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# Current Treatment of Peripheral T-Cell Lymphoma

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**Abstract:** Peripheral T-cell lymphoma (PTCL) constitutes a rare and biologically diverse group of non-Hodgkin lymphomas (NHLs) that arise from clonal proliferation of mature T cells and natural killer cells. PTCLs are aggressive lymphomas with unfavorable prognoses. Outcome varies by subtype, but long-term survival is only about 10–30% for most types. The rarity of the PTCL disorders, together with a lack of randomized trials, means that current treatment regimens are based on those used for B-cell NHLs, typically including combination, anthracycline-based chemotherapy. However, most PTCLs exhibit low rates of response to these regimens, as well as infrequent durable remissions. In recent years, advances in diagnostic methodologies have improved understanding of PTCL pathobiology and have resulted in better characterization of the different subtypes of PTCL. It is now acknowledged that these disorders behave differently than the B-cell NHLs and that each subtype warrants a distinct treatment approach. Development of PTCL-specific treatments has gained momentum, with much research focused on investigating ways to intensify the chemotherapy regimen, such as adding new drugs to frontline chemotherapy and consolidating first remissions with high-dose therapy and autologous stem cell transplant.

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# Introduction

Steven M. Horwitz, MD

Peripheral T-cell lymphoma (PTCL) is an uncommon and biologically diverse group of non-Hodgkin lymphomas (NHLs) that arise from clonal proliferations of mature (post-thymic) T cells. The closely related natural killer (NK) cell malignancies often have features overlapping with PTCL, and these disorders are frequently grouped together. The World Health Organization (WHO) classification currently identifies 22 subtypes of T-cell/NK-cell neoplasms based on distinguishable clinical, morphologic, immunophenotypic, and genetic features.[1] Previous divisions of predominantly leukemic (disseminated), nodal, extranodal, or cutaneous presentation have now been eliminated due to multiple presentations of some subtypes (Table 1). PTCLs overall affect men more commonly than women, and the median age at diagnosis has been reported at 61 years.[2,3] While the number of discrete PTCL subtypes can seem daunting, the most common subtypes are PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and the 2 subtypes of systemic anaplastic large cell lymphoma (ALCL)—which are subdivided based on their expression of anaplastic lymphoma kinase (ALK)—comprise approximately three fourths of PTCL cases encountered in North America and Europe.[4]

About 12% of patients with NHL have T-cell lymphoma or NK-cell lymphoma.[5] There is geographic variation in the frequency of the different PTCL subtypes. In a study by Vose and colleagues, PTCL-NOS was the most common PTCL subtype in both North America and Europe.[4] In Asia, the most common subtypes were NKTCL and adult T-cell leukemia/lymphoma (ATLL). ALK-positive ALCL was most common in North America, and enteropathy-type PTCL was most common in Europe (mainly Norway). In Europe, the angioimmunoblastic type was more common compared with other regions. Primary cutaneous ALCL was higher in North America than in Europe; Vose and colleagues suggested this may be because in Europe, such cases are referred to dermatologists.[4] In Asia, systemic and cutaneous ALCL, enteropathy-type, and hepatosplenic PTCL were uncommon.[3]

PTCLs are generally aggressive lymphomas that tend to have less favorable prognoses than the B-cell NHLs. Outcome varies by subtype in this heterogeneous group and, with the exception of ALK-positive ALCL, long-term survival is only 10–30%.[4] The rarity of PTCL, together with relatively few prospective data and a lack of random-

**Table 1.** 2008 WHO Classifications of Mature T-Cell and NK-Cell Neoplasms[2,7]

| Subtypes |
|---|
| T-cell prolymphocytic leukemia<br>T-cell large granular lymphocytic leukemia<br>Aggressive NK-cell leukemia<br>Adult T-cell leukemia/lymphoma (ATLL) |
| *Chronic lymphoproliferative disorders of NK-cells*<br>*Systemic EBV-positive T-cell lymphoproliferative disease of childhood*<br>*Hydroa vacciniforme-like lymphoma* |
| Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)<br>Angioimmunoblastic T-cell lymphoma (AITL)<br>Anaplastic large-cell lymphoma (ALCL), ALK-positive<br>*Anaplastic large-cell lymphoma (ALCL), ALK-negative* |
| Extranodal NK/T-cell lymphoma (NKTCL), nasal type<br>Enteropathy-associated T-cell lymphoma (EATL)<br>Hepatosplenic T-cell lymphoma (HSTL)<br>Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) |
| Mycosis fungoides<br>Sézary syndrome<br>Primary cutaneous CD30-positive T-cell lymphoproliferative disorders |
| Primary cutaneous ALCL<br>Lymphomatoid papulosis*<br>Borderline lesions |
| Primary cutaneous peripheral T-cell lymphomas, rare subtypes |
| Primary cutaneous γδ T-cell lymphoma<br>*Primary cutaneous CD8-positive aggressive epidermotropic T-cell lymphoma*<br>*Primary cutaneous CD4-positive small/medium T-cell lymphoma* |

ALK=anaplastic lymphoma kinase; EBV=Epstein-Barr virus; NK=natural killer. Provisional categories are in italics. Groups based on presentation have been eliminated in the 2008 classification scheme.

