How I treat the peripheral T-cell lymphomas

Alison J. Moskowitz, Matthew A. Lunning and Steven M. Horwitz
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The peripheral T-cell lymphomas (PTCLs) encompass a heterogeneous group of diseases that have generally been associated with poor prognosis. The most common PTCLs, peripheral T-cell lymphoma, not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALK-negative), despite their unique presentations and histologies, are currently treated similarly. Here we discuss our general approach to the treatment of the most common PTCLs.

Introduction

The peripheral T-cell lymphomas (PTCLs) represent ~10% to 15% of non-Hodgkin lymphomas and are composed of 23 different entities, encompassing marked heterogeneous diseases (Table 1). Despite their significant differences in pathologic appearance and clinical presentation, the most common entities, peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALK-negative ALCL), which account for ~60% of cases, tend to be treated similarly and represent the focus of this review. The management of other less common PTCLs, such as adult T-cell lymphoma/leukemia or extranodal natural killer (NK)/T-cell lymphoma, nasal type, for which treatments are unique, is beyond the scope of this review and is covered in depth elsewhere in this series.

In the absence of randomized clinical trials to drive treatment decisions in PTCL, we must rely on our interpretation of the best data currently available and our own experience. Our knowledge of the expected outcomes for patients with PTCL is largely based on 2 large retrospective series: the International T-Cell Project (ITCP) and the British Columbia Cancer Agency (BCCA) series, which reported outcomes on 1314 cases and 199 cases, respectively. When interpreting the results of prospective studies for new treatment strategies, we typically reference the ITCP or BCCA series, which is problematic given the potential biases in retrospective analyses and phase 2 clinical trials. As will be discussed here, our “standard” approach to the treatment of most people with PTCL involves induction chemotherapy, and we strongly consider consolidation with autologous stem cell transplant (ASCT).

However, this is an exciting time for clinical research in PTCL as we are in a time of transition. Multiple new agents are available with new strategies being designed and tested. As a result, conducting clinical trials of promising strategies is fundamental to our daily practice and patient care. We believe our current approaches are likely producing superior outcomes than seen in the historical datasets and we expect the management of PTCL to improve and become increasingly individualized in the upcoming years, although we are not there yet.

Case presentation

A previously healthy 60-year-old man developed intermittent fevers, night sweats, and fatigue. Initial physical exam and routine blood work were both unremarkable. About 2 months later, he developed acute onset abdominal pain, nausea, and vomiting and presented to an emergency room where he was diagnosed with infectious colitis and treated with antibiotics. He then developed a rash with swollen joints. Skin biopsy of his rash appeared reactive. He was empirically treated with prednisone with improvement of symptoms. Soon after, the abdominal pain returned, and a computed tomography scan showed intraperitoneal free air. He underwent emergent surgery for a perforated small bowel and was noted to have a large mass in the small bowel, which was resected with re-anastomosis.

Review of the resected mass showed (Figure 1A) complete effacement of the bowel wall with atypical intermediate to large lymphocytes with open chromatin and prominent nucleoli. Atypical cells infiltrated the surrounding fat. Immunohistochemistry demonstrated lymphocytes that were strongly positive for CD3, CD30 (positive in 80% of tumor cells) BCL-2, and MUM-1. CD4 was focally positive. CD8, CD10, EMA, CD5, CD20, CD56, EBER, ALK-1, CD25, CD15, and cyclin D1 were negative. The Ki-67 was 80%. Molecular studies showed a T-cell receptor (TCR) γ and β chain rearrangement. Changes
Diagnosis of PTCL

One of the more challenging aspects in managing PTCL is confidently arriving at the diagnosis. T-cell lymphomas are rare, and we try to approach new diagnoses with at least a little skepticism. For many B-cell lymphomas, reproducible immunophenotypic patterns and cytogenetic features allow for an algorithmic approach to diagnosis. On the contrary, T-cell lymphomas are often characterized by antigen aberrancy that may vary within a subtype or even over the course of disease. 7,8

Regarding our patient, the presentation raises the possibility of several entities including enteropathy associated T-cell lymphoma, ALCL, PTCL-NOS, and NK/T-cell lymphoma, nasal type. The diagnosis of PTCL-NOS was favored based on a combination of factors including our inability to document enteropathy clinically or serologically, the CD4 positivity, and the absence of NK markers or Epstein-Barr virus (EBV) antigens, as well as the somewhat smaller cell size and lack of uniform CD30 positivity.

