Changing the Paradigms of Treatment in Peripheral T-cell Lymphoma: From Biology to Clinical Practice

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Abstract

Despite enormous advances in our understanding of aggressive lymphomas, it is clear that progress in the peripheral T-cell lymphomas (PTCL) has lagged well behind other B-cell malignancies. Although there are many reasons for this, the one commonly cited notes that the paradigms for diffuse large B-cell lymphoma (DLBCL) were merely applied to all patients with PTCL, the classic “one-size-fits-all” approach. Despite these challenges, progress is being made. Recently, the FDA has approved four drugs for patients with relapsed/refractory PTCL over the past 5 years, and if one counts the recent Japanese approval of the anti-CCR4 monoclonal antibody for patients with adult T-cell leukemia/lymphoma, five drugs have been approved worldwide. These efforts have led to the initiation of no fewer than four randomized clinical studies exploring the integration of these new agents into standard CHOP (cyclophosphamide–Adriamycin–vincristine–prednisone)–based chemotherapy regimens for patients with newly diagnosed PTCL. In addition, a new wave of studies are exploring the merits of novel drug combinations in the disease, an effort to build on the obvious single-agent successes. What has emerged most recently is the recognition that the PTCL may be a disease characterized by epigenetic dysregulation, which may help explain its sensitivity to histone deacetylase (HDAC) inhibitors, and open the door for even more creative combination approaches. Nonetheless, advances made over a relatively short period of time are changing how we now view these diseases and, hopefully, have poised us to finally improve its prognosis.

See all articles in this CCR Focus section, "Paradigm Shifts in Lymphoma."

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Introduction

The T-cell lymphomas comprise approximately 10% to 15% of all cases of non-Hodgkin lymphoma, producing an incidence of approximately 6,000 to 10,000 cases per year in the United States. Presently, more than 22 different clinicopathologic subtypes of T-cell and natural killer (NK)–cell lymphomas/leukemias are recognized in the 2008 World Health Organization (WHO) Classification (1). As shown in Fig. 1, these entities can be generally categorized in two fashions: (i) as pre- or post-thymic disease; or (ii) based on primary anatomic site of origin as nodal, extranodal, cutaneous, or leukemic disease. Analogous to the role of the germinal center in B-cell ontogeny, the thymus represents the site of T-cell receptor gene rearrangement, and is the reference point that differentiates the pre- and post-thymic T-cell neoplasms. The sites of primary anatomic origin are not intended to be seen as the exclusive site of disease, but rather should be envisioned as a Venn diagram, with most entities variably involving multiple anatomic compartments.

In general, the mature or peripheral T-cell lymphomas (PTCL) exhibit an inferior outcome compared with aggressive B-cell lymphomas (2–6). Exceptions to this are the primary cutaneous cases, some indolent primary leukemic entities, and among the systemic noncutaneous, nonleukemic subtypes, the anaplastic lymphoma receptor tyrosine kinase (ALK)–protein expressing anaplastic large-cell lymphoma (ALCL), whose response to anthracycline-based regimens, such as CHOP (cyclophosphamide–Adriamycin–vincristine–prednisone), is similar to that seen in diffuse large B-cell lymphoma (DLBCL; refs. 7, 8). The PTCL entities originating from T cells belonging to the innate immune system occur often in adolescents or young adults and are predominantly extranodal in presentation, often recapitulating the physiologic homing of these cells to cutaneous and mucosal sites (9). Entities derived from...
T cells belonging to the adaptive immune system constitute more than two thirds of all PTCL cases, are found primarily in adults, and are more often nodal in origin (9). In this review, we will discuss the biologic and clinical heterogeneity of these rare diseases, and how treatment paradigms are beginning to change with the recognition of some disease principles, and the regulatory approval of several new drugs for patients with relapsed or refractory disease.

Genetic and Molecular Mechanisms of T-cell Lymphomagenesis

As noted above, mature T- and NK-cell lymphomas/leukemias, including PTCL, comprise a heterogeneous group of neoplasms derived from post-thymic T cells or NK cells. They are recognized for their diverse clinical presentations, aggressive clinical course, and poor response to conventional chemotherapy (10). Molecular and genetic characterization of these malignancies has lagged well behind B-cell lymphomas due to their rarity and often nonspecific morphologic and immunophenotypic features, which has hindered determination of the requisite cell of origin and classification into distinct biologic subtypes. Studies using conventional cytogenetic analyses over the past decades have revealed limited, recurrent karyotypic abnormalities, most lacking disease specificity (11–13). Recently, comparative genomic hybridization (CGH)

Figure 1. T-cell neoplasms: organ of origin or involvement and associated chromosomal and genetic alterations. Pre-thymic/thymic T-cell neoplasms represent malignancies of immature T cells and arise in central lymphoid organs (green), whereas mature T- and NK-cell neoplasms arise via oncogenic transformation of post-thymic T- and NK cells in peripheral lymphoid organs (blue). Recurrent chromosomal abnormalities and genetic mutations associated with the different entities, including putative transforming/driver chromosomal or genetic alterations (red) are listed. CLP, common lymphoid progenitor; CLPD-NK, chronic lymphoproliferative disorder of NK cells; ETP, early T-cell/thymocyte precursor; T-ALL, T-acute lymphoblastic leukemia; T-LGL, T-cell large granular lymphocytic leukemia; T-PLL, T-cell prolymphocytic leukemia.
studies, gene expression profiling, and gene sequencing studies have helped delineate genetic differences and similarities between different subtypes of PTCL (14–24).

