Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification

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Background: All peripheral T-cell lymphomas (PTCLs) diagnosed at a single institution were evaluated to determine the unique clinical features and outcome of specific entities and test the predictive validity of the International Prognostic Index (IPI).

Patients and methods: Cases of PTCL seen at the British Columbia Cancer Agency between 1981 and 2000 were identified. Pathologic material was re-assessed and classified according to the WHO classification, and patients were staged and treated uniformly according to era-specific guidelines. In total, there were 199 patients with PTCL and the most common subtypes were peripheral T-cell lymphoma unspecified (PTCL-US) (59%), anaplastic large-cell lymphoma, systemic type (ALCL) (17%) and extranodal NK/T-cell lymphoma, nasal and nasal-type (NASAL) (9%). Most patients were treated with CHOP-type chemotherapy.

Results: Three distinct prognostic subgroups were notable on survival analysis: favorable (cutaneous ALCL), 5-year overall survival (OS) 78%; intermediate [PTCL, ALCL and angioimmunoblastic lymphoma (AILT)], 5-year OS 35–43%; unfavorable [NASAL and enteropathy-type T-cell lymphoma (ETTL)], 5-year OS 22–24%. Furthermore, in PTCL-US and ALCL clinical separation of patients into good risk (IPI 0,1) and poor risk (IPI ≥2) subsets was demonstrated.

Conclusions: A large proportion of PTCL patients have poor risk disease and/or a histologically aggressive subtype with frequent relapse and unfavorable outcome. For these patients, treatment with CHOP chemotherapy is only minimally effective and new strategies need to be developed, an effort that will require a multi-institution international collaboration due to the rarity of most subtypes.

Key words: peripheral, T-cell lymphomas, WHO classification, IPI

Introduction

Peripheral T-cell lymphomas (PTCLs) are an uncommon type of non-Hodgkin’s lymphoma (NHL) accounting for ~12–15% of all cases in the North American Caucasian population [1]. The importance of the distinction between the mature B- and T-cell lymphomas and the impact on prognosis has only recently been fully appreciated. Immunophenotypic information was not available in the working formulation [2], and the updated Kiel classification, although recognizing the T-cell phenotype, required sub-classification of PTCLs based on morphologic subtypes with poor reproducibility and failed to recognize several clino-pathological entities [3]. The REAL (Revised European–American Lymphoma) classification integrated morphologic, phenotypic, molecular and clinical information into a unified scheme for all lymphoid neoplasms [4] and provided the basis for the recently published WHO (World Health Organization) classification with several notable refinements: subdivision of T-cell lymphomas into predominantly leukemic, extranodal and nodal types; separation of cutaneous and systemic anaplastic large cell lymphomas (ALCL); updated terminology for some diseases [T-cell prolymphocytic leukemia, enteropathy-type T-cell lymphoma (ETTL), extranodal NK/T-cell lymphoma, nasal and nasal-type (NASAL)]; recognition of subcutaneous panniculitis-type and hepatosplenic γδ T-cell lymphomas as separate entities [5].

The prognostic significance of the T-cell phenotype has been reviewed with conflicting results. Some studies have demonstrated no outcome differences between B- and T-cell lymphomas [6–9], however, more recent and comprehensive studies have demonstrated that the T-cell phenotype imparts a negative impact on overall survival [1, 10–13]. The prognostic impact of T- versus B-cell phenotype appears to vary within the subgroups, with ALCL demonstrating a survival comparable to diffuse large B-cell lymphoma (DLBCL) [1, 12, 13]. However, even within this subgroup there is clear
biological heterogeneity. Some cases of systemic ALCL are associated with the expression of anaplastic lymphoma kinase (ALK), most commonly due to t(2;5)(p23;35) which fuses the ALK gene on 2p23 to the nucleophosmin gene on 5q35 [14]. ALCL patients whose lymphoma lacks expression of the ALK protein (ALK-neg) have a significantly worse outcome when compared to those whose lymphoma does express the protein (ALK-pos) [15, 16].