Again compared with B-cell lymphomas, the diagnosis of PTCL relies more on an experienced pathologist combining histology, immunophenotype, molecular studies, and clinical presentation to assign a best diagnosis. Not surprisingly, agreement is not universal. In the ITCP, a consensus diagnosis (3 of 4 expert pathologists arriving at the same diagnosis) was only reached 74% to 81% of the time for ALK-negative ALCL, PTCL-NOS, and AITL. The diagnoses were significantly refined in 154 of 1314 cases when clinical information was added.6 This highlights the importance of communication with the pathologist, as clinical presentation can strongly influence the ultimate diagnosis for a number of PTCL subtypes.

Other key considerations include the importance of excluding a reactive process, particularly when aggressive clinical behavior is not seen (PTCL occasionally behaves in an indolent fashion), diagnosis is made on a fine needle aspiration only, or when a clonal TCR appears to be the primary or only reason for the diagnosis. There are described reactive or nonmalignant conditions that may mimic PTCL.9-11 The importance of distinguishing benign reactive infiltrates from malignant processes is obvious; however, it is not always clear that distinguishing 1 subtype of PTCL from another is critical, as the treatments are currently the same. However, with better understanding of the underlying biology, we expect a shift in management where treatment strategies are more specific to particular PTCL subtypes, and finetuned diagnoses are increasingly important.

Initial work-up

Returning to our patient, he underwent standard staging studies including computer tomography of the chest, abdomen, and pelvis, with bone marrow aspirate/biopsy, and human T-lymphotropic virus-1 (HTLV-1) serology. We add HTLV-1 testing for almost all our patients with PTCL as adult T-cell lymphoma/leukemia represents ~8% of our PTCL population and not all are present from endemic areas. The utility of this test will vary by geography; however, HTLV-1 status was the most common reason for reclassification in the ITCP, and knowledge of HTLV-1 status greatly affects our treatment strategy.

The great majority of patients with T-cell lymphoma have 18-fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET)-avid disease, and PET appears to be particularly helpful in identifying and following extranodal disease, which is common in PTCL (Figure 1B).12 Most patients have advanced stage disease on conventional staging and therefore stage or treatment plans rarely change following PET imaging; however, interim PET response is highly predictive of outcome in our patients treated with curative intent, and in that setting, a baseline study is needed.13,14

Outcomes with standard therapy: cyclophosphamide, doxorubicin, vincristine, and prednison

The ITCP and BCCA series are useful in informing us on the expected survival outcomes with CHOP (cyclophosphamide, doxorubicin, vincristine, prednison) in PTCL (Table 2). In the ITCP, >85% of

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Table 1. WHO 2008 mature T-cell and NK-cell neoplasms

<table>
<thead>
<tr>
<th>Mature T-cell and NK-cell neoplasms</th>
<th>Incidence (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell prolymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>T-cell large granular lymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Chronic lymphoproliferative disorder of NK cells†</td>
<td></td>
</tr>
<tr>
<td>Aggressive NK-cell leukemia</td>
<td></td>
</tr>
<tr>
<td>Systemic EBV-positive T-cell lymphoproliferative disease of childhood</td>
<td></td>
</tr>
<tr>
<td>Hydroa vacciniforme-like lymphoma</td>
<td></td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td>9.6</td>
</tr>
<tr>
<td>Extravascular NK/T-cell lymphoma, nasal type</td>
<td>10.4</td>
</tr>
<tr>
<td>Enteropathy-associated T-cell lymphoma</td>
<td>4.7</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>0.9</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td></td>
</tr>
<tr>
<td>Sézary syndrome</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous CD30+ T-cell lymphoproliferative disorders</td>
<td>1.7</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
<td>25.6</td>
</tr>
<tr>
<td>Primary cutaneous CD8+ T-cell lymphoma†</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous CD4+ small/middle T-cell lymphoma†</td>
<td>19.5</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, NOS</td>
<td></td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, ALK-positive</td>
<td>6.6</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, ALK-negative†</td>
<td>5.5</td>
</tr>
</tbody>
</table>