Although space constraints preclude a detailed discussion of the salient features of all the important PTCL subtypes, we discuss some of the more common subtypes below.

**Peripheral T-cell lymphoma, not otherwise specified**

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is the most common subtype, accounting for 20% to 30% of all PTCL occurring worldwide (8). It is a clinically and morphologically heterogeneous entity, not fulfilling diagnostic criteria of other well-defined subtypes, and is generally associated with poor survival (25). Early gene expression profiling studies were unable to distinguish PTCL-NOS from other PTCL subtypes (21), though recent studies have suggested a relationship with either activated helper CD4⁺ or cytotoxic CD8⁺ T cells (24), with CD8⁺ lymphomas being associated with inferior survival (20). PTCL-NOS lacks specific, recurrent cytogenetic abnormalities, though complex cytogenetic aberrations have been associated with a poor prognosis (13). Recurrent chromosome gains of 7q that target cyclin-dependent kinase 6 (16) and 8q involving the MYC locus (15) have been reported in PTCL-NOS. A recurrent translocation t(5:9)(q33:32) resulting in the fusion of the IL2 inducible T-cell kinase (ITK) gene with the spleen tyrosine kinase (SYK) gene has been described in 17% of PTCL-NOS (26). Interestingly, transgenic mice expressing the ITK–SYK fusion transcript develop a T-cell lymphoma mimicking the human disease (27, 28). Although recent studies have not been able to detect similar frequencies of this genetic aberration in PTCL-NOS, overexpression of total and phosphorylated Syk tyrosine kinase, in the absence of SYK translocations, (29), raised the prospect that Syk inhibitors could be active drugs in these subsets.

A genome-wide next-generation sequencing analysis of PTCL led to the identification of recurrent translocations involving p53-related genes, including rearrangements of the TP63 gene with TBL1XR1 and ATXN1 genes (30). These gene fusions encode proteins that inhibit the p53 pathway and are associated with adverse clinical outcomes. Whole-exome sequencing of PTCL-NOS has revealed recurrent mutations in RHOA (8%–18%) and FYN (<3%), as well as in genes regulating DNA methylation (see below), DNA-damage response, and immune surveillance, though their prognostic significance is unclear (31–33).

**Angioimmunoblastic T-cell lymphoma**

Angioimmunoblastic T-cell lymphoma (AITL) is the second-most common PTCL subtype worldwide (8). It has a characteristic clinical presentation, often manifesting features of immune dysregulation (10). This PTCL subtype is one of the more common ones to exhibit increased numbers of latent Epstein-Barr virus (EBV)-infected B cells (>80% of cases), likely due to T-cell dysfunction, which can progress to/give rise to clonal B-cell proliferations and overt B-cell lymphomas. It is thought to be derived from T follicular helper (TFH) cells, based on phenotypic features and overexpression of genes characteristic of normal TFH cells (19, 34). Gene expression profiling cannot distinguish between AITL and subsets of PTCL-NOS (24), and the biologic relationship between AITL and PTCL-NOS exhibiting the TFH phenotype is unclear at present (35). Gains of chromosomes 3q, 5q, and 21 are recurrent alterations in AITL, although the genes affected by these abnormalities remain unknown (13). Recently, epigenetic alterations have been observed in AITL more frequently than in the other subtypes. Inactivating TET2 mutations were observed in AITL, ranging from 33% to 76%, with a lower frequency reported in PTCL-NOS (38%; refs. 36–39). Subsequently, DNMT3A mutations were also detected in these entities, with a significant fraction of cases (73%) also harboring TET2 mutations, suggesting oncogenic cooperation and deregulation of cytosine methylation in subsets of PTCL (39). A recent study comprising large numbers of B- and T-cell lymphomas documented IDH2 mutations at the R172 residue, exclusively in AITL (20%–45% of cases), though these mutations lacked prognostic significance (40). Whether these will serve as targets for therapy remains to be seen.

More recent whole-exome and genome sequencing analysis studies by multiple groups reported recurrent RHOA G17V mutations in 53% to 68% of AITL, and low-frequency mutations in genes that affect other T-cell functions, including T-cell receptor (TCR) signaling (CD28, FYN; refs. 31, 32). The RHOA G17V mutation interferes with RHOA signaling, possibly by sequestering activated guanine-exchange factors (GEF) and inhibiting wild-type RHOA function, which alters cell motility and proliferation and chemokine signaling, in addition to other unexplored functions. Of note, coexistence of RHOA and TET2 mutations was observed (31, 32).