The International Prognostic Index (IPI) provides a prognostic score based on clinical and laboratory factors which have been validated in diffuse-large cell lymphoma and shown to accurately predict survival [17]. However, the influence of immunophenotype on survival was not evaluated because insufficient immunophenotypic data were available when the IPI was designed. The IPI has since been applied in several studies to PTCLs and it appears to predict outcome, independent of the T-cell phenotype [12], although many studies did not specifically examine the impact of the IPI for specific PTCL subgroups [11, 18].

The purpose of this study was three-fold. First, to review all PTCLs at a single institution where they were staged and treated according to standard guidelines after histologic assignment according to the WHO classification. Secondly, to analyze the various histologic subtypes with respect to presenting clinical features, response to treatment and survival. Thirdly, to test the predictive validity of the IPI, and, in the case of ALCL, ALK protein expression. The overall goal was to characterize the spectrum of T-cell lymphomas seen in North America, emphasizing the unique behavior of specific entities making up this family of related but quite distinct diseases.

Patients and methods

Patients

The computerized database of all lymphoma patients with adequate clinical and immunophenotypic records seen at the British Columbia (BC) Cancer Agency from 1 January 1980 to 1 May 2000 was searched to identify adult patients with a lymphoproliferative disorder and a proven T-cell phenotype. In total, 355 patients were found. Diagnoses were based on a combination of routine histology, immunohistochemistry and molecular genetics and, when fresh tissue was available, flow cytometry and cytogenetics. All cases were reviewed and re-classified according to the WHO classification by an experienced hematopathologist (R.D.G., M.C.).

Patients were excluded if less than 15 years of age (n = 1), or if the diagnosis was made outside of British Columbia (n = 19). Of the remaining 335 cases, the following T-cell diseases (n = 136) were excluded to limit analyses to the group of diseases usually referred to as PTCLs: lymphoblastic lymphoma (n = 28); mycosis fungoides (n = 75); T-cell PLL/CLL (n = 6); adult T-cell leukemia (HTLV-1 positive) (n = 3); lymphomatoid papulosis (n = 6); T-cell granular lymphocytic leukemia (large granular lymphocytosis) (n = 13); atypical lymphoid hyperplasia (n = 5). For the ALCL subtype, it is important to note patients with a null-cell phenotype were excluded as the original database screen included only those patients with a proven T-cell phenotype.

Clinical data were reviewed on the final group of 199; ALK protein expression was determined, when possible, in the ALCL subgroup and patients were assigned either an ALK-pos or ALK-neg designation. The IPI was calculated in subgroups with more than five patients using previously defined factors [17]: age (≤ 60 or > 60 years); performance status (PS; 0 or ≥ 2); stage (I/II or III/IV); serum LDH (normal or elevated); number of extranodal sites of involvement (≥ 1 or > 1). Patients were divided into three groups on the basis of the IPI score: low risk (0, 1 factor); intermediate risk (2, 3 factors); high risk (4, 5 factors). Survival analyses using the IPI were limited to subgroups with more than 10 patients. When LDH was not available it was assumed to be normal (n = 11). In one case, PS and stage were not available and, therefore, were assumed to be in the most favorable groups, that is, PS 0/1 and stage I/II.

Complete response (CR) was defined as disappearance of all evidence of disease as determined by clinical, radiographic and laboratory parameters. Partial response (PR) was defined as a reduction of 50% or more of measurable disease. No response (NR) was any response less than a PR. Progressive disease (PD) was defined as the recurrence of previously evident disease that had responded, measurable increase in known disease or the development of disease at a new site.

Outcome analysis and statistical methods

Overall survival (OS) was calculated from the date of diagnosis to death from any cause or last follow-up visit. Progression free survival (PFS) was determined from the date of diagnosis to the date of disease progression or recurrence or death from toxicity with patients dying from causes unrelated to lymphoma censored at the time of death. Survival curves were estimated according to the method described by Kaplan and Meier [19]. Survivals according to the IPI in subgroups with more than 10 patients and ALK expression in the ALCL subgroup were compared using the log-rank method [20].