*Incidence among peripheral T-cell and NK/T-cell lymphoma from the International T-Cell Project.†Provisional entities.
patients received CHOP-based therapy, and in contrast to ALK-positive ALCN where the 5-year failure-free survival (FFS) was 60%, the 5-year FFS for PTCL-NOS, AITL, and ALK-negative ALCN were only 20%, 18%, and 36%, respectively. Similar outcomes were observed in the BCCA series with 5-year progression-free survival (PFS) of 29%, 13%, and 28% for PTCL-NOS, AITL, and ALK-N, respectively.5

Several prospective clinical trials in PTCL are available to inform us on the expected response rate to CHOP. In a phase 2 study evaluating CHOP induction therapy followed by ASCT for untreated PTCL, the overall response rate (ORR) to CHOP was 79% with a complete response (CR) rate of 39%.15 Similarly, a small phase 3 study from the GOELAMS (Groupe Ouest Est d’Etude des Leucémies aiguës et Autres Maladies du Sang) group of CHOP vs etoposide, ifosfamide, cisplatin alternating with adriamycin, bleomycin, vinblastine, and dacarbazine showed no difference in outcome for the 2 arms and resulted in an ORR of 70% and a CR rate of 35% with CHOP.16 What we conclude from the available data is that combination chemotherapy with CHOP is adequate to provide initial responses for many, but fewer achieve CRs and even fewer achieve durable remissions, although those with ALCN consistently fared better than those with AITL and PTCL-NOS. This raises the following question: is CHOP a platform to build on?

Alternatives to CHOP

The great majority of patients will receive CHOP, but due to the lack of compelling data, there is no currently agreed on standard frontline treatment or approach for PTCL. The absence of randomized data guiding a preferred approach supports keeping this an open question for ongoing and future clinical trials. To date, a number of attempts have been made to improve on CHOP, primarily by adding an additional seemingly active agent. These studies have in general shown possible small improvements in response rate but less promising rates of PFS, often due to excess toxicity. The clearest example of this is the addition of the anti-CD52 antibody, alemtuzumab, to CHOP, which in several phase 2 studies demonstrated impressive CR rates of 65% to 71%; however, serious treatment-related complications were observed including John Cunningham virus encephalitis, invasive aspergillosis, Pneumocystis carinii pneumonia, sepsis, EBV-related lymphoma, and cytomegalovirus reactivation.17-19 The frequency of life-threatening infections observed in these studies makes long-term benefits from this combination unlikely, although an ongoing study may answer this question more definitively (see Table 6). Similarly, in a phase 2 study of denileukin diftitox plus CHOP, the ORR and CR rates were 65% and 55%, respectively; however, 3 deaths occurred
following 1 cycle of therapy and 4 other patients were taken off the study due to toxicity.\textsuperscript{20} Other trials adding additional agents have similarly failed to show any clear benefits.\textsuperscript{21,22} Recognizing its inadequacies, the Southwest Oncology group abandoned CHOP-based therapy altogether and replaced it with a gemcitabine-based regimen: cisplatin, etoposide, gemcitabine, and Solu-medrol. Despite the rationale of combining active drugs against PTCL, the results of this phase 2 study were disappointing, with an ORR of only 39% and 2-year PFS of 12%.\textsuperscript{23}