*Lymphomatoid papulosis is a cutaneous clonal lesion that undergoes spontaneous regression, causing some to question its classification as a malignancy.

ized trials, results in current treatment regimens that are derived from studies of aggressive lymphomas, with the majority of those enrolled having diffuse, large B-cell lymphoma. Typically, combination, anthracycline-based chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), is used. However, patients with PTCL exhibit lower rates of response and less frequent durable remissions with anthracycline-based chemotherapy than do those with B-cell lymphomas. ALK-positive ALCL is the exception; these patients tend to be younger and have lower risk factors, and treatment with CHOP conveys a good prognosis in this setting.[3,6]

In recent years, advances in diagnostic methodologies have improved our understanding of PTCL pathobiology and have resulted in better characterization of the different subtypes of PTCL.[2] It is now understood that these patients behave and respond to therapy differently than patients with B-cell NHLs and warrant a distinct treatment approach if outcomes are to be improved. Studies aimed at the development of PTCL-specific treatments have gained momentum, with research focused on investigating ways to intensify the chemotherapy regimen, such as adding additional drugs to CHOP and consolidating first remissions with high-dose therapy (HDT) and autologous stem cell transplant (ASCT). However, to date, these studies have only hinted at higher response rates and have not clearly demonstrated the ability to prolong or improve survival. This may in part be due to the size of the studies. Because PTCL is an uncommon lymphoma, the number of patients available to take part in clinical trials is small, and detecting a small improvement over standard therapy is difficult in relatively small studies. Moreover, novel or alternate approaches may not benefit all subtypes equally, adding another layer of complexity to developing better approaches for these heterogeneous diseases. Regardless, more effective frontline therapies for PTCL are clearly needed.[6]

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# Diagnosis of PTCL: Pathology

Eric D. Hsi, MD

It is important to differentiate PTCL from B-cell lymphoma early in the course of the disease because prognosis and therapeutic decisions are predicated upon correct diagnosis and subclassification using the WHO classification.[1] However, it is estimated that approximately 10% of PTCL cases are misclassified. Accuracy of diagnosis is good (≥92%) for ALK-positive ALCL, ATLL, and NKTCL because diagnostic tests for ALK, human T-lymphotropic virus-1 (HTLV-1), and Epstein-Barr virus (EBV), respectively, assist in arriving at the correct diagnosis in the proper diagnostic context. However, accuracy is generally poor (≤81%) for the other lymphoma subtypes that lack specific diagnostic markers.[2]

Fine-needle aspiration cytology may be carried out early in the clinical evaluation of PTCL to determine whether a mass lesion is likely to be benign or whether it requires further assessment by tissue biopsy. Tissue biopsies can take the form of a needle core biopsy, an excisional biopsy, or an endoscopic biopsy—if an extranodal site, such as the gastrointestinal tract, is involved. The modern diagnosis and subclassification of PTCL requires a substantial amount of tissue, as it involves immunophenotyping in conjunction with cellular morphology, analysis of lymph node architecture, and molecular genetic studies.[3] Cytology evaluation alone is generally inadequate for a primary diagnosis of lymphoma. In fact, a common cause

of failure to reach a definite lymphoma subclassification or diagnostic error in hematopathology is insufficient material; so, from the pathologist's perspective, an excisional biopsy is preferable. Important histopathologic and architectural clues can be lost with a needle core biopsy or due to sampling errors.[4]

Obtaining fresh tissue is critical for the diagnosis of lymphomas, including PTCL. Most diagnostic information can be derived from routine formalin-fixed, paraffin-embedded tissue, from which routine histology and immunohistochemistry are carried out. Fresh tissue, however, is required for flow cytometry and cytogenetic studies. Karyotypic information can be important because abnormalities can be used as markers of clonality and because some abnormalities may be specific or characteristic of certain PTCL subtypes.[3] In addition, snap frozen tissue is best for isolation of high-quality nucleic acids, which can be used for gene rearrangement studies to document monoclonality. This is of particular importance in PTCL since phenotypic surrogates for monoclonality, such as immunoglobulin light chain restriction, are not readily available for T-cell proliferations.

## Histology

The first evaluation of tissue is microscopic evaluation of the routine hematoxylin and eosin (H&E) stained section. Analysis of cellular morphology can suggest PTCL, but it is insufficient to make a diagnosis. Furthermore, morphology can vary widely among PTCL subtypes, or even within a single subtype. Pathologists first evaluate low-magnification architectural features, such as whether lymph node architecture is retained; presence of lymph node structures, such as follicles or sinuses; and whether an infiltrative process is nodular or diffuse. The types of cells in an infiltrate are also assessed to determine if an abnormal cell population (lymphoid or otherwise) is present. T-cell lymphomas typically have a mixed population containing non-neoplastic cells in the infiltrate. This can both aid and hinder diagnosis, as the characteristic feature of reactive cellular infiltrate can mask the neoplastic cells.[1,3,5]

## Immunohistochemistry

The immunohistochemistry stains available to pathologists can vary, but a broad panel of both B- and T-cell markers is important for assessing the immune architecture of the lymph node, to understand what types of T-cells are in the infiltrate, and to detect abnormal T-cell immunophenotypes characteristic of certain PTCL subtypes. These stains include pan B-cell markers, such as CD20 or PAX5, as well as a host of mature T-cell markers, including CD2, CD3, CD4, CD5, CD7, CD8, cytotoxic T-cell markers, and CD30 as an activation marker. Lack of expression of CD20 can initially indicate T-cell NHL, and high expression of CD3 suggests either T-cell NHL or T-cell proliferation associated with B-cell NHL (such as in T-cell/histiocyte-rich, large B-cell lymphoma). Normal T-cells express the pan T-cell markers CD2, CD5, and CD7, and malignant T-cells may lose one or more of these. Some subtypes of T-cell lymphoma, such as mycosis fungoides—which often lacks expression of CD7—are more likely to lose these markers than others. T-helper and T-cytotoxic cells normally express the CD4 and CD8 markers, respectively.[1,3,5] Additional markers that might be helpful in assessment of PTCL include, but are not limited to, CD10, CD21, PD1, CXCL13, ALK, CD15, and assessment for EBV. Studies have shown that diagnostic accuracy is increased when phenotypic and genetic information is available to pathologists.[6]

## The Importance of Clinical Information

Although pathology might be regarded as one of the most objective specialties in medicine, accurate diagnosis of PTCL subtypes relies on a clear understanding of the clinical setting as well as the pathologic features.[4] This is partly because classification of many PTCLs is based to some extent on the anatomic location of disease. For example, the WHO classification includes EATL, which typically occurs in the gastrointestinal tract; HSTL, which occurs in the liver and spleen; and subcutaneous panniculitis-like T-cell lymphoma (SPTCL), which occurs in the subcutaneous fat.[1] Thus, it is important to understand disease distribution during the workup of the case.

