62 years. However, several subtypes had a median age that was much younger, including ALCL, ALK positive (33 years); hepatosplenic type (34 years); and subcutaneous panniculitis-like PTCL (33 years). Bone marrow involvement was frequent in the

Table 2. Patient Characteristics by Histologic Type

Diagnosis	Median Age (years)	%					
		Male	Stage III/IV	Marrow Positive	IPI 0/1	IPI 2/3	IPI 4/5
PTCL-NOS	60	66	69	22	28	57	15
Angioimmunoblastic	65	56	89	29	14	59	28
Nasal NKTCL	52	64	27	10	51	47	2
Extranasal NKTCL	44	68	69	18	26	57	17
ATLL	62	55	90	28	19	65	16
ALCL, ALK+	34	63	65	12	49	37	14
ALCL, ALK−	58	61	58	7	41	44	15
Enteropathy-type	61	53	69	3	25	63	13
Primary cutaneous ALCL	55	64	14	0	86	14	0
Hepatosplenic	34	68	95	74	5	47	47
Subcutaneous panniculitis-like	33	75	83	8	42	42	17

Abbreviations: IPI, International Prognostic Index; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; NKTCL, natural killer/T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; ALCL, anaplastic large-cell lymphoma.

hepatosplenic type, but was uncommon in nasal NKTCL, ALCL of all types, enteropathy-type, and subcutaneous panniculitis-like PTCL. The standard IPI[11] was calculated for each subtype and is shown in Table 2.

Outcomes

The overall survival for the various subtypes of PTCL and NKTCL is shown in Figure 2A and Table 3. The 5-year OS for PTCL-NOS, angioimmunoblastic, and all NKTCLs was 32% compared with only 14% for ATLL (Fig 2A). Anaplastic large-cell lymphoma, ALK positive, demonstrated the best 5-year OS (70%), with ALCL, ALK negative, having an intermediate 5-year OS (49%). The 5-year OS of the uncommon subtypes is shown in Figure 2B. Although rare, primary cutaneous ALCL had an excellent 5-year OS of 90%. The 5-year OS for subcutaneous panniculitis-like PTCL was also good (64%) compared with enteropathy-type (20%) and hepatosplenic PTCL (7%). Overall survival for the subtypes of NKTCL is shown in Figure 2C. The 5-year OS for nasal NKTCL was 42%, with an apparent plateau, compared with a 5-year OS of only 9% for extranasal NKTCL and aggressive or unclassifiable NK-cell leukemia/lymphoma. Five-year FFS was as follows: PTCL-NOS (20%); angioimmunoblastic (18%); ATLL (12%); nasal NKTCL (29%); extranasal NKTCL (6%); ALCL, ALK positive (60%); and ALCL, ALK negative (36%). For the less common subtypes, the 5-year FFS was as follows: primary cutaneous ALCL (55%), subcutaneous panniculitis-like PTCL (24%), enteropathy-type PTCL (4%), and hepatosplenic PTCL (0%).