The most compelling data supporting the benefits of building on CHOP come from studies adding etoposide (CHOEP). The German high-grade non-Hodgkin lymphoma study group analyzed the subset of patients with PTCL treated on 7 different prospective phase 2 or phase 3 protocols.\textsuperscript{24} Of 320 patients with PTCL enrolled in these studies, most had 1 of 4 of the major subtypes of PTCL: 78 patients with ALK-positive ALCL, 113 patients with ALK-negative ALCL, 70 patients with PTCL-NOS, and 28 patients with AITL. The disproportionate inclusion of ALCL is not explained. The authors found that younger patients (<60 years old) with normal lactate dehydrogenase (LDH) had a significant improvement in outcome if they received CHOP plus etoposide compared with CHOP alone, with 3-year event-free survival (EFS) of 75.4% vs 51%, although no difference in overall survival (OS) was observed. The benefits were greatest in the more favorable ALK-positive ALCL subtype, but there was a trend toward improved EFS in favor of CHOP plus etoposide in the other subsets as well ($P = .057$). In elderly patients, the addition of etoposide added significant toxicity. Overall, CHOEP appears to offer an advantage for select patients; however, its superiority over CHOP in the PTCLs needs to be confirmed. The Nordic group adopted CHOEP induction in their prospective study evaluating upfront stem cell transplantation for PTCL.\textsuperscript{25} In this phase 2 study, patients received bi-weekly CHOEP-14 followed by ASCT for the responders. The ORR to CHOEP was 82% with a CR rate of 51%. Although we must be cautious about conclusions in a phase 2 trial, the CR rate does appear better than in the prospective trial using CHOP by Reimer et al, where only 39% achieved a CR.\textsuperscript{15} Furthermore, the Nordic study included patients with a higher median age, 57 vs 46 years, and higher risk, International Prognostic Index (IPI) $\geq 2$, 72% vs 51%. On the basis of these results, we believe that adding etoposide to CHOEP represents a reasonable approach as long as it can be given without significant excess toxicity.

**Returning to our patient**

Our patient was found to have stage IV PTCL-NOS with 4 IPI risk factors (age, stage, LDH, and performance status 2), which would have been associated with a 5-year OS of only 11% in the ITCP. Furthermore, our patient has PTCL-NOS with CD30 expression in 80% of the malignant cells. The presence of high CD30 expression in PTCL-NOS has been shown to carry a particularly poor outcome as well.\textsuperscript{26} CHOP-based chemotherapy alone is unlikely to produce long-term remission for our patient and therefore CHOEP was initiated.

**Consolidation with autologous stem cell transplant in the front-line setting**

Based on phase 2 data, our desire to improve on the results obtained with standard chemotherapy programs, and our own clinical experience, our current practice for fit patients with PTCL-NOS, AITL, ALK-negative ALCL, and high-risk ALK-positive ALCL is to strongly consider consolidation in first remission with ASCT. There are again no randomized trials to support this treatment approach; however, several prospective studies suggest benefit from upfront ASCT (Table 3). The largest was the Nordic study by d’Amore and colleagues mentioned above.\textsuperscript{25} This study enrolled 160 patients with PTCL, including 39% with PTCL-NOS, 19% with ALK-negative ALCL, and 19% with AITL, and excluded ALK-positive ALCL. Most patients (81%) presented with advanced stage disease and 72% had IPI scores of 2 or more. Patients received CHOEP for 6 cycles (etoposide was omitted for patients >60 years of age) and those in CR or partial response proceeded to high-dose therapy with carmustine, etoposide, cytarabine, and melphalan (or cyclophosphamide) and ASCT. One hundred fifteen (71%) patients underwent ASCT. By intent-to-treat analysis, the 5-year OS and PFS were 51% and 44%, respectively. The patients with ALK-negative ALCL performed particularly well, with 5-year OS and PFS of 70% and 61%, respectively. The 5-year OS and PFS for patients with PTCL-NOS were 47% and 38%, respectively, and for AITL were 52% and 49%, respectively. Reimer and colleagues conducted the second largest prospective study evaluating ASCT in first remission after CHOP, which enrolled 83 patients.\textsuperscript{15} By intent-to-treat analysis,

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**Table 2. Characteristics and outcomes in common PTCL subtypes\textsuperscript{5,6}**