Assessment of morphology, phenotype and genotype

Three-micron tissue sections were cut from B5 and formalin-fixed paraffin embedded tissue and stained with hematoxylin and eosin. Immunoperoxidase staining was performed using the streptavidin–biotin complex method, with microwave antigen retrieval and trypsin pre-treatment used as necessary. The stains done included CD3, 5, 15 (Leu M1), 20 (L26), CD21, 30 (Ber H2), 43 (MT1), 45 (LCA), 45RO (A6), Alk-1 and Tdt. Tissue, peripheral blood and bone marrow samples were analyzed using a direct antibody-labeling technique by flow cytometry with antibodies to CD2, 3, 4, 5, 7, 8, 10, 16, 19, 20, 45, 56, 57, kappa, lambda and FMC-7. Tdt was analyzed on relevant cases demonstrating a blastic morphology. All flow cytometry studies were performed using a Coulter EPICS Elite/ XL-MCL flow cytometer and the analysis was restricted to a gated population of abnormal cells. Two-color analysis was used for cases prior to 1998 whilst cases after this time were studied using three-color analysis. Gene rearrangement analysis by PCR was done using previously described methods from fresh frozen or formalin-fixed tissue [21]. Southern blot analysis was performed in cases where PCR results were equivocal [21]. ALK-pos or ALK-neg status was determined using routine immunohistochemistry utilizing the monoclonal ALK-1 antibody. A designation of ALCL was made for cases with typical morphology, a T-cell phenotype and/or genotype and uniform, strong expression of CD30. Cytogenetic studies were performed on selected cases using previously described techniques [22].

Results

Clinical features

Patient characteristics and extranodal sites of disease involvement are shown in Tables 1 and 2, respectively. There were
199 patients in total, 119 men and 80 women. Complete clinical and laboratory data were available on most patients (94%). Serum LDH level at diagnosis was not available in 11 cases. Cal and laboratory data were available on most patients (94%).

The most common histologic subtype was PTCL-US (n = 117, 59%). Patients frequently had advanced stage and extranodal disease involvement, particularly in the bone marrow and skin (Table 2). The next most predominant subtype was ALCL (n = 33, 17%) with ALK protein status available for 30 patients (18 ALK-neg, 12 ALK-pos). Analysis of the clinical features of the ALK-pos group versus the ALK-neg group revealed some differences. ALK-neg patients tended to be older, with elevated LDH, more frequent visceral disease involvement and intermediate/high risk IPI group assignment. Not surprisingly, patients with cutaneous AILT (CUTALCL) (n = 9, 8%) were also predominantly in the low risk IPI group.

Nasal involvement was seen at a higher frequency than prior North American reports (n = 17, 9%) [23], most likely due to the high proportion of Asians in our referral population. There were nine Asians, seven Caucasians and one Native Indian patient. Five had disease localized to the nasal region, while the other patients demonstrated a range of extranodal sites. The majority had low risk disease by the IPI (Table 1).

The remaining subtypes were all uncommon: angioimmunoblastic T-cell lymphoma (AILT) (n = 10, 5%); ETTL (n = 9, 5%); subcutaneous panniculitis-like T-cell lymphoma (SPTCL) (n = 4, 2%). Patients with AILT and ETTL were older, with advanced stage, B symptoms, elevated LDH, poor PS and bone marrow involvement. These subtypes were intermediate or high risk by the IPI (Table 1). Finally, the small group of patients with SPTCL had a mixture of prognostic features.