Symptomatology can also aid classification. For example, the clinical presentation of AITL includes hypergammaglobulinemia and anemia that are characteristic of that disease, and knowing HTLV-1 serology would be important in the diagnosis of ATLL because this subtype is uniformly associated with HTLV-1 infection.[5] Highlighting this point, the International Peripheral T-Cell and NK/T-Cell Lymphoma Study found that, overall, a 6.4% change in diagnosis occurred when clinical data were provided to the pathologist, and that a change in diagnosis from PTCL-NOS to ATLL occurred in 38.7% of cases when HTLV-1 status was added.[2]

Another reason why clinical information should be integrated into diagnosis is because pathologic features of PTCL are not always entirely specific. For example, lymph node involvement by mycosis fungoides might be diagnosed as PTCL-NOS unless the pathologist knew that there was a history of mycosis fungoides in the patient. Lymphomatoid papulosis, primary cutaneous ALCL, and even skin involvement in systemic ALCL are all CD30-

positive, cutaneous T-cell lymphoproliferative disorders. Thus, the interpretation of an individual biopsy would be heavily influenced by the clinical scenario to classify these cases. If a lesion that was biopsied was from one of several papules that was appearing and disappearing over a period of months, then the diagnosis would be much more consistent with lymphomatoid papulosis than ALCL.[5,7]

## Differentiation of PTCL Subtypes

Despite these examples of how the pathology of PTCL subtypes overlap, a number of features are specific to certain subtypes. For example, systemic ALCL exhibits strong expression of CD30, which is an activation marker for T cells and B cells. PTCL-NOS with high CD30 expression can be difficult to differentiate from ALK-negative ALCL, but gains in chromosome 1q are much more common in ALK-negative ALCL than PTCL-NOS. Overexpression of ALK protein or presence of the ALK gene translocation is also specific for ALK-positive ALCL. Molecular genetic studies are used to detect the non-random t(2;5)(p23;q35) translocation that produces a novel nucleophosmin-ALK fusion protein. The tyrosine kinase ALK is constitutively active in this chimera, resulting in significant oncogenic potential.[7] Virtually no other recurrent translocations can be used to definitively subclassify PTCL subtypes, although molecular genetic studies can aid in diagnosis of hepatosplenic T-cell lymphoma (HSTL) because of the high frequency of isochromosome 7q. This is not an entirely specific genetic feature, but it can be useful when evaluating a suspected T-cell lymphoma with presentation in the liver or spleen.[5] The recently described translocation of the IRF4/DUSP22 locus at 6p25.3 is seen in a subset of cutaneous ALCL.[8,9]

Studies of AITL have shown that it is a lymphoma of follicular helper T cells, which are a subset of CD4-positive T cells that provide functional help to B cells in reactive germinal centers.[10] There are now markers to detect these cells, and CD21 is currently the most sensitive for identifying the extensive proliferation of follicular dendritic cell networks that are characteristic of AITL.[11] CXCL13 and PD1, markers for follicular helper T cells, can also be useful in distinguishing AITL.[12] The neoplastic cells are usually CD4-positive/CD8-negative, and EBV-positive B cells are usually present.[7]

Two types of EATL are now recognized by the WHO classification.[1] Both subtypes are derived from intestinal intraepithelial lymphocytes, but type I EATL occurs as a complication of gluten-sensitive enteropathy (celiac disease), whereas type II EATL is not necessarily related to celiac disease. Presentation with intestinal disease is not sufficient to diagnose EATL because NKTCL and some γδ T-cell lymphomas can also present with intestinal involvement. Thus, there should be evidence of celiac disease in the adjacent uninvolved small bowel mucosa to make a diagnosis of type I EATL.[13] Type II EATL has distinct immunophenotypic features and can be subtyped by the expression of the CD56 marker. The genetic profiles of type I and type II EATL are also different: gains of 1q and 5q appear specific to type I, and type II EATL commonly has MYC oncogene amplifications at 8q24.[5,14] EATL type 1 is more common than type II (66% vs 34%, respectively), especially in Europe (79%), where celiac disease is more prevalent.[15]

Thus, while it is beyond the scope of this article to detail the many nuances of the pathologic features of PTCLs, it is clear from the above discussion that adequate tissue, morphologic and immunophenotypic data, genotypic data, and clinical correlation are needed to arrive at the proper diagnosis. This approach will allow clinicians to provide their patients with optimal care for this challenging disease.

