Peripheral T-cell lymphoma

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Abstract

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of clinically aggressive diseases associated with poor outcome. Studies that focus specifically on PTCL are emerging, with the ultimate goal of improved understanding of disease biology and the development of more effective therapies. However, one of the difficulties in classifying and studying treatment options in clinical trials is the rarity of these subtypes. Various groups have developed lymphoma classifications over the years, including the World Health Organization, which updated its classification in 2008. This article briefly reviews the major lymphoma classification schema, highlights contributions made by the collaborative International PTCL Project, discusses prognostic issues and gene expression profiling, and outlines therapeutic approaches to PTCL. These include the standard chemotherapeutic regimens and other modalities incorporating antifolates, conjugates, histone deacetylase (HDAC) inhibitors, monoclonal antibodies, nucleoside analogs, proteasome inhibitors, and signaling inhibitors. As this review emphasizes, the problem has now evolved into an abundance of drugs and too few patients available to test them. Collaborative groups will aid in future efforts to find the best treatment strategies to improve the outcome for patients with PTCL.
Introduction

Peripheral T-cell lymphomas (PTCL), a subdivision of T-cell non-Hodgkin’s lymphomas (NHLs) and distinct from the more common cutaneous T-cell lymphomas, are a diverse group of disorders that for the most part carry a poor prognosis. Classification of PTCL is complex, has resulted in many classification schemes, and has been further hampered by a paucity of molecular markers. Older lymphoma classification systems include the Rappaport system, which was used until the mid 1970s,1 the Kiel system, introduced in 1974,2 and the National Cancer Institute’s Working Formulation (IWF), introduced in the 1980s.3 The work of Lukes, Collins, and Lennert in the 1970’s first suggested that the T-cell lymphomas should be identified as distinct from B-cell lymphoma, but this was initially met with skepticism. In 1994, the International Lymphoma Study Group (ILSG) proposed the REAL classification (revised European-American Classification of Lymphoid Neoplasms), which featured the major histologic, immunologic, and genetic characteristics of B- and T-cell neoplasms and Hodgkin’s lymphoma.4 A clinical evaluation of the ILSG classification of NHL published in 1997 concluded that the classification could be readily applied and identified clinically distinctive types of NHL.5

The International Lymphoma Epidemiology Consortium (InterLymph) proposed in 2007 a nested classification of lymphoid neoplasm subtypes.6 They based their classification on the World Health Organization (WHO) classification of lymphoid neoplasms7 and the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).8 The fourth edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues was published in 2008.9 The new WHO classification includes many additional subtypes of PTCL (Table 1);
nevertheless, it does not necessarily help clinicians determine the best therapeutic strategy for each specific subtype. The International PTCL Project is a collaborative effort that was designed to gain better understanding of the distribution and outcomes of aggressive T-cell lymphomas. A total of 22 institutions and over 1300 eligible patients in North America, Europe, and Asia participated in and submitted clinical and pathologic information on PTCL diagnosed and treated at their respective centers.10

Treatment advances in PTCL have been slow when compared to other lymphomas. Very often, PTCL patients are treated with the same therapy used in B-cell lymphomas, but this approach generally has a very poor outcome. Relapse is common following the administration of most currently available agents, and there are few effective options for salvage therapy. In addition, only small numbers of patients have each type of PTCL, which further complicates studying new treatments for these diseases in clinical trials.

Classification

The WHO classification system classifies the mature T-cell lymphomas into four groups based on their clinical features. Most of the aggressive T-cell lymphomas are included within the nodal, extranodal, and leukemic groups.

The nodal lymphoma group includes PTCL, not otherwise specified (NOS), accounting for 25.9% of cases,10 anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL). ALCL is further separated into the ALK+ and ALK- entities. The ALK- ALCL are morphologically and immunophenotypically similar to ALK+ ALCL, but lack ALK expression and have distinctive molecular features.11 According to the International PTCL study, ALK+ ALCL accounts for 6.6% and ALK- ALCL for 5.5% of PTCL cases.10 The cutaneous ALCL are included as a separate disease entity because their treatment and prognosis are distinct
from the systemic ALCLs. Angioimmunoblastic T-cell lymphoma is the second largest category, accounting for 18.5% of cases in the International T-cell project.\textsuperscript{10} The lymphoepithelioid cell variant appears to be distinct from the others and is usually characterized by CD8\textsuperscript{+} T cells and a predominance of epithelioid cells in the background.\textsuperscript{12}

The extranodal group includes a number of less common entities described primarily by their tissue tropism. Hepatosplenic gamma-delta T-cell lymphoma is a disease of children and young adults\textsuperscript{13,14} accounting for 1.4% of PTCL cases.\textsuperscript{10} This tumor is derived from immature or non-activated gamma-delta T cells which infiltrate the liver, spleen, and bone marrow sinusoids. A characteristic chromosomal abnormality is isochromosome 7q, and patients with hepatosplenic T-cell lymphoma often have a poor outcome with a median survival of less than 2 years. The disease is more common in young males who often present with B-symptoms and cytopenias. The cells are typically CD2\textsuperscript{+}, CD3\textsuperscript{+}, CD4\textsuperscript{−}, CD5\textsuperscript{−}, CD7\textsuperscript{+}, CD8\textsuperscript{+} or CD8\textsuperscript{−} and may express NK-markers as well.

Enteropathy-associated T-cell lymphoma (EATL) accounts for 4.7% of cases of T-cell lymphoma.\textsuperscript{10} EATL is more common in geographic areas with a higher incidence of celiac disease, as evidenced by the fact that it represents 5.8% and 9.1% of the PTCLs in North America and Europe, but only 1.9% of those in Asia. The disease often presents with pain, weight loss, and bowel perforation. There are two morphologic variants that are the pleomorphic type, associated with celiac disease and usually CD3\textsuperscript{+}, CD7\textsuperscript{+} and CD56\textsuperscript{−}, and the monomorphic type, which is CD56\textsuperscript{+} and often not associated with celiac disease.\textsuperscript{15} Chromosomal abnormalities found in EATL include gains at chromosome 9q33-q34 in up to 70% of cases.\textsuperscript{16} The intestinal T- and NK-cell lymphomas diagnosed in Asian countries are associated with Epstein-Barr virus (EBV) infection and are part of the spectrum of nasal-type natural killer
The mucocutaneous gamma-delta T-cell lymphomas,\textsuperscript{18} the nasal type NK/T cell lymphomas, and even ALCL can present as an intestinal lymphoma.\textsuperscript{19,20}

Panniculitis-like T-cell lymphomas constitute only 0.9\% of PTCLs, and in the International Peripheral T-cell Lymphoma Project were more common in men (75\% of cases) than in women. Patients usually present with subcutaneous nodules that may become necrotic. The neoplastic cells are typically CD3\textsuperscript{+}, CD4\textsuperscript{-}, and CD8\textsuperscript{+}, with either TCR-\[\text{alpha}]\textsuperscript{+}/\[\text{beta}]\textsuperscript{+} or TCR-\[\text{gamma}]\textsuperscript{+}/\[\text{delta}]\textsuperscript{+} and infiltrate in a rim-like fashion around the fat cells. The gamma/delta panniculitis-like T-cell lymphomas have now been reclassified as cutaneous gamma/delta T-cell lymphoma because their outcome is significantly inferior to that of patients with the alpha/beta type.\textsuperscript{21}

The leukemia group consists of adult T-cell lymphoma (ATL) associated with human T-lymphotropic virus type I (HTLV-1), T-cell chronic large granular lymphocytic (LGL) leukemia, aggressive NK-cell leukemia, and T-cell prolymphocytic leukemia. Most patients with LGL leukemia have an indolent disorder that is often associated with neutropenia and that can be treated with immunosuppressive agents, while those with aggressive NK cell leukemia and ATL often have a poor outcome.