<table>
<thead>
<tr>
<th>PTCL subtype</th>
<th>N</th>
<th>Median age (years)</th>
<th>Percent IPI</th>
<th>5-year OS*</th>
<th>5-year FFS*</th>
<th>5-year OS by IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-1</td>
<td>2-3</td>
<td>4-5</td>
<td></td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| IPTCL        | 229 | 60 | 28 | 57 | 15 | 32% | 20% | 50% | 11% |}
| BCCA         | 117 | 64 | 30 | 47 | 22 | 35% | 29% | 64% | 22% |}
| AITL         |   |                   |     |     |     |       |                  |
| IPTCL        | 213 | 65 | 14 | 59 | 28 | 32% | 18% | 56% | 25% |}
| BCCA         | 10  | 66 | 0  | 30 | 70 | 36% | 13% | NR  | NR  |}
| ALCL ALK−    |   |                   |     |     |     |       |                  |
| IPTCL        | 72  | 58 | 41 | 44 | 15 | 49% | 36% | 74% | 13% |}
| BCCA         | 18  | 55 | 44 | 22 | 33 | 34% | 28%† | 66%† | 25%† |}
| ALCL ALK+    |   |                   |     |     |     |       |                  |
| IPTCL        | 76  | 34 | 49 | 37 | 14 | 70% | 60% | 90% | 33% |}
| BCCA         | 12  | 32 | 67 | 25 | 8  | 58% | 28%† | 66%† | 25%† |}

\*Data from International T-Cell Lymphoma Project in which >85% patients received an anthracycline-based regimen without upfront transplant.
†BCCA ALCL reported as both ALK− and −.
similar results were seen, with a 3-year OS rate at 48%. For those who were transplanted (66% of patients enrolled), outcomes were considerably more favorable, with a 3-year OS of 71%. Our institutional results closely mirror these experiences. Our standard approach has been induction chemotherapy with a CHOP-based regimen followed by consolidation with ASCT for those with PTCL-NOS, AITL, and ALK-negative ALCL. In an intent-to-treat analysis of 62 patients with a median age of 58 years (range, 22-75 years), 63% proceeded to transplantation, with a 4-year OS and PFS of 53% and 40%, respectively.13 The most powerful predictor of outcome in our series was interim PET; 53% of patients normalized their PET after 4 cycles of chemotherapy and in those who achieved interim PET-negative status, 59% were progression free at 5 years, including 53% of those with IPI of ≥3.

The results from both prospective studies compare favorably to historical controls from the ITCP and BCCA series. Furthermore, our institutional experience reinforces our ability to achieve these results in our patient population, thus providing rationale for upfront ASCT in PTCL. However, given the lack of randomized trials to guide upfront treatment in PTCL, whenever possible, we favor offering eligible patients enrollment on clinical trials. Outside of a clinical trial, we most frequently use the treatment approach evaluated in the Nordic study with 6 cycles of CHOEP-14 followed by consolidation with ASCT as this is the largest dataset with the best phase 2 outcomes.

Returning to our patient

He obtained a PET-negative CR to CHOEP and went on to consolidation with ASCT. He remains in remission now 9 months after ASCT. Had he presented today, he would have been offered enrollment in the ECHELON-2 (described below) study comparing brentuximab vedotin with CHOP without vincristine to CHOP in CD30-positive T-cell lymphomas with the plan for subsequent ASCT consolidation.

### Investigational approaches

In recent years, several promising new agents have become available for the treatment of PTCL in the relapsed setting (Table 4). Pralatrexate and romidepsin are both approved broadly for PTCL with ORRs in large phase 2 studies of 29% and 25%, respectively.27,28 Brentuximab vedotin is also approved in relapsed ALCL with an ORR of 86% in a smaller phase 2 trial.29 In addition, data from a phase 2 study in CD30 expressing non-Hodgkin lymphoma showed that brentuximab vedotin resulted in 54% and 33% ORRs in evaluable patients with AITL (N = 13) and PTCL-NOS (N = 21), respectively.30 These drugs have now been combined with standard upfront therapy: a phase 1 trial of brentuximab vedotin combined with CHOP without vincristine in CD30-expressing PTCL showed safety and efficacy at full doses, and a phase 1 study of romidepsin added to CHOP has determined the maximum tolerated dose for the combination.31,32 Both of these strategies are now being tested in international, randomized, phase 3 trials and once complete may be the first to challenge our current standards of care. In addition, a non-anthracycline treatment approach, with pralatrexate given in an alternating fashion with cyclophosphamide, etoposide, vincristine, and prednisone as part of initial therapy, was evaluated in a recently completed phase 2 study.33 Finally, a randomized study of maintenance pralatrexate vs observation after completion of CHOP or CHOP-like therapy is underway and will be the first to test this approach in PTCL.