### Table 1. Characteristics of 199 patients with peripheral T-cell lymphoma according to histologic subtype [n (%)]

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gender</th>
<th>Median age (years)</th>
<th>B Symptoms</th>
<th>Stage</th>
<th>LDH &gt; normal</th>
<th>Performance status</th>
<th>IPI risk</th>
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<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>I/II</td>
<td>III</td>
<td>IV</td>
<td>0.1</td>
<td>≥ 2</td>
</tr>
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<td>7 (78)</td>
<td>2 (22)</td>
<td>66</td>
<td>0</td>
<td>7 (78)</td>
<td>0</td>
</tr>
<tr>
<td>PTCL-US</td>
<td>117 (59)</td>
<td>71 (61)</td>
<td>46 (39)</td>
<td>64</td>
<td>44 (38)</td>
<td>38 (33)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>ALCL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33 (17)</td>
<td>19 (58)</td>
<td>14 (42)</td>
<td>42</td>
<td>22 (67)</td>
<td>16 (48)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>ALK-pos</td>
<td>12 (36)</td>
<td>8 (67)</td>
<td>4 (33)</td>
<td>32</td>
<td>10 (83)</td>
<td>5 (42)</td>
<td>4 (33)</td>
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<tr>
<td>ALK-neg</td>
<td>18 (55)</td>
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<td>55</td>
<td>10 (56)</td>
<td>9 (50)</td>
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<td>NASAL</td>
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<td>10 (59)</td>
<td>7 (41)</td>
<td>47</td>
<td>6 (35)</td>
<td>11 (65)</td>
<td>1 (7)</td>
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<tr>
<td>SPTCL</td>
<td>4 (2)</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>49</td>
<td>2 (50)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AILT</td>
<td>10 (5)</td>
<td>4 (40)</td>
<td>6 (60)</td>
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<td>8 (80)</td>
<td>0</td>
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<tr>
<td>ETTL</td>
<td>9 (5)</td>
<td>6 (67)</td>
<td>3 (33)</td>
<td>61</td>
<td>7 (78)</td>
<td>3 (33)</td>
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</tbody>
</table>

<sup>a</sup>n(%) data not available: LDH, n = 11; performance status, n = 1; stage, n = 2; B symptoms, any one of fever >38°C, night sweats or weight loss >10% body weight.

<sup>b</sup>ALK (anaplastic lymphoma kinase) data only available in 30 cases.

<sup>c</sup>International Prognostic Index (IPI) risk scores determined for histologic subtypes with more than five patients.

AILT, angioimmunoblastic T-cell lymphoma; ALCL, T-cell systemic anaplastic large cell lymphoma; CUTALCL, cutaneous ALCL; ETTL, enteropathy-type T-cell lymphoma; NASAL, extranodal NK/T-cell lymphoma, nasal type; PTCL-US, peripheral T-cell lymphoma unspecified; SPTCL, subcutaneous panniculitis-type PTCL.

### Treatment

Treatment regimens were heterogeneous for several reasons: this was not a prospective study but rather data were gathered over several treatment eras; patients presented with widely varying stages and sites of disease and, finally, physiologic compromise due to age, co-morbid illness or advanced disease often limited treatment options. The majority of patients were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) type chemotherapy: CUTALCL (78%); PTCL-US (76%); ALCL (91%); AILT (90%); ETTL (89%); NASAL (71%). In 1990, having recognized the adverse impact of the T-cell phenotype on survival, we attempted to improve outcome by employing an intensified chemotherapy regimen (ECV) consisting of: etoposide 2100 mg/m²; cyclophosphamide 5400 mg/m²; vincristine 1.2 mg/m² on day 8 and day 22; with G-CSF (filgrastim) support, administered after 4 cycles of induction therapy with CHOP. In total, 32 patients received this regimen but, disappointingly, there was no gain in efficacy (results not shown) and these patients were included in the above proportions of patients who received CHOP-type treatment and in the summary of outcomes below. Radiation was utilized in all cases of NASAL subtype presenting with localized disease, including two patients for whom it was the sole treatment. In the ETTL subgroup, one patient had surgery only as primary treatment. Patients who had sinus involvement with any histological subtype received intrathecal chemotherapy. Of note, two patients were initially diagnosed as having Hodgkin’s lymphoma. One received MOPP/ABV...
Table 2. Sites of extranodal involvement according to histologic subtypes [n (%)]