Several other types are delineated in the WHO classification: hydroa vacciniforme-like lymphoma, which is usually of a T-cell origin, NK-cell lymphoma caused by mosquito bite allergy, and systemic EBV-positive T-cell lymphoproliferative disease of childhood, which is part of the spectrum of chronic, active EBV infection.

\textbf{Incidence of T-cell Lymphomas}
Based on the US SEER registry, the incidence of PTCL is less than 1 case per 100,000 people in the United States. Results from the International PTCL Project showed that around the world, the most common subtypes are the nodal T-cell lymphomas, with PTCL-NOS (25.9%) being the most frequent, along with angioimmunoblastic T-cell lymphomas (18.5%) and the anaplastic large-cell lymphomas (12%). NK/T-cell lymphomas comprised 10.4%, while enteropathy-associated T-cell lymphomas (4.7%), hepatosplenic T-cell lymphomas (1.4%), and panniculitis-like T-cell lymphomas (0.9%) were rare, even in this large study. Among the common subtypes, there are regional differences in frequency. PTCL-NOS is more common in North America and less common in the European and Asian countries; AITL is more common in Europe than in Asia or North America; ALK+ ALCL is more common in North America; ALK- ALCL is slightly more common in Europe; and the NK/T-cell lymphomas and ATL are more common in Asia. The epidemiology of EATL is closely associated with the human leukocyte antigen DQ, which results in either overt or silent celiac disease, a European disease. The EBV-associated lymphoproliferative, T-cell, and NK-cell neoplasms are seen mainly in Japan, Korea, and Northern China, but also in Native American populations from Central and South America. NK-cell nasal and nasal-type lymphomas, occurring more frequently in Asia and Latin America, have a greater incidence in males than in females.

**Viral associations with T-cell lymphomas**

The increased incidence of T/NK cell lymphomas in East Asia related to the frequency of endemic HTLV-1 and Epstein-Barr viral infections. The HTLV-1 virus was first identified by Gallo’s group at the National Cancer Institute from a cell line established from a patient with cutaneous T-cell lymphoma. At the same time, Yoshida et al in Japan identified a retrovirus
that was immunoreactive to sera from patients with T-cell leukemia.\textsuperscript{26} The unique genome structure of HTLV-1 identified it as distinct from any other animal retroviruses, thus founding a new retroviral group. Other members of this viral group include HTLV-2, STLV, and BLV. Viral transmission is thought to require the transfer of live infected T lymphocytes, that is, T cells in breast milk, T cells in semen, and fresh T cells in blood carriers of HTLV-1 proviruses.

\textbf{HTLV-1-associated lymphoma}

HTLV-1-associated lymphomas include adult T-cell leukemia-lymphoma (ATL), smoldering ATL, which is characterized by small numbers of circulating leukemia cells without nodal involvement, lymphomatous ATL, which presents with lymphadenopathy without leukemic involvement, and chronic ATL which is characterized by skin lesions, leukemic, nodal and visceral disease without hypercalcemia, GI involvement, bone, or CNS disease. The geographic distribution is reflective of the areas where HTLV-1 infections are prevalent, specifically Japan and the Caribbean basin. ATL is characterized by a clonal expansion of CD4\textsuperscript{+} T lymphocytes frequently associated with skin rash, lymph node and visceral involvement, and hypercalcemia. It is suggested that the transformation of T cells in the early stages of ATL is mediated by HTLV-1 Tax protein and persistent NF-κB activation.

\textbf{Angioimmunoblastic T-cell lymphoma}

AITL shows distinctive features, with a polymorphous infiltrate containing medium-sized neoplastic cells, prominent arborizing blood vessels, proliferation of follicular dendritic cells, and scattered EBV\textsuperscript{+} B-cell blasts.\textsuperscript{27} Recent studies indicate that AITL is derived from the unique T-cell subset located in the germinal center, which are called the follicular helper T cells (T\textsubscript{FH}).\textsuperscript{28-31} Viruses have been implicated in the transformation of these T\textsubscript{FH} cells. Besides EBV, which is found in B-cell blasts and is likely to play a role in the development of an EBV-associated B-cell
lymphoma in some AITL patients, HHV6B, another human herpes virus, has been reported in around half of AITL cases. Although viral infection most likely reflects the underlying immune dysfunction, it could also suggest that EBV and/or HHV6B may modulate cytokines, chemokines, and membrane receptors.

NK/T cell lymphoma

NK-cell lymphomas include extranodal NK/T-cell lymphoma, nasal type, blastic NK-cell lymphoma, and aggressive NK-cell leukemia account for 10.4% of PTCL cases. Most NK-cell lymphomas have been recognized and are included in the classification of lymphoid neoplasms, but some other NK-cell lineage neoplasms are not yet categorized by the WHO. These include myeloid/NK-cell precursor acute leukemia, precursor NK-cell acute lymphoblastic leukemia, and chronic reactive NK-cell lymphocytosis.32 EBV has been implicated and found in the tumor cells of nasal/NK-cell lymphomas and aggressive NK-cell leukemia.33 However, there may be other causative factors. In one recent study from China, the occurrence of epithelial carcinomas in 10 of 23 cases of NK/T cell lymphoma of the oral cavity suggests that other oncogenic factors may be implicated as well as EBV.34

Prognostic Features of T-cell Lymphomas

Overall, patients with PTCL had a very poor outcome when compared to patients with aggressive B-cell lymphomas.10 The International T-cell Lymphoma Study demonstrated that the overall survival (OS) and failure-free survival (FFS) with PTCL-NOS at 10 to 15 years was 10% (Figure 1). The International Prognostic Index (IPI), when applied to patients with aggressive T-cell lymphomas, identified a group with high IPI score who had an adverse outcome compared to patients with low IPI, similar to diffuse large B-cell lymphoma.35 However, even patients in the
best prognostic category did not have a favorable outcome, and patients in the highest risk
category had very short survival. When examined by histopathologic subset, the 5-year OS for
patients with PTCL-NOS and AITL with IPI of 0-1 were 56% and 50%, respectively, whereas
those with IPI of 4 or 5 were 11% and 25%, respectively. For patients with ALCL, the 5-year
survivals for IPI 0-1 patients were excellent at 90% and 74% for ALK+ and ALK- patients,
respectively; however, patients with IPI of 4-5 had a poor outcome with 5-year survivals of 33%
and 13%, suggesting that IPI is an important predictor, even in ALK+ patients.23 The IPI has not
been predictive of outcome in patients with ATLL, enteropathy associated and hepatosplenic T-
cell lymphoma, or extranasal NK/T cell lymphoma.