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# Diagnosis of PTCL: Workup and Clinical Presentation

Barbara Pro, MD

As noted, PTCLs comprise a heterogeneous group of diseases that can have a wide variety of clinical presentations. The typical characteristic of PTCL, as compared with diffuse large B-cell NHL, is that the majority of patients will present with more advanced stage disease, meaning generally more aggressive disease with a poor prognosis. One challenge in diagnosing PTCL is that some patients will present with extranodal involvement with a high degree of necrosis, such that the biopsy specimen is too small for thorough examination. Most cases also lack distinct genetic or biologic alterations, but progress has been made in the classification of a number of PTCL subtypes.[1,2]

## Initial Patient Evaluation

The diagnostic workup of PTCL is similar to that performed for other types of lymphoma; an essential part of the initial workup is complete physical examination with attention to the nodal areas. More specific to PTCL is careful examination of the nasal cavity if one suspects extranodal nasal-type NKTCL, and careful evaluation of the skin for the presence of rash or lesions that can be associated with some subtypes. The patient is also assessed for the presence of B symptoms, such as drenching night sweats, fever, and unintentional weight loss of more than 10% of normal body weight. In terms of laboratory studies, a complete blood count is performed with white blood cell differential and platelet count, as well as a comprehensive metabolic panel and measurement of lactate dehydrogenase (LDH) to assess the aggressiveness of the disease. Radiographic studies are also carried out, the most important being computed tomography (CT) scans, which should include the head and neck, chest, abdomen, and pelvis. Given that a number of PTCL subtypes can present with extranodal disease, it is also very important to obtain a positron emission tomography (PET) scan to assess possible skin involvement and involvement of other organs.[1] One study found that diagnostic CT scanning failed to detect disease in 29% of patients in whom PET scanning was positive, illustrating the value of this technology in T-cell lymphoma diagnosis.[3] In patients who are candidates for anthracycline-based chemotherapy, an evaluation of their cardiac functions through a scan or an echocardiogram should be acquired. Furthermore, if ATLL is suspected, blood tests for HTLV-1 infection should be requested.[1,4]

## Differentiation of PTCL Subtypes

The most common subtype of PTCL is PTCL-NOS, which accounts for approximately 26% of all cases of PTCL and NKTCL[5] Patients generally present with advanced disease (65% present with stage IV disease[6]), peripheral lymph node enlargement, and B symptoms.[7,8]

The second most common PTCL subtype worldwide is AITL, which comprises about 19% of all cases of PTCL and NKTCL[5] and is characterized not only by generalized adenopathy, but also by the presence of B symptoms in the majority of patients. Patients can present with a skin rash that is maculopapular in most cases, and can be pruritic and diffuse. Splenomegaly can also be present, and AITL is often associated with other autoimmune phenomena. Occasionally, AITL can have a benign course, and in such cases, corticosteroids can be used without the need for aggressive chemotherapy. However, it is very difficult to assess which patients will run this course of disease.[9]

ALCL accounts for approximately 12% of all cases of PTCL and NKTCL,[5] and it can be divided into ALK-positive and ALK-negative disease, which has very important prognostic implications. ALK-positive ALCL usually occurs in younger men and has more favorable prognosis (5-year overall survival [OS] 70%[10]). A significant percentage of patients are cured by systemic chemotherapy, such as CHOP. Presentation can be nodal or extranodal, involving the skin, bone, soft tissues, lung, and liver. Prognosis is significantly worse for ALK-negative ALCL (5-year OS, 49%[10]), and patients do not usually respond well to anthracycline-based chemotherapy. Thus, it is essential that ALK protein status be assessed as soon as possible at diagnosis. When the WHO revised its classification of ALCL in 2008, the decision to segregate ALK-negative ALCL from PTCL-NOS was controversial. However, recent clinical stud-

ies have shown that ALK-negative ALCL has a better prognosis than PTCL-NOS; 5-year failure-free survival is 36% versus 20% for PTCL-NOS (*P*=.012), and OS is 49% versus 32% for PTCL-NOS (*P*=.032).[10]

In study by Au and colleagues of 1,153 new cases of adults diagnosed with peripheral/T-cell lymphoma, 136 cases (11.8%) of extranodal NKTCL were identified (nasal 68%, extranasal 26%, aggressive/unclassifiable 6%).[11] This subtype is more common in Asia and Latin America.[12-14] It is EBV-associated, and the typical presentation is different from other types of PTCL, with patients usually presenting with lesions involving the nasal cavity and paranasal sinuses. NKTCL can also involve other sites, such as the skin, gastrointestinal tract, testis, kidney, upper respiratory tract, and, rarely, the orbit/eye. Such cases are associated with more adverse clinical features and poor survival; median OS for early-stage disease, extranasal is 0.36 years versus nasal 2.96 years (*P*=.001); median OS for late-stage disease extranasal is 0.28 years versus nasal 0.8 years (*P*=.031).[11] NKTCL has a characteristic morphology including a high degree of necrosis, so diagnosis of this subtype can be challenging. However, accurate diagnosis is important because, in contrast to other subtypes, radiation therapy is a fundamental part of initial treatment of NKTCL. The use of radiation therapy for early-stage nasal cases provides a survival benefit (*P*=.045).[11]

In a study by Vose and colleagues, EATL was identified in approximately 6% of patients with PTCL or NKTCL in North America.[5] This subtype is more common in Europe than North America or Asia, and it is often associated with gluten-sensitive enteropathy (celiac disease).[5] Patients usually have gastrointestinal symptoms, such as abdominal pain and weight loss. They can also have significant complications, including small bowel perforation or obstruction and gastrointestinal bleeding. Thus, it is very difficult to manage EATL patients, and they typically do not respond well to systemic chemotherapy due to poor performance status at presentation and significant gastrointestinal symptomatology. EATL is associated with very poor prognosis, with a median failure-free survival of only 6 months and median OS of only 10 months.[15]

A more rare subtype is hepatosplenic lymphoma, which accounts for only 3.0% of all cases of PTCL and NKTCL in North America.[5] Again, patients are usually younger men, with a median age ranging from 30[6] to 34.[5] Hepatosplenic lymphoma is difficult to diagnose because patients will present with hepatosplenomegaly without the presence of distinct masses. Instead, hepatosplenic lymphoma presents as a diffuse proliferation of malignant T-cells, and bone marrow infiltration is common at the time of diagnosis. Patients have dismal prognosis with standard treatments (5-year OS, 7%[5]), and they typically relapse quickly.[7]