### Is there a favorable risk PTCL who should be treated differently?

As seen in Table 2, the number of IPI risk factors greatly influences outcomes for each PTCL subtype, although the utility in AITL has been questioned.34 The prognostic index for PTCL-NOS, which includes age, performance status, LDH level, and bone marrow involvement, was prognostic for the patients with PTCL-NOS in the ITCP as well.8,35 Other prognostic indices such as the modified Prognostic Index for T-cell lymphoma and international peripheral T-cell lymphoma project score have been suggested for PTCL, and each has some value, although none of them provide a significant improvement over IPI in terms of impacting treatment strategies.36 Although we track the IPI in our daily practice, it rarely alters therapy, as even low-risk PTCL patients based on IPI have disappointing outcomes. For example, in the ITCP, the 5-year FFS for patients with 0 or 1 IPI risk factors was only 33% and 34% for PTCL-NOS and AITL, respectively. Clearly, even for these more favorable patients, reduced therapy is not validated. The 1 entity where IPI does factor into our treatment recommendations is in ALK-positive ALCL. This subtype is typically associated with a more favorable...
prognosis; however, the FFS for patients with 0/1, 2, 3, and 4/5 IPI risk factors is 80%, 60%, 40%, and 25%, respectively, suggesting that CHOP-based therapy alone may not be adequate for patients with higher-risk disease. This may be particularly true for patients presenting with ALK-positive ALCL over the age of 40. We therefore treat these higher-risk ALK-positive ALCL patients similar to patients who present with the less favorable PTCL entities. Likewise, younger patients with ALK-negative ALCL may represent a more favorable subset. In a retrospective analysis from the Groupe d’Etudes des Lymphomes de l’Adulte of 138 patients with ALCL treated on various prospective clinical trials, age (using a cutoff of 40) was determined to be one of the strongest prognostic factors in ALCL (even stronger that ALK status). Patients with ALK-negative ALCL who were <40 years old had similarly favorable outcomes to the ALK-positive patients in this age group; however, the majority of patients in this series received intensified chemotherapy (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone plus sequential consolidation) or up-front ASCT, and therefore it is unclear if these favorable patients would perform just as well with less intense treatment such as CHOP alone. Thus, we generally treat these patients as we treat the less favorable diseases with induction chemotherapy and ASCT consolidation.

### Relapsed and refractory disease

**Overall principles**

We recently described our approach to the treatment of relapsed/refractory PTCL. We typically aim for allogeneic stem cell transplant (alloSCT) in fit patients, as in our experience this has been more reliably curative than ASCT in the relapsed setting (discussed further below). Our initial choice of therapy at the time of relapse depends largely on the patients’ eligibility for transplant and donor status. Thus, patients with relapsed/refractory PTCL fall into 3 categories: transplant soon, transplant never, and transplant unclear. Transplant soon patients are those who have a donor identified and are physiologically eligible for alloSCT based on their lack of comorbidities. Transplant never patients are not eligible for transplant due to age, comorbidities, lack of donor, or personal choice. Finally, the transplant unclear patients represent those for whom a donor is not yet identified or whose comorbidities may preclude alloSCT; however, evaluation by a transplant physician is warranted to make this determination. The purpose for separating patients into these categories is that our choice of second-, third-, and subsequent-line regimens for PTCL include 2 major types of treatments. The first are multiagent regimens, such as ifosfamide, carboplatin, and etoposide or dexamethasone, cytarabine, and cisplatin, that have a higher potential to induce remission, but responses cannot be sustained due to inability to continue treatment beyond 3 or 4 cycles. The second category includes more tolerable treatments, such as romidepsin and pralatrexate, and an increasing number of promising agents in clinical trials such as alisertib, for which the ORR may not be as high, but responses can be sustained due to ability to tolerate continuous therapy. A recent review provides an overview of these agents, and available agents are summarized, along with associated responses and response durations, in Table 4. As seen in Table 4, the response to most of these therapies is similar, and therefore, the choice of therapy relies largely on expected side effects and treatment schedule. An exception is brentuximab vedotin, which should be the first choice for relapsed ALCL for patients who have not previously received it. We prefer the multiagent regimens for patients who are ready to proceed to alloSCT the moment they achieve an adequate response to therapy. Conversely, the other agents are better suited for patients in the transplant unclear or transplant never groups because sustained responses are desired to either buy time to find donors, undergo assessments by transplant specialists, or simply because there is no plan for transplant. For the transplant unclear and transplant never patients in particular, we favor enrollment in clinical trials testing promising agents for PTCL.