A new prognostic index specifically designed for PTCL,36 the prognostic index for
PTCL (PIT), is similar to the IPI, including age, LDH, performance status, and then bone
marrow involvement. When applied to patients with PTCL-NOS, the index separated patients
into more specific prognostic groups than the IPI. Of 322 patients studied, 20% had no adverse
features, 34% had one feature, 26% had two features, and 20% had three or more. The 5-year
overall survival for the most favorable group with no adverse prognostic features was 62%
compared to 18% for patients with 3 or 4 adverse prognostic factors.

Aside from conventional histopathology, chemokine expression and proliferative
signature have been shown to have prognostic significance, including p53 and Ki-67 (Table 2).
In one study, p53 was the most important prognostic factor and was correlated with expression of
p-glycoprotein, which confers resistance to chemotherapy.37 In addition, 40%-60% of patients
with PTCL express BCL2 and BCLX_{L} associated proteins.38 ALK+ ALCL is usually BCL2
negative, while other subtypes with worse outcomes may be BCL2+.
Two chemokine receptors, CXCR3 and CCR4, were found to be expressed in 63% and 34% of PTCL-NOS cancers, respectively. The dominant chemokine expression found in this study was CXCR3-positive/CCR4-negative; this phenotype was shown by multivariate analysis to be an independent prognostic factor and significantly prognostic of a poor prognosis in both PTCL-NOS and ALK-negative ALCL.

In a study reported by Rudiger et al of PTCL-NOS category, which excludes AITL, the presence of >70% transformed blasts, >25% Ki67 proliferation, CD56 and CD30 expression, EBV infection, and a background of >10% CD8+ cells were all adverse prognostic factors. The results indicated that immunophenotyping is absolutely necessary to determine prognosis. In another study, multivariate analysis of all prognostic factors indicated that, upon controlling for IPI, if the number of transformed cells is >70%, the hazard ratio for OS is 2.2 and 1.6 for FFS. In patients with ALCL, the presence of the small cell variant can be associated with a worse prognosis. Finally, the expression of cytotoxic molecules also has an adverse impact on survival.

Gene expression, cytogenetic and comparative genomic hybridization data

Several studies of gene expression profiling of PTCLs have been published. Importantly, expression profiling of purified normal T-cell subpopulations has provided the framework for understanding cell-of-origin and functional properties of T-cell malignancies. In aggregate, these studies have helped define the normal counterpart of several specific PTCLs, identified pathways frequently altered in PTCL, including NF-κB signaling and cell cycle deregulation, and highlighted the importance of proliferation as a potential biomarker for prognosis. However, most of these studies are largely underpowered to allow definitive statements regarding survival.
prediction. As described above, large sample sizes will be needed to build molecular outcome predictors in PTCL and will likely require international collaboration.

More recently, gene expression profiling studies of larger numbers of patients have been undertaken and do provide novel insights into several PTCL entities. Iqbal and colleagues studied 144 cases and were able to confirm several previous observations. Additionally they were able to show a major role for the microenvironment in AITL and developed a 15-gene outcome predictor highly correlated with survival and independent of the IPI. Similarly they discovered a subgroup of PTCL-NOS with cytotoxic characteristics and inferior survival. Huang and colleagues studied a much smaller number of extranodal NK/T cell lymphomas, nasal type by combining microarray analysis with array CGH. These authors established marked differences in gene expression in these tumors in comparison to normal NK cells, particularly the significant over-expression of granzyme H; provided evidence for over-expression of PDGFRA similar to PTCL-NOS; and suggested a possible role for the novel tumor suppressor gene, HACE1, mapping to the 6q21 region, in NK/T cell lymphomas.

Classical cytogenetic studies have also provided insight into copy number alterations in PTCL (Table 3). A recent study of PTCL-NOS, AITL, and ALK- ALCL revealed recurrent alterations associated with specific entities including gains of 5q, 21, and 3q in AITL, commonly associated with trisomies of chromosome 5 and 21. Loss of genetic material involving chromosome 6q was also frequent. ALK- ALCL was characterized by gains of 1q and 3p and losses of 16pter, 6q13-21, 15, 16qter, and 17p13. PTCL-NOS showed frequent gains of 7q22-31, 1q, 3p, 5p, and 8q24qter and losses of 6q22-24 and 10p13pter. Cases with a complex karyotype had shorter overall survival.
While many subtypes of PTCL are characterized by clonal expansion of TCR rearranged lymphocytes, this may not be a characteristic of all cases of NK neoplasms. Two studies recently examined the lack of TCR rearrangements in these patients and reported rearrangements at the TCR locus in 0.8%-1.2% of cases.61,62

Comparative genomic hybridization (CGH) was used to examine genomic alterations in patients with ALK+ and ALK- ALCL. A study of 74 patients showed that ALK+ ALCL samples had gains of 17p and losses of 4q13-q21 and 11q14, whereas gains of 1q and 6p21 were more frequent in ALK- samples.11 Another study, which used genomic profiling in patients with PTCL-NOS (n = 42) and ALK- ALCL (n = 37),63 showed that genetics of PTCL-NOS and ALK- ALCL differ substantially from other T-cell lymphomas, including EATL, T-cell prolymphocytic leukemia (PLL), and ATL. Those with PTCL-NOS had recurrent chromosomal gains, high-level amplifications, and recurrent chromosomal losses on 13q, 6q, 9p, 10q, 12q, and 5q. Cutaneous ALCL and ALK+ ALCL did not show imbalances, whereas ALK- ALCL showed chromosomal gains of 1q and losses of 6q and 13q.

Lastly, it is likely that significant progress in our understanding of the genetic complexity of PTCL will require an international effort to study a number of well annotated cases using next-generation sequencing strategies.64 It can safely be hypothesized that this approach will yield important information about recurrent mutations and novel fusions that underlie the critical events in the biology of these tumors. Matched constitutional DNA will be required to properly annotate all of the somatic changes.

**Therapeutic approaches**

*Standard first-line therapy*
T-cell lymphomas have traditionally been treated much like the B-cell lymphomas, with a combination chemotherapy regimen. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was the most widely used, although there were no randomized studies that proved that it was the best therapy. A retrospective meta-analysis of 2912 patients treated with CHOP or CHOP-like regimens reported a 5-year overall survival of 37%. Several groups have tried more intensive chemotherapeutic treatments for PTCL patients. The French Groupe d'Etude des Lymphomes de l'Adulte (GELA) used more intensive chemotherapy—ACVBP (dose-intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) plus consolidation with autologous stem cell transplant (ASCT) for younger, fitter patients. The German High Grade Non-Hodgkin’s Lymphoma Study Group (DSHNHL) used several variations of CHOP, and an Italian group used high-dose sequential chemotherapy with ASCT. The MD Anderson Cancer Center used an alternating triple therapy regimen and hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone). The GELA demonstrated that ACVBP had higher toxicity but superior event-free survival (EFS) and OS compared to CHOP. CHOP-14 proved superior to CHOP-21 or CHOP + etoposide (CHOEP) in elderly patients, and CHOEP should be used in younger patients.