<table>
<thead>
<tr>
<th></th>
<th>CUTALCL</th>
<th>PTCL-US</th>
<th>ALCL</th>
<th>ALK-pos</th>
<th>ALK-nega</th>
<th>NASAL</th>
<th>SPTCL</th>
<th>AILT</th>
<th>ETTL</th>
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<tr>
<td>n</td>
<td>9</td>
<td>117</td>
<td>33</td>
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<td>18</td>
<td>17</td>
<td>4</td>
<td>10</td>
<td>9</td>
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<tr>
<td>Bone marrow</td>
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<td>31 (26)</td>
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<td>4 (22)</td>
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<td>1 (25)</td>
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<td>Skin</td>
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<td>21 (18)</td>
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<td>0</td>
<td>4 (22)</td>
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<td>2 (50)</td>
<td>2 (2)</td>
<td>1 (11)</td>
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<td>Soft tissue</td>
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<td>3 (25)</td>
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<td>10 (9)</td>
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<tr>
<td>Extranodal (any)</td>
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<td>91 (78)</td>
<td>24 (73)</td>
<td>7 (58)</td>
<td>15 (83)</td>
<td>17 (100)</td>
<td>4 (100)</td>
<td>7 (70)</td>
<td>9 (100)</td>
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<td>10 (30)</td>
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<td>8 (44)</td>
<td>8 (47)</td>
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<td>3 (33)</td>
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aALK data available in 30 cases of ALCL.
For abbreviations, see Table 1.

Table 3. Response to therapy, overall survival, progression-free survival and overall survival by the International Prognostic Index (IPI)

<table>
<thead>
<tr>
<th>Histologic subtype</th>
<th>ORR (CR) rate %</th>
<th>5-year OS %</th>
<th>5-year PFS %</th>
<th>5-year OS % by IPI risk a</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
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<tr>
<td>Favorable</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CUTALCL</td>
<td>100(89)</td>
<td>78</td>
<td>56</td>
<td>NA</td>
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<tr>
<td>Intermediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PTCL-US</td>
<td>84(64)</td>
<td>35</td>
<td>29</td>
<td>64</td>
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<tr>
<td>ALCL</td>
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<td>43</td>
<td>28</td>
<td>66</td>
</tr>
<tr>
<td>AILT</td>
<td>90(70)</td>
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<td>NA</td>
</tr>
<tr>
<td>Unfavorable</td>
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<td>38</td>
</tr>
<tr>
<td>ETTL</td>
<td>78(33)</td>
<td>22</td>
<td>22</td>
<td>NA</td>
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</table>

aOverall survival by IPI calculated for histologic subgroups with >10 patients.
CR, complete response; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
(mechloretamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine) (correct diagnosis, PTCL-US) and the other ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) (correct diagnosis ALCL). One patient with AILT was originally diagnosed as having atypical hyperplasia and subsequently progressed and died before systemic treatment could be administered. Two patients, both with PTCL-US, were too ill at diagnosis to receive any treatment.

**Treatment response and survival**

Treatment responses and survival data are shown for subgroups with more than five patients in Table 3 and Figure 1. Three groups emerge with clearly distinguishable survival outcomes. Thus, the PTCLs can be divided into three prognostic groups: favorable, intermediate and unfavorable.

**Favorable group**

Only the CUTALCL patients have a truly favorable prognosis with a high CR rate (89%) and excellent 5-year OS (78%). Indeed, one patient who was treated with primary surgery only and refused further systemic treatment is free of disease more than 3 years from initial diagnosis. PFS was lower than OS, indicating that relapse is common and that secondary regimens are effective in this group. Four patients relapsed, one following chemotherapy, one following surgery only and two following combined chemotherapy and radiation.