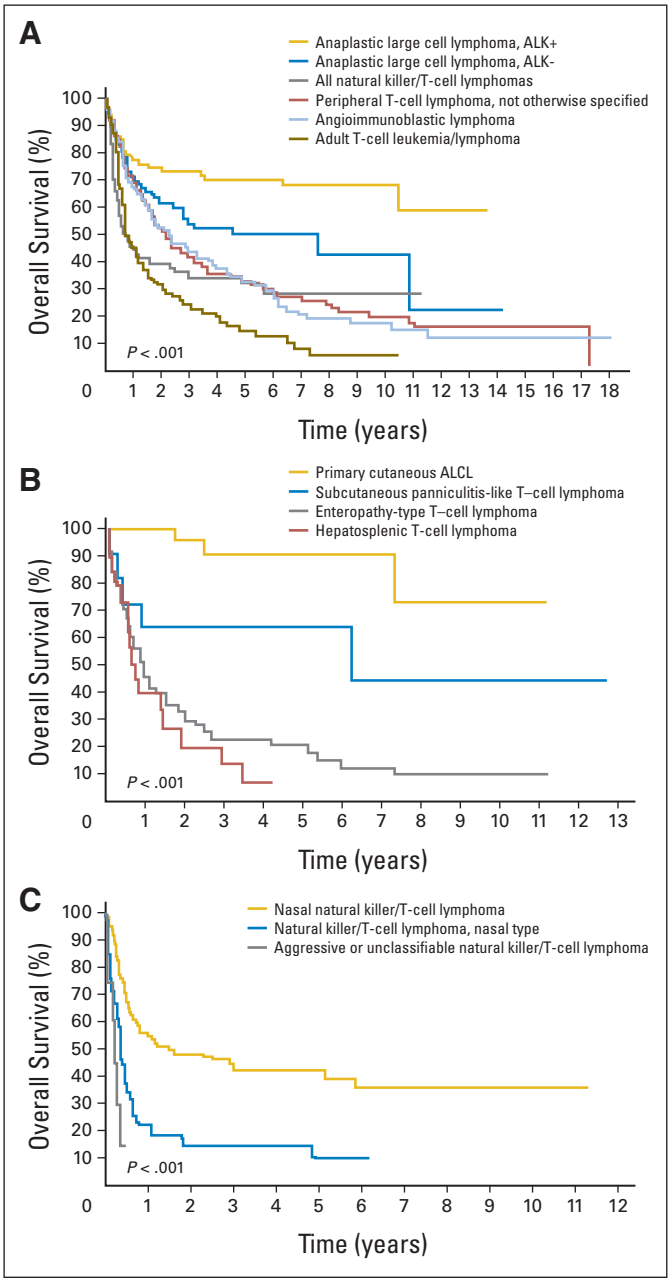

Fig 2. (A) Overall survival of patients with the common subtypes of peripheral T-cell lymphoma (PTCL). (B) Overall survival of patients with the less common subtypes of PTCL. (C) Overall survival of patients with natural killer T-cell lymphoma.

Prognostic Characteristics

The 5-year OS and FFS by low- and high-risk IPI for each histologic subtype are shown in Table 3. Although the IPI was helpful for most of the histologic types, even patients in the low-risk IPI groups with ATLL, enteropathy-type, hepatosplenic PTCL, and extranasal NKTCL, had poor outcomes. An example of the OS using the standard IPI for patients with PTCL-NOS is shown in Figure 3A. The Prognostic Index for T-Cell Lymphoma was also calculated for PTCL-NOS and was slightly more discriminatory for that subtype.[12] This will be further discussed in a separate PTCL-NOS article.

Analysis of Treatments

Because this is a retrospective study of cases from 22 worldwide centers, the initial therapeutic approaches varied widely. The majority of patients (> 85%) with the most common subtypes such as PTCL-NOS, angioimmunoblastic type, ATLL, and ALCL, ALK positive and ALK negative, received an anthracycline-containing regimen. Radiation therapy was used mostly for patients with localized disease, such as primary cutaneous ALCL, and for patients with nasal NKTCL. Unlike diffuse large B-cell lymphoma, the majority of patients with PTCL or NKTCL, other than ALCL, ALK positive, did not benefit from the use of an anthracycline-containing regimen over a non–anthracycline-containing regimen. This is demonstrated in Figures 3B and 3C for patients with PTCL-NOS and angioimmunoblastic type, respectively.