Anthracycline-containing regimens for PTCL have been associated with median 5-year OS rates less than 40%. ALCL patients have better outcomes than non-ALCL patients, with an overall response rate (ORR) over 75% and 5-year OS rates over 60%. ALK+ ALCL patients have slightly higher OS and failure-free survival (FFS) rates compared to ALK- ALCL patients, but this may be due to a difference in age, as ALK+ patients tend to be younger than ALK- patients. However, even in ALK+ ALCL patients, 5-year FFS rates were only 49%, suggesting a definite need for new therapies or different subtype-specific treatments. It is unclear why patients
with aggressive T-cell lymphomas are less responsive to conventional B-cell lymphoma regimens, but data is emerging regarding the expression of p-glycoprotein and other drug resistance pathways in subsets of patients, particularly patients with NK/T-cell lymphomas.

**Novel approaches**

New therapeutic approaches and the incorporation of novel agents into these therapeutic regimens are necessary to improve the outcome for PTCL patients. Table 4 lists some of the new agents that are currently being used or are in clinical trials.

**Monoclonal antibodies and immunoconjugates**

The addition of the anti-CD20 monoclonal antibody (MAb) rituximab to chemotherapy regimens like CHOP has significantly improved treatment outcomes in B-cell lymphoma. As such, several monoclonal antibodies and targeted immunoconjugates and fusion proteins are currently being tested in PTCL, including alemtuzumab, iratumumab, siplizumab, zanolimumab, denileukin diftitox, and brentuximab vedotin.

Alemtuzumab, an anti-CD52 MAb, has been shown to have activity in heavily treated patients with PTCL with an ORR of 36% in one early study.\(^{72}\) Alemtuzumab has been used in combination with CHOP or EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with some success in PTCL, with half of patients achieving a complete response (CR).\(^{73,74}\) Another study compared combinations of alemtuzumab with CHOP, EPOCH, and IMVP16-PL (ifosfamide plus mesna, methotrexate, etoposide, and prednisone),\(^{75}\) and a third study used alemtuzumab with CHOP and ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) in newly diagnosed PTCL patients.\(^{76}\) While overall response rates have been high, there has been an increased risk of opportunistic infections associated with the immunosuppressive effects of alemtuzumab. Patients on these trials have required routine
surveillance for reactivation of cytomegalovirus. A randomized trial comparing CHOP-14 to alemtuzumab-CHOP 14 is currently underway as a European intergroup study.

Two anti-CD30 MAbs, iratumumab and SGN-30, have shown efficacy in CD30+ ALCL. In vitro studies have shown that both drugs are synergistic or additive with conventional chemotherapy. An immunoconjugate of SGN-30 and monomethyl auristatin, brentuximab vetodin (SGN-35) has demonstrated an ORR of 41% with a median response duration of 7.3 months in patients with relapsed and refractory CD30+ lymphomas. A study is currently underway to evaluate the combination of CHOP with brentuximab vetodin in newly diagnosed patients with ALCL.

Siplizumab is an anti-CD2 MAb. CD2 is an adhesion molecule highly expressed on activated T cells and NK cells and on the majority of cells from patients with T-cell lymphoma and leukemia. Siplizumab eliminated both CD4+ and CD8+ T cells and NK cells without affecting B cells. In a phase I trial in patients with CD2+ lymphoproliferative disease, spilizumab showed clinical activity, inducing CRs in 2 patients with large granular lymphocyte leukemia (LGL), 3 partial responses (PRs) in patients with ATL, and 1 PR in a patient with CTCL. A subsequent dose escalation study produced a PR in a patient with NK-cell LGL and a CR in a PTCL patient. However, sipilizumab also predisposes patients to the development of lymphoproliferative syndrome, though it may be possible to prevent that with prophylactic rituximab.

CD4 is expressed in half of all T cells and by most CTCL and nodal PTCL cells. Zanolimumab, an anti-CD4 MAb, is being used in both disease types, though clinical development for CTCL is farther along. Zanolimumab was shown to be active and well-tolerated in a study of 21 PTCL patients, with an ORR in 24% of patients. Clinical studies of
zanolimumab in combination with CHOP are ongoing and include a phase I/II dose escalation trial in patients with noncutaneous CD4+ PTCL.

Bevacizumab, an antivascular endothelial growth factor (VEGF) MAb, will most likely have the largest impact in AITL, as AITL is characterized by the overexpression of angiogenic factors, such as VEGF. At least one relapsed AITL patient has achieved a CR following treatment with bevacizumab, and was being studied along with CHOP in a clinical trial for patients with PTCL or NK-cell neoplasms by the Eastern Cooperative Oncology Group. However, preliminary results of this trial reported a high incidence of cardiac events related to the therapy.

Denileukin diftitox, a fusion protein that combines interleukin-2 receptor-binding domain with diphtheria toxin, has demonstrated activity in both cutaneous and aggressive T-cell lymphomas. In a single center phase II study at MD Anderson Cancer Center, denileukin diftitox at a dose of 18 µg/kg/day for 5 days on a 21 day cycle demonstrated a response rate of 48% in heavily pretreated patients with relapsed PTCL. Responses were seen in 4 of 10 patients with PTCL-NOS, 2 of 3 with AITL, and 2 of 2 with ALCL. In this trial, the expression of CD25 by immunohistochemistry was not predictive of response to denileukin diftitox.

Based on these data, a combination of denileukin diftitox and CHOP was studied in untreated patients with PTCL. This study enrolled 49 patients. Denileukin diftitox was administered at 18 mcg/kg/day on Days 1 and 2 of each cycle, followed by CHOP chemotherapy on Day 3, and G-CSF support starting Day 4 of each 21-day cycle. In 37 efficacy-evaluable patients (>2 cycles), the ORR was 86% (CR 75%). Median PFS was 15 months and 2-year estimated OS was 60%. A large randomized study comparing CHOP to denileukin diftitox with CHOP is being initiated.
LMB-2 is an anti-Tac (anti-CD25) single chain monoclonal antibody (Mab) conjugated to *Pseudomonas* toxin. LMB-2 has shown clinical activity in phase II trials in CLL, CTCL, and hairy cell leukemia. ATL is the PTCL subtype that is most sensitive to LMB-2, but clinical responses have been limited to do rapid disease progression after >95% tumor reduction and immunogenic reactions.\(^9\) A phase II clinical trial for this population is being planned in which LMB-2 will be given after chemotherapy with fludarabine and cyclophosphamide.