**Intermediate group**

The group with intermediate survivals includes patients with PTCL-US, ALCL or AILT. For PTCL-US the overall CR rate was 64%, however, 5-year OS was poor (35%). One patient died during treatment, of septic shock, and therefore was not assessable for response. Three other patients died as a result of treatment toxicity, all related to infection. Five patients underwent high dose chemotherapy followed by bone marrow transplant for relapsed disease (two autologous, three allogeneic) with three long-term survivors: one autologous transplant (alive and well 6 years after transplant), two allogeneic (alive and well 3 and 6 years after transplant).

The 5-year OS for ALCL patients was somewhat superior compared to the other groups, however, relapse was common. The ALK-pos group (5-year OS, 58%) fared better than the ALK-neg group (5-year OS, 34%) \((P=0.35)\) (Table 3). Two patients received an allogeneic transplant due to progressive disease on initial CHOP treatment, one of which died of progressive disease and the other remains disease-free \(~8\) years after transplant. Three patients received an autologous bone marrow transplant at relapse following initial treatment with CHOP, however, only one remains in a sustained remission 2 years after transplant. Interestingly, two patients with systemic ALCL relapsed with cutaneous-only disease and refused further therapy but remain alive 17 months and 4 years, respectively, following recurrence.

In the AILT subgroup, the overall CR rate was 70%, however, the majority of these patients relapsed. Similar to ALCL,
the 5-year OS of 36% was superior to the PFS (13%) suggesting that salvage therapy was effective in some cases.

**Unfavorable group**

Both the NASAL and ETTL subgroups had very unfavorable outcomes. In the NASAL group, despite a reasonable CR rate (73%), relapse was frequent and salvage regimens ineffective, with a 5-year OS of only 24%. Two patients died while receiving treatment, both due to infections, and were not considered in response assessment. Only three patients had a sustained CR following treatment with combined modality therapy. All but one of the patients who relapsed died of their disease between 2 and 15 months from the date of progression.

Complete responses were rare in the ETTL group and secondary treatments were ineffective. Only one patient with early stage disease, no B symptoms and a normal LDH is alive and free of disease 7 years from original treatment with CHOP-type chemotherapy.

Survival data according to the IPI risk groups for subtypes with more than 10 patients (PTCL-US, ALCL and NASAL) are shown in Table 3 and Figures 2–5. In PTCL-US, the IPI could predict survival, however, only two subgroups were identified: poor risk IPI ≥2 (5-year OS of 20%); low risk IPI 0, 1 (5-year OS of 64%) (P<0.00001) (Figure 2). Similarly, in ALCL, the same two risk groups were found: poor risk IPI ≥2 (5-year OS of 15–20%); low risk IPI 0, 1 (5-year OS of 65%) (Figure 3) (P=0.006). The IPI was also applied to the ALK-pos and ALK-neg cases within ALCL (Figure 4). The majority of patients with ALK-pos disease fell into the low risk IPI group and had an excellent 5-year OS (75%). However, the remainder had an IPI score of ≥2 and 5-year OS of 25%. Within the ALK-neg group, those in the low risk group had an intermediate survival rate at 5 years of 50%; however, those with an IPI score of >2 had a 5-year OS of 18%. In contrast, the IPI was not useful in the NASAL subtype and could not identify any subgroup with a better prognosis (Figure 5).

**Discussion**

There is little information on the comparative natural histories or appropriate management of PTCLs due to the wide diversity of the histologic subgroups, and disease rarity has limited the experience at any one institution. The prognostic significance of the T-cell phenotype has been confirmed, however, due to the unique features of the specific PTCL subtypes; combining dissimilar T-cell lymphomas under the term ‘PTCL’ potentially obscures their heterogeneous behavior and response to treatment. In fact, as shown in this study, some PTCLs have a highly favorable outcome, some have an intermediate prognosis while others have a very poor prognosis.