**Transplant in the relapsed/refractory setting**

Our preference for fit patients is for alloSCT in the relapsed/refractory setting. Our institutional data and others have shown that the use of autologous stem cell transplantation for relapsed PTCL, with a possible exception of ALCL, has rarely resulted in long-term disease control. This is somewhat controversial and a recent analysis from the Center for International Blood and Marrow Transplant Research registry points to better results with ASCT at relapse, although the series is overrepresented by ALCL including many with ALK-positive ALCL. Meanwhile, the emerging experience with allogeneic transplantation looks promising. Both

Table 4. Studies exclusively in relapsed/refractory PTCL

<table>
<thead>
<tr>
<th>Agents</th>
<th>Patients</th>
<th>Central response review</th>
<th>ORR</th>
<th>CR</th>
<th>PFS (months)</th>
<th>DOR (months)</th>
<th>OS (months)</th>
</tr>
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<tbody>
<tr>
<td>Romidepsin</td>
<td>130</td>
<td>Yes</td>
<td>25%</td>
<td>15%</td>
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<td>17</td>
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<tr>
<td>Belinostat</td>
<td>129</td>
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<td>26%</td>
<td>10%</td>
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<td>8.3</td>
<td>NA</td>
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<td>Pralatrexate</td>
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<td>13%</td>
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<td>10.5</td>
<td>14.5</td>
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<td>Bendamustine</td>
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<td>No</td>
<td>50%</td>
<td>28%</td>
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<tr>
<td>Brentuximab vedotin</td>
<td>58</td>
<td>Yes</td>
<td>86%</td>
<td>57%</td>
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<td>12.6</td>
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<td>Brentuximab vedotin</td>
<td>34</td>
<td>No</td>
<td>41%</td>
<td>24%</td>
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<td>7.6</td>
<td>NA</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>20</td>
<td>No</td>
<td>55%</td>
<td>30%</td>
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<tr>
<td>Alemtuzumab</td>
<td>14</td>
<td>No</td>
<td>36%</td>
<td>14%</td>
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<td>NA</td>
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</tbody>
</table>

PFS, DOR, and OS are all medians in months. DOR, duration of response; NA, not applicable.

†ALK patients only.
‡Non-ALCL patients; reported in abstract form: Lugano 2013.
§Reports only patients with PTCL-NOS; excludes patients reported with mycosis fungoides.

Table 5. Larger phase 2 studies of new agents with response by subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>PTCL-NOS</th>
<th>AITL</th>
<th>ALCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate by common subtype</td>
<td>31%</td>
<td>8%</td>
<td>29%</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>29%</td>
<td>30%</td>
<td>24%</td>
</tr>
<tr>
<td>Belinostat</td>
<td>23%</td>
<td>46%</td>
<td>15%</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>33%</td>
<td>54%</td>
<td>86%</td>
</tr>
</tbody>
</table>
myeloablative and reduced intensity allogeneic stem cell transplantation have demonstrated up to 60% 3-year PFS.\textsuperscript{43-45} Taken together, ASCT may be appropriate for some patients with relapsed ALCL who did not receive ASCT in the front-line setting; however, for the majority of patients with relapsed/refractory PTCL, we believe that alloSCT is more likely to be curative.