**Histone deacetylase inhibitors**

Histone deacetylase (HDAC) inhibitors are potent inducers of histone acetylation, which results in the expression of tumor suppressor genes that had been previously silenced by deacetylation. This gene expression leads to cell cycle arrest and apoptosis. There are a number of HDAC inhibitors being used or studied in T-cell lymphoma, including vorinostat, romidepsin (also known as depsipeptide), panobinostat, and belinostat. Vorinostat and romidepsin have shown single-agent activity in CTCL,\(^9\)^\(^2\)^\(^3\) and vorinostat was approved by the FDA in 2006 for the treatment of advanced and refractory CTCL. Romidepsin was also recently FDA-approved in 2009 for advanced and refractory CTCL based on a demonstrated ORR in two clinical trials of 34%.\(^9\)\(^4\) The median response duration was 15 months (range 1-20+) and median time to progression was 8.3 months in early and 6.4 months in more advanced disease. A phase II study of romidepsin was completed in patients with relapsed and refractory PTCL.\(^9\)\(^5\) This phase II, open-label, multi-arm, multicenter study enrolled 43 PTCL pts from the NCI and 9 extramural sites. Of 43 patients, 31 received ≥2 cycles of therapy. Mean number of prior therapies was 3.9 (range 1 to 12). Objective response rate was 39% overall or 55% for patients who received at least 2 cycles of therapy. The overall median duration of response was 8.3 months (range 1.6
months to 4.8+ yrs) for all patients. A multicenter, multinational phase IIB registration study of romidepsin at the same dose and schedule in relapsed and refractory PTCL has completed accrual and results have been recently reported. Of 130 patients with a median of 2 prior therapies, the ORR was 26% with 15% CR by radiographic documentation. The median response duration was 12 months, and toxicities included gastrointestinal and constitutional events and thrombocytopenia.

Belinostat, a hydroxamic acid-derived HDACi, has been studied in both intravenous and oral formulations. Belinostat was administered intravenously at 1000 mg/m²/daily for 5 days every 3 weeks in 53 patients including 19 with refractory PTCL and 29 with refractory CTCL. The objective response rate in PTCL was 32% with 2 CR and a median response duration of 8.9+ mo, and 14% in CTCL, with a response duration of 9.1 months. A multicenter phase II registration trial of belinostat in relapsed PTCL patients is underway, and a cohort dose escalation study of oral belinostat is ongoing in patients with relapsed lymphoma.

Additive and synergistic activity has been demonstrated in vitro for combinations of HDACi with a number of agents, including topoisomerase inhibitors, bortezomib, and cytotoxic chemotherapy drugs and clinical trials are underway to explore the activity of these combinations in T-cell lymphomas.

**Antifolates**

Pralatrexate is a novel folate antagonist whose activity is associated with binding to the reduced folate carrier. In a phase I/II dose escalation trial of pralatrexate in refractory lymphoma patients, the ORR was 31%, with response durations ranging from 3-26 months. The response rate in that trial was 54% for patients with T-cell lymphomas. Based on these encouraging data, the PROPEL trial was initiated. In this trial, 111 patients with relapsed or
refractory PTCL were treated with pralatrexate weekly for 6 weeks on a 7-week cycle. The median prior therapies was 3, and 63% of patients had no response to their last line of therapy. The ORR was 29% and the median response duration was 10.1 months. Five patients with relapsed/refractory PTCL who responded to single-agent pralatrexate went onto stem cell transplant.99 Toxicities included mucositis in 70% of patients and thrombocytopenia in 40%. Pralatrexate was approved in September 2009 by the US Food and Drug Administration (FDA) as a single agent to treat relapsed or refractory patients with PTCL. A number of recent studies have explored the potential synergy between pralatrexate and other active agents in T-cell lymphoma. A phase I study combining pralatrexate with gemcitabine is underway.

**Immunomodulators and immunosuppressants**

Cyclosporine is an immunosuppressive agent that inhibits the NF-AT transcription complex, which activates the genes encoding cytokines and cell surface molecules involved in cell-to-cell communication and death.100 Because AITL is characterized by immune dysregulation, cyclosporine was administered to 12 patients in a phase II trial.101 Two-thirds (3 CRs, 5 PRs) of the patients responded, but there were 4 deaths. A phase II trial of cyclosporine in AITL was conducted by ECOG but closed early due to slow accrual.

Other immune modulating and antiangiogenic agents, including bevacizumab,87 rituximab,102 lenalidomide, and thalidomide, are also being explored as single agents and in combination with chemotherapy. A phase II study of lenalidomide at a dose of 25 mg/m² daily for 21 days of a 28 day cycle was conducted in 24 relapsed PTCL patients.103 The overall response rate was 30% with a PFS of 95 days. Toxicities included neutropenia and thrombocytopenia in 20% and 33% of patients, respectively.

**Nucleoside analogs**
Nucleoside analogs are chemotherapeutic agents that primarily inhibit DNA replication and repair. Gemcitabine is the most effective pyrimidine nucleoside analog in PTCL. It has been active both as a single agent and in combination with alemtuzumab and bortezomib. The purine nucleoside analogs include cladribine, fludarabine, clofarabine, and nelarabine. Both cladribine and fludarabine have shown efficacy in PTCL, and clofarabine and nelarabine are currently in several clinical trials in T-cell lymphoma.

The metabolic enzyme inhibitors, which include deoxycoformycin (pentostatin) and forodesine, do not incorporate into DNA, unlike the other nucleoside analogs. Pentostatin inhibits adenosine deaminase, increasing the deoxyadenosine triphosphate pool, and forodesine inhibits phosphorylase, increasing the deoxyguanosine triphosphate pool. Both agents have shown some efficacy in CTCL. A phase I/II study of oral forodesine in relapsed and refractory CTCL patients reported a 53% overall response rate, and a phase II trial has been completed.

**Proteasome inhibitors**

Bortezomib, a proteasome inhibitor, has been well tolerated and active as a single agent in relapsed or refractory CTCL patients. In a phase II study of bortezomib in relapsed CTCL or PTCL patients, the ORR was 67% with 2 CR and no grade 4 toxicity. The GELA has conducted a phase II study of bortezomib with ACVBP chemotherapy in 57 untreated PTCL patients and has reported that 29 patients were withdrawn prematurely due to toxicity. The ORRs were similar to ACVBP alone. Bortezomib has been used in combination with gemcitabine + doxorubicin, and recent evidence shows that bortezomib may synergize with pralatrexate in T-cell lymphoma (see antifolates section above).

**Signaling inhibitors**
Enzastaurin is a selective inhibitor of protein kinase C (PKC), which acts in part through the AKT pathway. By targeting the PI3K/AKT pathways, enzastaurin inhibits cell proliferation, induces tumor cell apoptosis, and suppresses tumor-induced angiogenesis in CTCL cell lines.\textsuperscript{113} Enzastaurin is currently in two phase II trials: one for patients with several types of NHL, including PTCL and CTCL, and another for relapsed CTCL patients.