To our knowledge, the present study is the largest series to date of PTCLs from a single institution sub-classified according to the WHO classification [5]. The most frequently identified histologic subtype, PTCL-US, had an intermediate prognosis with a 5-year survival of 35%, consistent with other reports [1, 10, 12, 13]. Attempts have been made to identify prognostic subgroups within this morphologically and, likely, biologically heterogeneous PTCL subtype. Chemokine receptor expression patterns have been correlated with outcome [24], where cases positive for CCR5, CXCR3 or ST2(L) (IL-1R family) appear to have a more favorable prognosis but the functional significance is unknown. Further, high blast counts correlate with poor failure-free survival, however this observation remains to be reproduced [25]. Prior studies have found the IPI effective in predicting outcome in patients with T-cell lymphoma as defined by either the Kiel or the REAL classification [11–13, 18, 26]. However, many of these studies evaluated all histologic subtypes together, thus obscuring the impact of the prognostic model in specific disease entities [11, 18, 25]. In the current study the IPI was highly predictive of survival in PTCL-US, however, only two groups were identified: low risk (IPI 0, 1; 5-year OS 64%) and poor risk (IPI ≥2; 5-year OS 30%). Two other studies have also specifically addressed the utility of the IPI in the PTCL-US subtype according to either the REAL [13] or WHO classification [27]. Like the current report, one group found a superior survival in the low risk group (IPI 0, 1; 5-year OS ~75%) [13].
Another prognostic model has recently been proposed for PTCL-US, which incorporates many of the current IPI factors (age, PS, LDH) but also determined that bone marrow involvement correlated with survival in multivariate analysis [27]. With the widespread familiarity of the IPI and consistent predictability of survival across studies, it still appears to be the best current prognostic model in PTCL. Unfortunately, it appears that for PTCL-US only about one-third of patients have low risk disease and for all others current treatment protocols are only minimally effective.

Systemic T-cell ALCL also had an intermediate prognosis and we observed a survival lower than the published literature where estimates have been closer to DLBCL [13, 28]. It is important to note that many prior studies are based on the REAL classification without clear separation of primary cutaneous ALCL from the primary systemic form and/or did not specify ALK status, leading in some cases to an over-estimation of survival. Further, we encountered a higher proportion of ALK-neg cases in our series, for which we have no clear explanation. This likely influenced our modest cure rates as this phenotype has a confirmed negative prognostic influence [16, 29]. A review of more recent cases reveals a frequency of ALK-pos ALCL of ~75%, which more closely reflects the current literature. Prognostic evaluation of either low risk IPI (0, 1) and/or ALK-pos patients confirmed a superior survival than those with poor risk (IPI ≥2) or ALK-neg status. Other studies have also applied the IPI to patients with systemic ALCL and, like ours, have found identifiable groups with different prognoses [15].

The IPI remained predictive in the ALK-pos and ALK-neg subgroups, although survival differences between the risk groups were more striking in the ALK-pos group. Clearly, both ALK expression and clinical factors must be considered in ALCL to estimate prognosis and should guide future treatment strategies.

In contrast to systemic ALCL, we found that the cutaneous type of ALCL had a very favorable prognosis, confirming prior reports [30], and the relapsing nature suggests this is an indolent PTCL subtype. Careful identification of this subtype is necessary to avoid exposing patients to systemic therapy.

The final subtype in the intermediate prognostic group is AILT. Like others, we found that these patients tend to have an intermediate or high risk assignment by the IPI and poor OS [31]. We were unable to evaluate the predictive value of the IPI due to low patient numbers in this subtype; however, given the absence of a low risk group by the IPI, it is unlikely to be of value.

The two remaining histologic subtypes, ETTL and NASAL, fall into an unfavorable prognostic group. Patients with ETTL are often compromised nutritionally making treatment delivery difficult and have a significant risk of bowel perforation, both at presentation and during treatment, further complicating management. Similar to our results, other investigators have reported low CR rates and poor outcome with long-term survivors after chemotherapy being rare [32]. In our experience, secondary treatments were unsuccessful and no patients underwent high-dose chemotherapy and stem cell transplant, due to advanced age and poor fitness level.