DISCUSSION

This study represents the largest evaluation of PTCL and NKTCL to our knowledge to date. The geographic variation in the relative frequency of PTCL and NKTCL has been well documented previously, ranging from 21% of all NHL in Hong Kong to only 4.0% in Vancouver, British Columbia.[9] The current study validates these geographic variations and presents new data on the various subtypes of PTCL and NKTCL, such as the high prevalence of ATLL

Table 3. Survival by Histologic Type and the IPI

Diagnosis	5-Year OS			5-Year FFS		
	%	IPI 0/1	IPI 4/5	%	IPI 0/1	IPI 4/5
PTCL-NOS	32	50	11	20	33	6
Angioimmunoblastic	32	56	25	18	34	16
Nasal NKTCL	42	57	0	29	53	0
Extranasal NKTCL	9	17	20	6	21	20
ATLL	14	28	7	12	26	0
ALCL, ALK+	70	90	33	60	80	25
ALCL, ALK−	49	74	13	36	62	13
Enteropathy-type	20	29	14	4	7	14
Primary cutaneous ALCL	90	100	NA	55	62	NA
Hepatosplenic	7	0	0	0	0	0
Subcutaneous panniculitis-like	64	60	0	24	30	0

Abbreviations: IPI, International Prognostic Index; OS, overall survival; FFS, failure-free survival; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; NKTCL, natural killer/T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; ALCL, anaplastic large-cell lymphoma; NA, not applicable.

and NKTCL in Asian countries. Some of this variation may reflect exposure or genetic susceptibility to pathogenic agents such as HTLV-1 and EBV in Asian countries.[16] In addition, some new geographic variations are evident from this study, such as the increased relative frequency of angioimmunoblastic type in Europe compared with North America and Asia. The increased frequency of ALCL, ALK positive, in North America and the increased frequency of enteropathy-type PTCL in Europe were also new findings in this study. The biologic reasons for these geographic differences remain largely unknown; however, there is a known association between enteropathy-type PTCL and gluten-sensitive enteropathy, in part because of the higher frequency of the human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 alleles, in the northern European population.

Our study demonstrates that expert hematopathologists can apply the WHO classification[6] to this group of disorders. Although agreement of the experts with the consensus diagnosis (diagnostic accuracy) was good (> 90%) for ALCL, ALK positive; ATLL; and NKTCL, mainly because of specific diagnostic markers (ie, ALK, HTLV-1, and EBV, respectively), the agreement was generally poor (< 85%) for the rest of the lymphoma subtypes. The reproducibility of diagnosis by the experts was also rather poor (81%). These results are similar to the prior studies in which the diagnostic accuracy of some lymphoma subtypes was poor (< 85%).[5,7] In our study, 10.4% of the cases were either misdiagnosed by the local site pathologists or could not be adequately classified by the experts. These findings indicate that better and more specific diagnostic markers, as well as more objective criteria for diagnosis, are clearly needed to increase the accuracy and reproducibility of diagnosis for these entities. For example, use of the new immunostains for CXCR13 should improve the diagnostic accuracy of angioimmunoblastic PTCL.[17] Current efforts to update the WHO classification[6] should also seek to provide more specific and objective diagnostic criteria for these entities.

Although several studies have demonstrated the inferior outcome of patients with PTCL in single-center studies or clinical trials,[18-22] no large multinational studies have been performed to evaluate the WHO classification and demonstrate the outcomes of a large number of patients with the various subtypes of PTCL and NKTCL. Histologic subtypes with the worst outcomes included ATLL, PTCL-NOS, angioimmunoblastic, hepatosplenic, and enteropathy-type PTCL, and extranasal NKTCL. The 5-year OS of these subtypes was as follows: ATLL (14%), PTCL-NOS (32%), angioimmunoblastic (32%), hepatosplenic (7%), enteropathy-type PTCL (20%), and extranasal NK/T-cell lymphoma (9%). However, a few subtypes were identified with a better prognosis including primary cutaneous ALCL with a 5-year OS of 90%; ALCL, ALK positive (70%); ALCL, ALK negative (49%); nasal NKTCL (42%); and subcutaneous