**Treatment approaches for HTLV-1 associated ATL and NK/T cell lymphomas**

Optimal treatment approaches for patients with NK/T cell lymphoma have not yet been established. A phase I/II study of concurrent chemoradiotherapy for untreated localized NK/T-cell lymphoma was conducted in Japan.\textsuperscript{114} Extranodal NK/T-cell lymphoma, nasal type, is generally refractory to CHOP associated with a high expression of the multidrug resistance gene, P-glycoprotein. Patients in this trial were concurrently treated with radiotherapy and chemotherapy consisting of carboplatin, etoposide, ifosfamide, and dexamethasone. With a median follow-up of 32 months, the 2-year OS was 78% (95% CI, 57% to 89%). This compared favorably with the historical control of radiotherapy alone (45%). Of the 26 patients assessable for a response, 20 (77%) achieved a CR, with one PR. The ORR was 81%. The most common grade 3 nonhematologic toxicity was mucositis related to radiation (30%). The investigators concluded that concurrent chemoradiotherapy using multidrug resistance-nonrelated agents and etoposide is a safe and effective treatment for localized nasal NK/T-cell lymphoma.

A novel approach for patients with advanced NK/T cell lymphomas incorporates L-asparaginase along with ifosfamide, etoposide, dexamethasone, and methotrexate (SMILE). Overexpression of p-glycoprotein in NK/T cell lymphomas has contributed to relative chemoresistance and poor outcomes after CHOP-based therapies with 5-year survivals of 20% or
less in patients with advanced stage disease. A study by Yong et al treated 18 patients who were refractory to CHOP with L-asparaginase, vincristine, dexamethasone, and involved field radiotherapy and reported a response rate and 5-year OS of 55%. A phase I study escalating methotrexate and etoposide was completed and reported a response rate of 67%. A prospective phase II trial has been reported with SMILE regimen in patients with newly diagnosed stage IV or relapsed refractory NK/T cell lymphomas. Of 39 enrolled patients, 29 (74%) completed the planned treatment. The responses were complete remission (CR) in 15, partial remission in 14, and early death due to infection in 4. ORR and CR were 74% (95% CI, 58-87) and 38%, respectively. The most common grade 3 nonhematologic toxicity was infection (41%).

For patients with ATL, results with conventional chemotherapy regimens have been uniformly poor. A phase III Japanese study evaluated a combination regimen of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECP (vindesine, etoposide, carboplatin, and prednisone) against CHOP-14 in ATL. The study demonstrated superiority for VCAP-AMP-VECP for newly diagnosed aggressive ATL patients. A phase II study is in preparation to investigate the ability of allogeneic stem cell transplant after induction with the VCAP-AMP-VECP regimen to prolong the median survival time, which is currently 13 months with the VCAP-AMP-VECP regimen.

The use of interferon and zidovudine has been shown to induce responses in up to 50% of patients with acute or lymphomatous ATL. In a recent meta-analysis, 116 patients with acute ATL, 18 patients with chronic ATL, 11 patients with smoldering ATL, and 100 patients with ATL lymphoma were evaluated. Five-year OS rates were 46% for 75 patients who received first-line antiviral therapy (P=.004), 20% for 77 patients who received first-line chemotherapy, and 12% for 55 patients who received first-line chemotherapy followed by antiviral therapy. The
authors claimed that patients with acute, chronic, and smoldering ATL significantly benefited from first-line antiviral therapy, whereas patients with ATL lymphoma experienced a better outcome with chemotherapy. In acute ATL, 82% of patients were alive at 5 years with antiviral therapy, and 100% of patients with chronic and smoldering ATL were alive at 5 years. Multivariate analysis showed that first-line antiviral therapy significantly improved overall survival (hazard ratio, 0.47; 95% CI, 0.27 to 0.83; \( P = .021 \)). However, considering the potential selection bias in this retrospective study, future prospective studies are needed.

Finally, a humanized anti-CCR4 antibody, KW-0761, has shown promise as a single agent in Japan for the treatment of ATL. KW-0761 was used for relapsed patients with CCR4-positive ATL and PTCL in a phase I study.\(^{120}\) The ORR was 31% (5/16; 95% CI, 11-59). There were no dose-limiting toxicities, and no anti-KW-0761 antibodies were detected.\(^{120}\) A phase II trial for relapsed ATL patients was recently completed. Of 27 enrolled patients (14 acute, 6 lymphomatous, 7 chronic ATL), the ORR was 54% with 7 CR. Toxicities included cytopenias (lymphopenia 96%, neutropenia 33%), skin rash (52%), and mild transaminitis.

**Transplantation**

Several retrospective studies suggest that there are populations of patients with PTCL that will benefit from transplantation. The National Cancer Consortium Network (NCCN) guideline includes transplant as an option for consolidation after first remission in patients with histologies other than ALK+ ALCL and in patients with intermediate or high IPI scores. Disease status at transplant is a major predictor of success, particularly for autologous transplant.\(^{121}\) Results are better for patients who are in chemosensitive remission, while only 25% to 30% of refractory patients benefit.\(^{122, 123}\) In the studies where 5-year outcomes are reported, OS and FFS average 34% and 18%, respectively.\(^{124}\) The single center experience at Stanford reported only a modest
benefit after autologous transplant (5-year OS of 36%) for patients with relapsed disease and a 5-year OS of 76% in patients transplanted in first remission.\textsuperscript{125}

A prospective study from Germany using chemotherapy and up-front autologous transplantation for PTCL has been reported. The treatment regimen consisted of 4–6 cycles of CHOP, followed by mobilizing therapy with either dexaBEAM (dexamethasone, carmustine, melphalan, etoposide, and cytarabine) or ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin). Patients in complete or partial remission then underwent myeloablative chemoradiotherapy and autologous stem cell transplant (ASCT). Two thirds (66\%) of the patients had a disease response to chemotherapy and thus went on to receive ASCT. At a median follow-up time of 33 months, the estimated 3-year OS and PFS for patients in complete response were 48\% and 36\%, respectively. Patients who did not experience a response to chemotherapy and therefore did not undergo ASCT had a very poor outcome, with a median survival of less than 2 years.\textsuperscript{126} The role of autologous transplantation in second or subsequent remission is less well defined.

There are currently no randomized studies comparing outcomes between autologous and allogeneic transplant in the US. The Nordic and German lymphoma groups are launching a large, prospective randomized trial to compare the different strategies as consolidation after first line therapy. Additionally, the Center for International Blood & Marrow Transplant Research (CIBMTR) is currently conducting a database review comparing allogeneic and autologous transplants in PTCL patients. In a retrospective single-institution study that compared autologous and allogeneic transplant, outcomes for autologous transplant were best when conducted in first remission, and allogeneic transplant was better for patients with resistant or relapsed disease.\textsuperscript{127}
Further prospective studies are needed to define which subsets of PTCL patients will optimally benefit from allogeneic or autologous stem cell transplant.