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# Current Treatment Approaches to PTCL

Steven M. Horwitz, MD

The National Comprehensive Cancer Network (NCCN) recommends CHOP as standard first-line therapy for patients with ALK-positive ALCL.[1] No truly validated standard of care exists for the other PTCL subtypes, as recommendations for treatment are based on case studies, phase II trials, extrapolation from treatments for other aggressive lymphomas, and expert opinion.[2] That said, for the most common subtypes of PTCL-NOS, AITL, and ALK-negative ALCL, the NCCN guidelines do recommend multidrug chemotherapy (4–6 cycles) with consideration of adjuvant radiation therapy for patients with stage I–II disease (low/low-intermediate risk), and multidrug chemotherapy (6–8 cycles) with or without radiation therapy for patients with stage I–II (high/high-intermediate risk) or stage III–IV disease.[1] In accordance with these recommendations, the International Peripheral T-Cell and NK/T-Cell Lymphoma Study reported that more than 85% of patients with the most common subtypes of PTCL received anthracycline-based chemotherapy for initial treatment. However, in this retrospective analysis, the benefits of including an anthracycline could not clearly be demonstrated, as would be expected in diffuse large B-cell lymphoma.[3] Nevertheless, CHOP is by and large the most common first-line treatment of PTCL in the United States, and nothing to date has been proven superior to this regimen. The chemotherapy regimens most commonly used for first relapse or primary refractory disease are typical second-line regimens, such as ifosfamide; carboplatin; etoposide (ICE); dexamethasone, cytarabine, and cisplatin (DHAP); and etoposide, dexamethasone, cytarabine, and cisplatin (ESHAP). One survey showed that approximately one-third of patients participate in clinical trials at second relapse (Table 1).[4] However, participation is only 4–6% for frontline therapy,[4] despite the inadequacies of CHOP and the NCCN recommendation that clinical trials be used for initial treatment of PTCL when available.[1,4]

Few reports have described the clinical outcome of large numbers of PTCL patients since the WHO revised its classification of T-cell/NK-cell lymphomas in 2008 to take into account key features that significantly influence prognosis, such as ALK status.[5] However, some insightful data on the activity of CHOP can be derived from a prospective multicenter study—excluding ALK-positive ALCL—of CHOP followed by autologous stem cell transplant. Patients were younger than average and received standard-dose CHOP for 4–6 cycles, with responders proceeding to high-dose therapy. The overall response rate [ORR] to CHOP was 79% (39% complete response [CR] and 40% partial response [PR]).[6] Durability of the responses to CHOP alone cannot be evaluated in this study due to consolidation therapy, but even with subsequent high-dose therapy, the majority of responses were not sustained.

**Table 1.** Most Commonly Used Chemotherapeutic Regimens for PTCL[4]

| Stage | Treatment Frequency (%) | | | |
|---|---|---|---|---|
| | CHOP | ICE/ DHAP/ ESHAP | EPOCH/ HyperCVAD | Clinical Trial |
| Early (I/II) | 55.8 | 2.5 | 4.2 | 4.2 |
| Advanced (III/IV) | 48.1 | 6.1 | 17.6 | 6.1 |
| Refractory | 3.9 | 31.5 | 21.3 | 13.4 |
| Relapsed (1st) | 1.6 | 36.8 | 12.8 | 11.2 |
| Relapsed (2nd) | 2.6 | 13.1 | 4.9 | 32.8 |

CHOP=cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; DHAP=dexamethasone, cytarabine, cisplatin; ESHAP=etoposide, dexamethasone, cytarabine, cisplatin; EPOCH=etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin; hyperCVAD=hyperfractionated cyclophosphamide, vincristine, hydroxydaunorubicin, dexamethasone; ICE=ifosfamide, carboplatin, etoposide.

## Intensifying CHOP

Although CHOP chemotherapy is the most commonly used first-line treatment for PTCL, outcomes are too often disappointing. Adding more drugs to CHOP is one strategy that has been investigated to improve patient outcomes. The German High-Grade Non-Hodgkin Lymphoma Study Group analyzed the effect of adding etoposide to conventional doses of CHOP (CHOEP) in a large, prospective, randomized study of patients with common PTCL subtypes (Table 2). The study also evalu-

**Table 2.** Frequency and Outcomes for PTCL Patients Treated With CHOP/CHOEP[5]

| PTCL Subtype | Frequency (%) | 3-Year EFS (%) | 3-Year OS (%) |
|---|---|---|---|
| PTCL-NOS | 21.9 | 41.1 | 53.9 |
| AITL | 8.8 | 50.0 | 67.5 |
| NKTCL | 5.9 | 36.1 | 46.3 |
| ALCL, ALK-positive | 24.4 | 75.8 | 89.8 |
| ALCL, ALK-negative | 35.3 | 45.7 | 62.1 |

AITL=angioimmunoblastic T-cell lymphoma; ALK=anaplastic lymphoma kinase; ALCL=anaplastic large cell lymphoma; EFS=event-free survival; NKTCL=natural killer/T-cell lymphoma; OS=overall survival; PTCL-NOS=peripheral T-cell lymphoma not otherwise specified.

ated the effect of shortening the treatment interval from every 3 weeks (CHOP-21) to every 2 weeks (CHOP-14).[5]

The results were reported for younger patients with normal LDH. The overall difference in 3-year event-free survival (EFS) between CHOP and CHOEP across all PTCL patients, except those with ALK-positive ALCL, showed a trend toward improvement that was not statistically significant (48.3% vs 60.7%; *P*=.057). In patients older than 60 years, the use of CHOEP did not appear to show any improvement in EFS or OS, as CHOEP was poorly tolerated. This analysis highlights that while standard-regimen CHOP may not be ideal for patients with T-cell lymphoma, demonstrating a superior alternative may not be simple.[5]