NASAL is uncommon in Western populations [33]. At our institution, a large fraction of the population is of Asian descent and this may have increased the frequency relative to other North American cities. Despite favorable presenting clinical features the 5-year OS was only 24%, consistent with prior reports [34]. Further, the IPI failed to differentiate a group with a more favorable prognosis. Another study also did not find any utility of the IPI in localized NK/T-cell lymphomas [34]. However, in contrast, a recent report which also included more patients with advanced stage disease did find that the IPI could define prognostic subgroups [35]. The discrepancy between these studies is unclear but may reflect the relatively high proportion of patients that present with low risk IPI scores, limiting the usefulness of the index [34]. Many investigators advocate upfront radiotherapy in the management of these patients [34, 35] and, similarly, we found that directed radiotherapy reduced local relapse rates.

CHOP-type chemotherapy is the standard treatment for DLBCL. However, it appears to be much less effective for the treatment of the majority of PTCLs. In most studies, including ours, CR rates are low and relapse is common [10, 36]. We attempted to use a highly intensified chemotherapy regimen to improve outcome, but it failed to demonstrate a significant improvement over CHOP-type chemotherapy. Other studies have investigated the role of intensified treatment in poor risk patients, some of which included patients with PTCL [9]. Karakas et al. [9] found that PTCL patients (by the updated Kiel classification) treated with a higher dose intensity regimen, had a 5-year OS of 48%, similar to that found in the comparison group of B-cell lymphomas. However, this was a young population (median age 53 years) and many had ALCL, thus may have been a better risk group. Simple dose escalation may be ineffective at improving survival in this poor risk group.

The role of high-dose chemotherapy and hematopoietic transplantation in the treatment of PTCL is unknown. Small uncontrolled transplant trials in PTCL are heterogeneous with respect to: usage of different lymphoma classification systems; inclusion of varied histologic subtypes; transplant type; salvage and conditioning regimens; evaluation of the role of transplant in both primary therapy and in relapsed patients as well as inclusion of pediatric cases in some analyses [37–40]. With respect to primary transplant in poor risk patients, some reports suggest more favorable results in ALCL, but in the absence of a definitive randomized study, this therapy remains experimental in this patient population [39, 40].

For many PTCL patients, current treatment strategies are largely ineffective and new treatments are needed. Gemcitabine has shown activity in relapsed PTCLs as a single agent prompting consideration of new combinations [41]. Recently, 13-cis retinoic acid showed encouraging results in heavily pretreated patients [42] and depsipeptide, an inhibitor of histone deacetylation has demonstrated activity in PTCL patients and trials with this agent are ongoing in this population [43].
Recently, immunotherapy has emerged as an important adjunct to traditional cytotoxic chemotherapy in B-cell lymphomas [44] but experience in TCLs has been limited. Alemtuzumab, a humanized monoclonal antibody directed against the CD52 antigen, is widely expressed but concerns of profound immunosuppression have restricted combination with chemotherapy.

Gene expression profiling has been applied to DLBCL, further defining molecular differences in this heterogeneous disease and elucidating new therapeutic targets [45, 46]. Microarray technology has been evaluated in cutaneous T-cell lymphomas [47] but would be of great value in the PTCLs, particularly in the diverse PTCL-US subgroup, to aid in identifying new prognostic markers and elucidating biologic targets for therapy.

This large single institution series emphasizes the heterogeneity of PTCLs and the need to consider each subtype separately when evaluating new prognostic factors and developing treatment strategies. We were able to delineate three distinct groups of PTCLs: favorable (CUTALCL), intermediate (AILT, ALCCL and PTCL-US) and unfavorable (ETTLL, NASAL). Furthermore, in the more common subtypes of PTCL-US and ALCCL, both ALK-pos and ALK-neg, we could demonstrate clinically helpful separation of patients into good risk (IPI 0, 1) and poor risk (IPI ≥2) subsets. For the majority of patients with PTCL, treatment with conventional CHOP chemotherapy is ineffective and new strategies need to be developed, an effort requiring multi-institution collaboration due to the rarity of most subtypes.

### References

9. Karakas T, Bergmann L, Stutte HJ 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.