**Evidence-based treatment approaches for PTCL**

Because of the inferior outcomes with CHOP-based regimens, novel strategies are needed for patients with aggressive T-cell lymphomas. The NCCN has established evidence-based treatment approaches for T-cell lymphoma and stratifies patients based on stage. For early stage patients with localized disease, chemotherapy should be followed by involved field radiotherapy. It is recommended that all patients except for those with low IPI be consolidated with autologous stem cell transplant. ALK+ ALCL is identified as the one subtype which has an excellent outcome and should not be transplanted in first remission. Recent data suggest that ALK+ patients with high IPI could be an exception to this rule. In prospective trials where up to 40% of patients do not undergo a complete remission and therefore cannot be consolidated with transplant, new approaches are necessary.

Selection of first-line therapy based on histopathologic features has not yet been widely employed but should be considered. For nodal T-cell lymphomas (PTCL-NOS, AITL, ALCL) the standard regimen used is a CHOP-based therapy. For extranodal subtypes, regimens may be individualized. For panniculitis-like T-cell lymphoma, distinction should be made between the alpha-beta type and the gamma-delta type, which is now included in the category of cutaneous gamma-delta T-cell lymphoma. The alpha-beta patients may be treated with single-agent therapies or combination chemotherapy and generally have an excellent outcome. The cutaneous gamma-delta T-cell lymphomas overall do poorly and should be treated with aggressive chemotherapy followed by transplantation. Likewise, hepatosplenic and intestinal T-cell
lymphomas have a poor outcome. In one study, 26 enteropathy-associated T-cell lymphoma patients were treated with CHOP then methotrexate alternating with ifosfamide, etoposide, and epirubicin. Patients who achieved CR went on to transplant (n = 33). For the transplanted enteropathy-associated patients, the PFS and OS were 52% and 60%, respectively. NK/T-cell lymphoma patients have also had inferior outcomes with CHOP-based regimens, and consideration of alternative regimens such as SMILE and asparaginase combinations should be strongly considered for these patients.

The role of autologous vs allogeneic stem cell transplantation in patients with poor prognosis subtypes such as NK/T cell and gamma-delta T-cell lymphomas has not been ascertained. In retrospective series, results with these subtypes are inferior to those of the more common PTCL-NOS and AITL subtypes after autologous transplantation. Therefore, consolidation with allogeneic stem cell transplantation should be considered in patients who have appropriate donors.

Conclusion

From this summary of the current state of classification, prognosis, and therapeutic approaches in PTCL, it is apparent that much progress has been made. While the problem with PTCL treatment in the past was a lack of available therapies, the development of novel therapies necessitates the development of paradigms to combine these agents to improve response rates and durability of responses. Based on the success of the Chronic Lymphocytic Leukemia and the Mantle Cell Lymphoma consortiums, investigators from North America have formed a North American PTCL Collaborative Group, which will collaborate with the International T-cell Project to develop new treatment strategies to improve outcome in PTCL. An international
registry is currently open and registering patients with newly diagnosed PTCL. Additionally, an international tissue bank has been initiated to capture sufficient quantities of clinically annotated and well-characterized specimens.
Authorship and Disclosure of Conflicts of Interest

Drs Foss, Zinzani, Gascoyne, Vose, Rosen, and Tobinai assisted with the writing of the manuscript and reviewed the finished manuscript. Dr. Foss prepared the manuscript for publication.

Relevant Conflict of Interest:

Dr Foss- consultant Eisai, Celgene; research funding Merck, Bayer

Dr Vose- Allos-research funding

Dr. Rosen- (Celgene: Scientific Advisory Board; Genzyme: Speakers Bureau; Merck: Speaker Bureau; Eisai: Advisory Panel; Allos: Advisory Panel.

Dr. Tobinai- research funding from Kyowa Kirin, Mundipharma, and Merck

Dr Zinzani-none

Dr. Gascoyne - none
References


42. Chtanova T, Kemp RA, Sutherland AP, Ronchese F, Mackay CR. Gene microarrays reveal extensive differential gene expression in both CD4(+) and CD8(+) type 1 and type 2 T cells. *J Immunol.* 2001;167(6):3057-3063.


74. Gallamini A, Zaja F, Patti C, et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL


86. d'Amore F, Radford J, Jerkeman M, et al. Zanolimumab (HuMax-CD4™), a fully human monoclonal antibody: Efficacy and safety in patients with relapsed or treatment-


Table 1. The WHO classification for PTCLs was updated in 2008. The new classification expanded some existing disease types and added several new provisional diseases.

<table>
<thead>
<tr>
<th>Old WHO Classification</th>
<th>New WHO Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor T-cell lymphoma</td>
<td>T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>T-lymphoblastic lymphoma/leukemia</td>
<td>T-cell large granular lymphocytic leukemia</td>
</tr>
<tr>
<td>Mature T-cell lymphomas</td>
<td>Aggressive NK-cell leukemia</td>
</tr>
<tr>
<td>T-cell prolymphocytic leukemia</td>
<td>Indolent large granular NK-cell lymphoproliferative disorder (provisional)</td>
</tr>
<tr>
<td>T-cell granular lymphocytic leukemia</td>
<td>Enteropathy-associated T-cell lymphoma</td>
</tr>
<tr>
<td>Aggressive NK-cell leukemia</td>
<td>Hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>Adult T-cell lymphoma/leukemia (HTLV1+)</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma (αβ only)</td>
</tr>
<tr>
<td>Extramedullary NK/T-cell lymphoma, nasal type</td>
<td>Primary cutaneous γδ T-cell lymphoma</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
<td>Mycosis fungoides &amp; Sézary syndrome</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td>Anaplastic large cell lymphoma- ALK+</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>Anaplastic large cell lymphoma- ALK− (provisional)</td>
</tr>
<tr>
<td>Mycosis fungoides/Sézary syndrome</td>
<td>Peripheral T-cell lymphoma, not otherwise specified</td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma, systemic or cutaneous</td>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, unspecified</td>
<td>Primary cutaneous CD30+ T-cell LPD</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>LYP and primary cutaneous ALC</td>
</tr>
<tr>
<td>Systemic EBV+ T-cell LPD of childhood</td>
<td>Primary cutaneous CD4+ small/medium T-cell lymphoma (provisional)</td>
</tr>
<tr>
<td></td>
<td>Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)</td>
</tr>
<tr>
<td>Hydroa vacciniforme-like lymphoma</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Biological factors and outcome in PTCL