Patients with AITL, especially the elderly or those with comorbidities, are an additional subset that may be intolerant to CHOP, let alone intensified CHOP. In these cases, the NCCN guidelines recommend a trial of corticosteroids for symptom management.[1] Cyclosporine is another immunosuppressive agent that can be effective in AITL patients with relapsed disease.[7]

## Frontline Consolidation of Remissions

Another way to intensify the treatment regimen is to consolidate remissions with HDT followed by ASCT. A number of retrospective studies have shown that HDT-ASCT is a reasonable approach in refractory or relapsed PTCL. Its use in the frontline setting remains controversial due to the heterogeneous nature of PTCLs and a lack of randomized studies. However, several retrospective studies have demonstrated that HDT-ASCT can be used as first-line consolidation to possibly improve outcome in patients with a CR or PR after induction chemotherapy (OS ranging from 53% at 3 years to 62–68% at 5 years).[8] The European Group for Blood and Marrow Transplantation reported on one of these large retrospective studies. In 146 patients with AITL, the result of HDT-ASCT showed an actuarial OS of 67% at 2 years and 59% at 4 years.[9]

The prospective studies of HDT-ASCT consolidation have generally reported inferior survival benefits to the retrospective studies, but this is most likely due to intention-to-treat analyses that include the approximately one-third of patients who fail induction and do not proceed to ASCT.[10] In 5 prospective studies, the OS ranged from 48–73% at 3 years to 34% at 12 years. Disease-free survival (DFS), EFS, or progression-free survival (PFS) ranged from 36–53% at 3 years to 30% at 12 years.[8] In one of the larger prospective studies—an intent-to-treat analysis of PTCL patients after myeloablative therapy and ASCT—Reimer and colleagues reported estimated 3-year OS, DFS, and PFS rates of 48%, 53%, and 36%,[6] respectively. Treatment-related mortality (TRM) was low at 3.66%.[6]

## Treatment of Relapsed or Refractory Disease

As yet, only limited data are available for frontline treatment of PTCL with allogeneic stem cell transplant (allo-SCT), but in the relapsed or refractory setting, allo-SCT is looked to as one of the only treatments with the potential to be curative in a significant number of patients.[8] The largest series to date is a retrospective analysis of 77 patients, most of whom had received myeloablative conditioning before allo-SCT. The favorable 5-year OS and PFS rates of 57% and 53%, respectively, must be balanced against a 33% TRM.[11] In another study, a reduced intensity conditioning (RIC) approach produced an impressively low TRM of 6%. In that prospective study, 17 patients underwent RIC followed by alloSCT, with estimated 3-year OS and PFS rates of 81% and 64%, respectively.[12]

Positive outcomes from allo-SCT appear most frequent for those with good performance status, adequate disease control, and, of course, an available donor. Thus, possible selection bias must be considered when interpreting or applying the data we have. When plans are to proceed immediately to alloSCT, combination regimens such as ICE—which has a high response rate in the relapsed setting (an ORR of 70% with 35% CR and 35% PR) but little durability—are often used.[13] However, the toxicities associated with that approach usually require moving to allo-SCT after only 2–3 cycles, often leaving little time to identify, evaluate, and collect materials from an unrelated donor. Thus, therapies such as ICE are best used when a donor is already available for subsequent stem cell transplant. When this is not the case, the selected therapies are often those that lack cumulative toxicities and can offer the ability to control disease and maintain responses.[1]

In 2009, pralatrexate was approved by the US Food and Drug Administration (FDA) for relapsed and refractory PTCL.[14] In the pivotal PROPEL (Pralatrexate in

Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma) study, pralatrexate was administered intravenously at 30 mg/m$^2$ weekly for 6 of 7 weekly cycles and demonstrated high activity with durable responses. ORR in the 109 evaluable patients was 29% (11% CR, 18% PR), with a median duration of response of 10.1 months. The most common grade 3/4 toxicities were thrombocytopenia, mucositis, neutropenia, and anemia.[15] When pralatrexate was used as second-line therapy, an ORR of 47% (20% CR, 27% PR)[16] post-CHOP and an ORR of 40% (15% CR, 25% PR) post-ICE were seen.[17]

The histone deacetylase (HDAC) inhibitor romidepsin is another promising drug for use in the relapsed or refractory setting. In June 2011, romidepsin was approved by the FDA for the treatment of PTCL in patients who have received at least 1 prior therapy. Piekarz and colleagues conducted a phase II study of romidepsin in patients with various subtypes of PTCL, including PTCL-NOS, angioimmunoblastic, ALK-negative anaplastic large cell lymphoma, and enteropathy-associated T-cell lymphoma PTCL.[18] Among the 45 evaluable patients, the ORR was 38% (95% CI, 24–53%), with 18% achieving a CR and 20% achieving a PR. The CR duration of response was 29.7 months. Responses were observed among the various subtypes. The overall median duration of response was 8.9 months (range, 2–74 months). The most common grade 3 and 4 toxicities were leukopenia, granulocytopenia, lymphopenia, and thrombocytopenia.

At the 2010 meeting of the American Society of Hematology, Coiffier and coworkers presented final results from a multicenter, international, open-label, phase II study of romidepsin in progressive or relapsed PTCL following prior systemic therapy.[19] The ORR was 26% (13% CR, 13% PR) in 130 evaluable patients. Similar complete response rates were observed by a central Independent Review Committee across the 3 major PTCL subtypes (NOS, AITL, and ALK-1 negative ALCL).[20] For overall response, the median duration of response was 12 months (range, 1–801+ days). The median duration of response was not reached for the CR/unconfirmed CR (CRu; range, 1–801+ days). The most common grade 3 or higher adverse events with romidepsin included pneumonia (5%), pyrexia (5%), sepsis (5%), and vomiting (5%).