**Moving toward more individualized therapy**

We have thus far described a general approach to the treatment of the most common PTCL subtypes that, aside from a few exceptions, rarely takes into account the particular disease entity or underlying biology. The historical data we have thus far supports this one size fits all approach. As more studies are completed, we are seeing examples of differential responses and potentially unique activity in specific PTCL subtypes (Table 5). In the studies adding etoposide to CHOP and the use of ASCT consolidation, the ALCL subset seems to derive the greatest benefit.\textsuperscript{24,25} Perhaps the most obvious example for subtype-specific activity is brentuximab vedotin, which targets cells expressing CD30, the marker universally expressed on ALCL. Brentuximab vedotin induced responses in patient with relapsed/refractory ALCL, AITL, and PTCL-NOS.\textsuperscript{49,50} Likewise, crizotinib, an ALK inhibitor, demonstrated significant activity in a small number of patients with relapsed ALK-positive ALCL.\textsuperscript{46} The histone deacetylase inhibitors appear to have preferential activity in AITL, as was seen in the large phase 2 trial with belinostat, in which higher efficacy in AITL was observed.\textsuperscript{47} Furthermore, romidepsin was associated with the longest response durations in AITL compared with other entities in the phase 2 pivotal trial.\textsuperscript{48} Romidepsin is currently being evaluated in combination with CHOP in the front-line setting for PTCL, and this regimen has particular promise in AITL. Adding new agents to CHOP seems to be the most direct path forward, and with particularly active new agents, this carries the promise of real progress. However, as discussed above, previous attempts at this strategy have often been met with additional toxicity that outweigh the incremental improvements in efficacy. Based on the limitations of CHOP, it may ultimately take entirely new regimens to dramatically improve our results. This will, of course, be on a longer timeline with these new regimens likely coming from increased understanding of PTCL biology, which is already underway.

Recently, gene expression profiling identified molecular classifiers that improve classification and prognostication among ALK-negative ALCL, AITL, and PTCL-NOS.\textsuperscript{49,50} Furthermore, additional translocations and recurrent mutations have been identified that may help better classify PTCLs and identify potential treatment targets. Next-generation sequencing identified a novel translocation within ALK-negative ALCL: t(6;7).\textsuperscript{51} This typically led to reduced expression of the DUSP22 gene, which likely functions as a tumor suppressor and potentially identifies a unique entity within ALK-negative ALCL. A translocation producing an interleukin-2-inducible T cell kinase-spleen tyrosine kinase (ITK-SYK) fusion gene, t(5;9), was initially found in a subset of PTCL-NOS cases.\textsuperscript{52} SYK expression was subsequently evaluated in 141 PTCL cases by immunohistochemistry and found to be overexpressed in 94%, although the translocation was only detected in 39%.\textsuperscript{53} These findings suggest a potential role for SYK inhibitors in these entities.\textsuperscript{54} Mutations involving the TET2 gene appear to be common in AITL and PTCL-NOS expressing T-helper follicular cell markers; they are less frequent among the other PTCL-NOS cases (24%) and absent in ALCL.\textsuperscript{55} TET2 is involved in epigenetic control of transcription through DNA methylation, and inactivating mutations of this gene were first identified in myeloid malignancies. Theses mutations signify a biological connection between AITL and PTCL-NOS with AITL features (T-helper follicular-like PTCL-NOS) and suggest a role for hypomethylating agents.

We anticipate changes in our recommendations as we gain more knowledge about the underlying biology of the heterogeneous PTCLs and develop drugs and regimens that specifically target these distinct diseases.

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**Authorship**

Contribution: A.J.M., M.A.L, and S.M.H. designed and wrote manuscript.

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**Table 6. Ongoing phase III induction/maintenance clinical trials in PTCL**

<table>
<thead>
<tr>
<th>Trials</th>
<th>NCT #</th>
<th>Title</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECHELON-2</td>
<td>01777152</td>
<td>A Comparison of Brentuximab Vedotin and CHOP With Standard-of-care CHOP in the Treatment of Patients With CD30-positive Mature T-cell Lymphomas</td>
<td>Induction</td>
</tr>
<tr>
<td>Ro-CHOP</td>
<td>01796002</td>
<td>Phase 3 Multi-center Randomized Study to Compare Efficacy and Safety of Romidepsin CHOP (Ro-CHOP) Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma</td>
<td>Induction</td>
</tr>
<tr>
<td>A-CHOP-14</td>
<td>00725231</td>
<td>Immunotherapy in Peripheral T Cell Lymphoma - the Role of Alemtuzumab in Addition to Dose Dense CHOP</td>
<td>Induction</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>01420679</td>
<td>Study of Pralatrexate Versus Observation Following CHOP-based Chemotherapy in Previously Undiagnosed Peripheral T-cell Lymphoma Patients</td>
<td>Maintenance</td>
</tr>
</tbody>
</table>

NCT, national clinical trial.
References