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prognostic significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>worse</td>
</tr>
<tr>
<td>Ki-67</td>
<td>worse</td>
</tr>
<tr>
<td>BCL-2, BCL-XL</td>
<td>worse</td>
</tr>
<tr>
<td>CD26</td>
<td>worse</td>
</tr>
<tr>
<td>EBV</td>
<td>worse</td>
</tr>
<tr>
<td>MDR</td>
<td>worse</td>
</tr>
<tr>
<td>CCND2</td>
<td>worse</td>
</tr>
<tr>
<td>CCR4</td>
<td>worse</td>
</tr>
<tr>
<td>NFkB</td>
<td>favorable</td>
</tr>
<tr>
<td>CCR3</td>
<td>favorable</td>
</tr>
<tr>
<td>CXCR3</td>
<td>variable</td>
</tr>
<tr>
<td>PRDM1</td>
<td>worse</td>
</tr>
<tr>
<td>ALK-1</td>
<td>favorable</td>
</tr>
<tr>
<td>TCR BF1</td>
<td>favorable</td>
</tr>
<tr>
<td>TCR gamma1</td>
<td>worse</td>
</tr>
</tbody>
</table>
Table 3. Cytogenetics of PTCL subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>TCR</th>
<th>Chromosomal /Histopathologic features</th>
<th>Distinguishing features</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCLnos</td>
<td>αβ</td>
<td>Loss 13q22.3 adverse prognosis</td>
<td>Heterogeneous, variable morphology</td>
<td>20-3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gains 8q,9p,19q,loss 3q,9p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AITL</td>
<td>αβ</td>
<td>Follicular dendritic cell signature</td>
<td>Immunodeficiency and immune dysregulation</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CXCL13+, PD-1+ Gains 2,5,13q22.3 adverse prognosis</td>
<td>Helper B-cells, May respond to cyclosporine</td>
<td></td>
</tr>
<tr>
<td>ALCL ALK+</td>
<td>αβ</td>
<td>(2,5) translocation Gain 1q,loss 6q,13q</td>
<td>Bone marrow involvement in only 29%, median age 34</td>
<td>70%</td>
</tr>
<tr>
<td>ALK ALK-</td>
<td>αβ</td>
<td>Pax 5-,CD15-</td>
<td>Median age 58</td>
<td>49%</td>
</tr>
<tr>
<td>NK/T cell</td>
<td></td>
<td>CD56+, often EBV+</td>
<td>Stage I/II pts respond to radiotherapy or radiochemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serum EBV copy number predictive of outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nasal type 64</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extranasal type &lt;20%</td>
<td></td>
</tr>
<tr>
<td>SPTCL- αβ</td>
<td>αβ</td>
<td>CD3+CD8+CD56-5q,13q gains</td>
<td>Nodules and plaques</td>
<td>82%</td>
</tr>
<tr>
<td>SPTCL- γδ</td>
<td>γδ</td>
<td>CD3+CD8-CD56+/−</td>
<td>Nodules, often ulceration, Hemophagocytic syndrome</td>
<td>11%</td>
</tr>
<tr>
<td>Hepatosplenic T-cell Lymphoma</td>
<td>γδ</td>
<td>Isochromosome 7q, CD3+,CD4-CD8-, may be CD56+</td>
<td>Infiltration of sinusoids in liver, spleen, bone marrow, Erythrophagocytosis</td>
<td>2-year OS 20%</td>
</tr>
<tr>
<td>Enteropathy associated T-cell</td>
<td>αβ</td>
<td>Gains at chromosome 9q33-q34</td>
<td>Associated with celiac sprue, malabsorption</td>
<td>4%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td>CD3+CD7+, may be CD8+CD56+ with monomorphic type</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Novel agents in use or trials in PTCL*

<table>
<thead>
<tr>
<th>Type of Agent</th>
<th>Name</th>
<th>Description</th>
<th>Disease(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifolates</td>
<td>Pralatrexate</td>
<td>10-deazaminopoterin</td>
<td>PTCL, CTCL</td>
<td>Approved for PTCL</td>
</tr>
<tr>
<td></td>
<td>LMB-2</td>
<td>Anti-Tac (anti-CD25 fused to <em>Pseudomonas</em> toxin)</td>
<td>CTCL, PTCL (esp ATL)</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Denileukin dftitox</td>
<td>IL-2 targeting domain fused with diphtheria toxin</td>
<td>CTCL, PTCL</td>
<td>Approved for CTCL</td>
</tr>
<tr>
<td></td>
<td>Brentuximab vedotin</td>
<td>CD30 antibody conjugated to monomethylauristain-E</td>
<td>CD30+ T-cell lymphoma</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Belinostat</td>
<td>PXD101</td>
<td>CTCL, PTCL</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Panobinostat</td>
<td>LBH589</td>
<td>CTCL, ATL</td>
<td>Phase II</td>
</tr>
<tr>
<td>HDAC inhibitors</td>
<td>Romidepsin</td>
<td>Depsipeptide</td>
<td>CTCL, PTCL</td>
<td>Approved for CTCL</td>
</tr>
<tr>
<td></td>
<td>Vorinostat</td>
<td>Suberoylanilide hydroxamic acid (SAHA)</td>
<td>CTCL</td>
<td>Approved for CTCL</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>Lenalidomide</td>
<td>Derivative of thalidomide</td>
<td>PTCL, CTCL</td>
<td>Phase II</td>
</tr>
<tr>
<td>agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alemtuzumab</td>
<td>Anti-CD52</td>
<td>PTCL</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>Anti-VEGF</td>
<td>PTCL (esp AITL), NK-cell</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Itratumumab</td>
<td>Anti-CD30</td>
<td>CD30+ ALCL</td>
<td>Phase I/II</td>
</tr>
<tr>
<td></td>
<td>KW-0761</td>
<td>Anti-CCR4</td>
<td>ATL, PTCL</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>SGN-30</td>
<td>Anti-CD30</td>
<td>CD30+ ALCL</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Siplizumab</td>
<td>Anti-CD2</td>
<td>PTCL, NK-cell, ATL</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Zanolimumab</td>
<td>Anti-CD4</td>
<td>CTCL, PTCL</td>
<td>Phase II</td>
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<td>Monoclonal</td>
<td>Alemtuzumab</td>
<td>Anti-CD52</td>
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<td>antibodies</td>
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<td>Anti-VEGF</td>
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<td>Itratumumab</td>
<td>Anti-CD30</td>
<td>CD30+ ALCL</td>
<td>Phase I/II</td>
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<td>KW-0761</td>
<td>Anti-CCR4</td>
<td>ATL, PTCL</td>
<td>Phase II</td>
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<tr>
<td></td>
<td>SGN-30</td>
<td>Anti-CD30</td>
<td>CD30+ ALCL</td>
<td>Phase II</td>
</tr>
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Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALL, acute lymphoblastic leukemia; ATL, adult T-cell leukemia-lymphoma; CTCL, cutaneous T-cell lymphoma; esp, especially; IL-2, interleukin-2; MAb, monoclonal antibody; NHL, non-Hodgkin's lymphoma; Ph, phase; PTCL, peripheral T-cell lymphoma

*There are several other experimental agents in various stages clinical trials for T-cell lymphoma.
Figure 1. Overall survival of patients with the common subtypes of PTCL.

Vose et al (International T-cell Lymphoma Project), J Clin Oncol 2008; 26:4124-4130. Figure 2A p 4127.
Peripheral T-cell lymphoma

Francine M. Foss, Pier Luigi Zinzani, Julie M. Vose, Randy D. Gascoyne, Steven T. Rosen and Kensei Tobinai