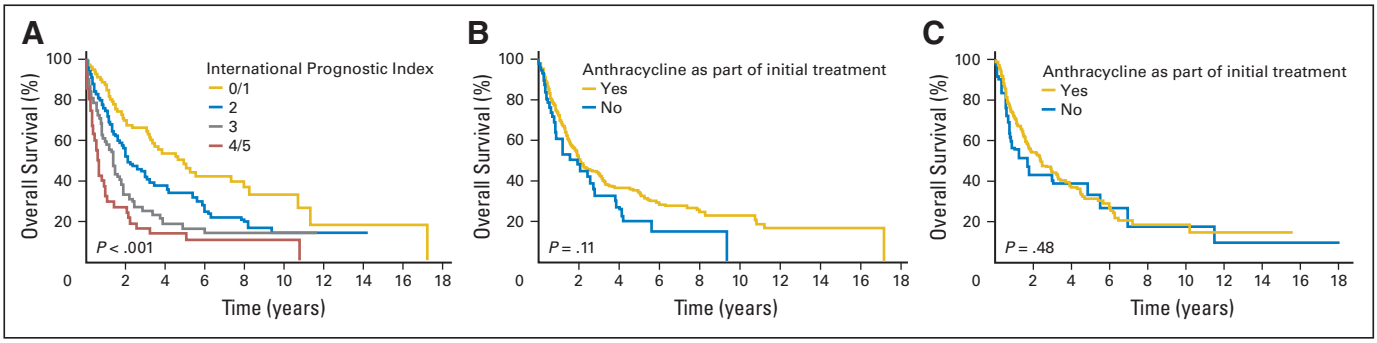

Fig 3. (A) Overall survival of patients with peripheral T-cell lymphoma (PTCL) not otherwise specified (NOS) by the standard International Prognostic Index. (B) Overall survival of the patients with PTCL-NOS who were treated with or without an anthracycline-based induction therapy. (C) Overall survival of the patients with angioimmunoblastic type who were treated with or without an anthracycline-based induction therapy.

panniculitis-like PTCL (64%). The data presented in this study for the differences in outcome for ALCL is consistent with that reported in the literature.[23,24]

The standard IPI is helpful in prognosticating some subtypes of PTCL and NKTCL. However, compared with diffuse large B-cell lymphoma,[11] many patients with these lymphomas have a poor outcome, even those in the low-risk IPI category. Examples of subtypes for which the IPI was not helpful include ATLL, enteropathy-type, hepatosplenic PTCL, and extranasal NKTCL.

Most types of PTCL and NKTCL have traditionally been treated with an anthracycline-containing regimen, and complete response rates of 50% to 70% have been reported.[25-29] However, patients in these studies have a long-term survival of only 10% to 30%. Our international study confirms the poor prognosis of patients with the aggressive forms of PTCL and NKTCL with many standard treatment regimens. Clearly, better therapeutic regimens are needed to improve the long- term outcome of these patients.

Important observations from this study include the fact that expert hematopathology review is necessary for differentiating the various subtypes of PTCL and NKTCL, which may dictate the therapy chosen for a given patient. Interesting geographic variations in the distribution of the various subtypes of these lymphomas were also identified and should lead to further evaluation of genetic and environmental etiologies beyond those already identified. Because most of the lymphoma subtypes in this study had a poor clinical outcome with the standard therapies employed, the next step will be to evaluate novel chemotherapies, new targeted agents, and additional modalities to treat patients with PTCL and NKTCL. High-dose chemotherapy and autologous stem-cell transplantation have been used in the salvage setting for PTCL with marginal success.[30,31] However, given the dismal prognosis, transplantation has been employed more recently as part of the up-front treatment after induction therapy for patients with advanced PTCL.[32] Another approach is the evaluation of new drugs with novel mechanisms of action for the therapy of patients with PTCL. Examples of novel drugs demonstrating promising results in PTCL include gemcitabine,[33] histone deacetylase (HDAC) inhibitors such as depsipeptide and vorinostat,[34] immunotoxins such as denileukin diftotox,[35] and new agents such as pralatrexate.[36] New molecular genetic markers and prognostic models to better define these entities will also assist clinical investigators in designing improved therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