Updated results from this trial were presented at the 2011 ASCO meeting. Romidepsin was associated with a CR/CRu rate of 15%, with a median time to CR/CRu of 4 months (range, 2–9 months).[21] After a median follow-up of 8.2 months, 16 of 17 patients (94%) had not progressed. The median time to overall response was 1.8 months. The most common grade 3/4 adverse events were thrombocytopenia (24%), neutropenia (20%), and anemia (10%).

Belinostat, another HDAC inhibitor, has also shown activity in relapsed and refractory PTCL. The ORR in 20 patients was 25% (10% CR, 15% PR).[22] Thus, HDAC inhibitors as a class appear to show encouraging activity in PTCL.

Denileukin diftitox is a recombinant interleukin-2/diphtheria toxin fusion protein that has also shown activity in relapsed/refractory PTCL. ORR in 27 evaluable patients was 48.1% (22.2% CR, 25.9% PR).[23] Other treatments for relapsed or refractory PTCL described by the NCCN guidelines include alemtuzumab, bortezomib, gemcitabine, and cyclosporine (specifically for patients with AITL).[1]

## Palliative Approaches

Elderly patients or those with comorbidities are often not candidates for the most aggressive treatments, such as intensified chemotherapy or stem cell transplant. In such cases—given the low likelihood of a durable response to CHOP—initial treatment may be given with palliative intent. Approaches may include radiation therapy or treatment strategies used in the relapsed or refractory setting that can be given without cumulative toxicity (discussed above) and continued in a maintenance fashion, and at times provide durable disease control on therapy. Participation in a clinical trial is also strongly recommended.[1]

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# Novel Treatment Approaches to PTCL

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With no standard of care for PTCL, clinical trials are an important avenue for treatment of patients. Current trials are now focusing on PTCL-specific treatment regimens. In the last few years, a number of drugs have demonstrated activity in the relapse setting, including pralatrexate, romidepsin, and denileukin diftitox. Only romidepsin has been associated with true, CR and with long duration of survival in CR.[1] Pralatrexate and denileukin diftitox were more likely to be associated with a more PR.

## New Frontline Combination Regimens

In order to cure PTCL, first-line treatments that elicit complete and durable responses are needed. Currently none are available, and relapse after CHOP therapy occurs relatively rapidly in most patients. The current challenge is to make active first-line regimens by combining new drugs with old, and a number of phase I/II studies are currently under way to assess the efficacy and tolerability of pralatrexate, romidepsin, and gemcitabine in combination with CHOP and other regimens.[2-5] Toxicities may prevent certain combinations. For example, HDAC inhibitors, such as romidepsin, have been associated with thrombocytopenia. If these agents are combined with CHOP, there is the potential for a very profound thrombocytopenia. This also holds true for pralatrexate, which has been associated with cytopenia, neutropenia, thrombocytopenia, and mucositis.

Clinical trials with denileukin diftitox and CHOP were slated after a preliminary study demonstrated that this combination was clinically active and well tolerated. The ORR in all 49 patients was 65% (51% CR), and in the efficacy-evaluable patients, it was 86% (73% CR). The most common grade 3/4 toxicities were leukopenia, thrombocytopenia, and febrile neutropenia.[6]

Studies of response maintenance after remission is achieved with first-line CHOP are also proposed for some of these new drugs. Lenalidomide, a derivative of thalido-

mide that produced an ORR of 30% in 23 relapsed or refractory PTCL patients, could also be used in this setting.[7] This maintenance strategy may succeed in reducing relapse in patients who respond, and it should minimize toxicity, but it is not likely to increase the CR rate in the manner achieved by combination regimens.

## Novel Monoclonal Antibodies

A number of monoclonal antibodies have been investigated for activity in PTCL, including alemtuzumab, SGN-30, MDX-060, zanolimumab, siplizumab, KW-0761, and daclizumab. Their use is complicated by the depletion of normal T-cells, which predisposes patients to the development of opportunistic infections and secondary malignancies.[7] Brentuximab vedotin, an antibody-drug conjugate that targets CD30-positive lymphomas, has demonstrated promising data in recent studies. At the 2011 ASCO meeting, Pro and colleagues reported results from a phase II, single-arm, multicenter study that evaluated the efficacy and safety of brentuximab vedotin in patients with relapsed or refractory systemic ALCL.[8] Among 50 patients, the ORR was 86% (53% CR). The most common treatment-related adverse events of any grade were peripheral sensory neuropathy (36%), nausea (24%), fatigue (22%), diarrhea (19%), and neutropenia (17%). The most common grade 3/4 adverse events were neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (10%). There were no grade 5 adverse events.

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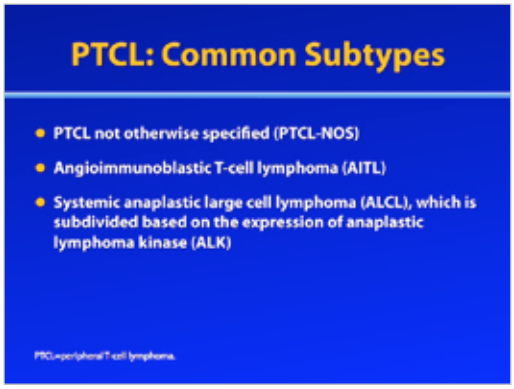


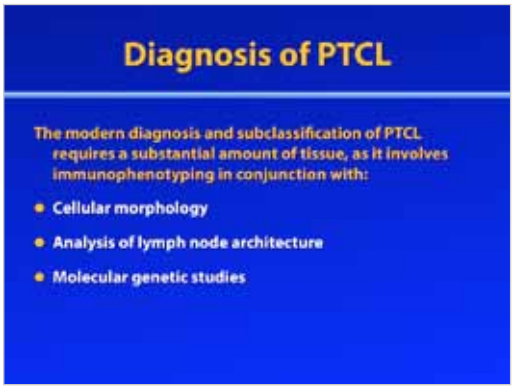


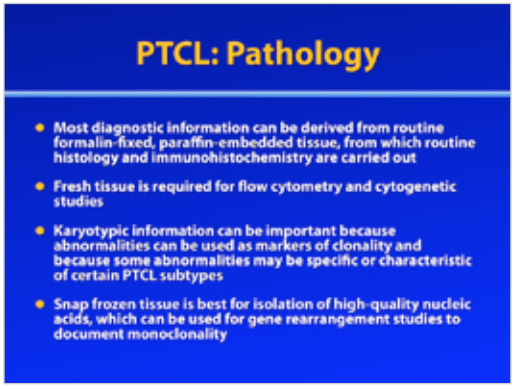


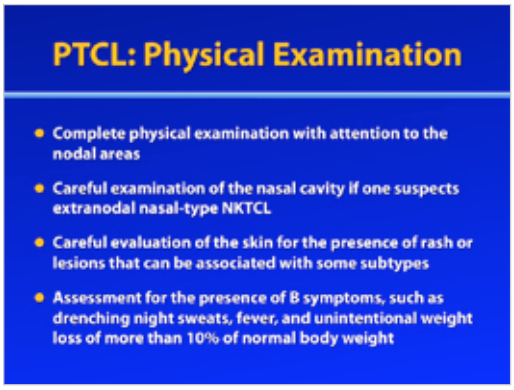


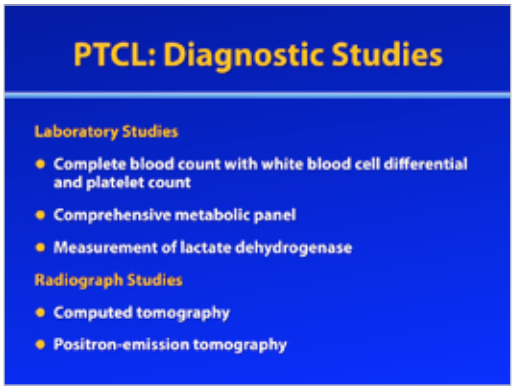


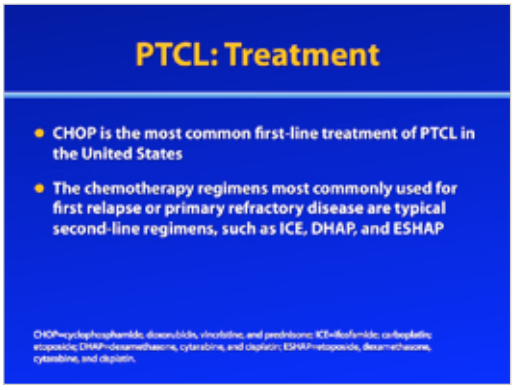

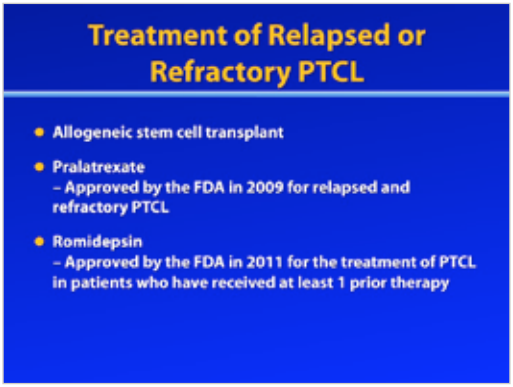


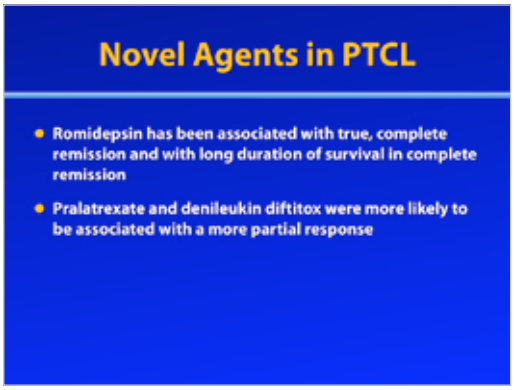


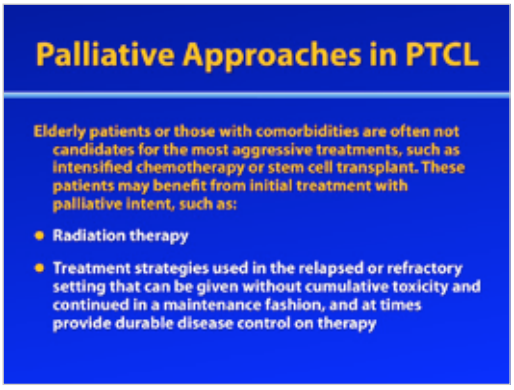


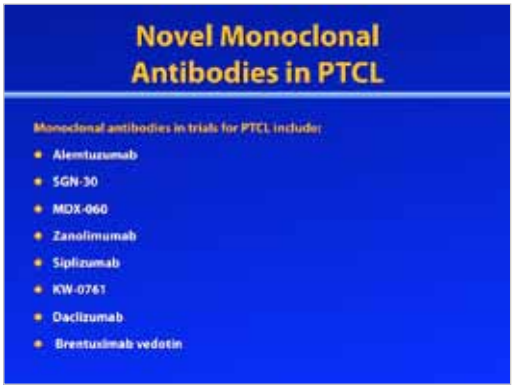


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