**Anaplastic large-cell lymphoma, ALK-positive**

ALCL, ALK-positive (ALCL, ALK⁺) remains the only PTCL to date defined by recurrent chromosomal rearrangements. These involve the ALK gene located on chromosome 2p23. The nucloephosphmin gene, NPM, on 5q35 is the most common translocation partner, resulting in t(2;5)(p23; q35), in 55% to 85% of cases, while variant translocations involving ALK and other partner genes are detected in the remainder (41, 42). The translocation t(2;5)(p23;q35) results in the fusion protein NPM-ALK leading to constitutive activation of the ALK tyrosine kinase and alterations in signaling, metabolic, and prosurvival pathways. Other pathways also known to be altered by the translation have been shown to include the JAK3/STAT3, the PI3K/ AKT/mTOR, and the phospholipidase C-γ (PLC-γ)–mediated RAS–ERK pathways (41). Activation of Notch1 signaling by its ligand Jagged1, expressed on neoplastic and non-neoplastic cells ALK⁺ ALCL has also been reported (43). Overexpression of MYC is noted in a significant number of cases
and secondary MYC translocations have been associated with aggressive behavior (44, 45). A partial overlap of gene expression profiles between variant ALK translocations and NPM–ALK has been described (46). Interestingly, array CGH analysis of NPM–ALK and variant ALK translocations has revealed similar recurrent secondary genetic abnormalities, including gains of 17p and losses of 4q and 11q (17).

Anaplastic large-cell lymphoma, ALK-negative

ALCL, ALK-negative (ALK−) is a provisional entity in the WHO 2008 Classification. Although this PTCL subtype shares morphologic and immunophenotypic features with ALCL, ALK+, including CD30 expression, it characteristically lacks ALK translocations. ALCL, ALK− occurs in older individuals and has a poorer prognosis compared with ALCL, ALK+ (10). Array CGH analysis of ALCL, ALK− and ALCL, ALK+ has highlighted differences in secondary genetic aberrations between the two subtypes (17), and differential expression of microRNAs (47). Gene expression analysis of ALK− and ALK+ ALCL has revealed shared deregulation of kinase signaling cascades and regulators of apoptosis (48). ALCL, ALK+ shows overexpression of genes implicated in immune or inflammatory responses, regulation of the NF-κB signaling, and lymphocyte migration and adhesion, whereas ALCL, ALK− exhibits overexpression of genes involved in certain cytokine signaling pathways (49). A recent large genome-wide SNP array analysis study has shown recurrent losses of 17p13.3-p12 (TP53) and 6q21 (PRDM1) at a significantly higher frequency in ALCL, ALK− compared with ALCL, ALK+; with loss of either PRDM1 or TP53 conferring a worse prognosis (50).

Distinguishing between subsets of PTCL-NOS expressing CD30 and ALCL, ALK− remains a diagnostic challenge (51). This is reflected at the chromosomal and molecular level. PTCL, NOS, and ALCL, ALK− share karyotypic abnormalities, including gains of chromosomes 1q and 3p and losses on chromosome 6q, although the loci on 6q differ (13). CGH analysis has shown overlapping aberrations, including 6q and 13q losses, as well as subtype-specific abnormalities (14). Some groups have been able to discriminate between PTCL, NOS, and ALCL, ALK+ (52); a three-gene model, comprising TNFRSF8, BAXF3, and TMOD1 was reported to distinguish between PTCL, NOS, and ALCL, ALK+ (53). However, others showed overlapping profiles between PTCL, NOS CD30−, and ALCL, ALK− except for higher levels of pSTAT3 in the latter entity (54).

Next-generation sequencing analysis has identified a recurrent balanced translocation t(6;7)(p25.3;q32.3) in 10% of ALCL, ALK−, leading to the juxtaposition of the DUSP22 phosphatase gene on chromosome 6p25.3 with the fragile site FRA7H on 7q32.3, resulting in the down-regulation of DUSP22 and upregulation of MIR29 microRNAs located on 7q32.3 (29). A recent study reported mutually exclusive rearrangements of DUSP22 and TP63 in 30% and 8% of ALCL, ALK−, respectively, and significantly better 5-year overall survival (OS) for cases harboring DUSP22 rearrangements compared with those with TP63 rearrangements (55).

Principles of Upfront Treatment in PTCL

Notably, the conventional upfront treatment paradigms used for patients with PTCL are essentially derived from our experiences with aggressive B-cell lymphomas. Until 2009, no drug had ever been approved in the disease, thus, in the absence of specific drugs with activity in the disease, the best that could be done was to extrapolate from other aggressive lymphoma experiences.

CHOP/CHOEP/EPCH/other chemotherapy regimens

With the exception of ALCL, ALK+, outcomes with CHOP in PTCL have been modest, with encouraging overall response rate (ORR) of 60% to 70%, but subsequent OS rates at 5 years in the range of 25% to 35% and even lower progression-free survival (PFS; ref. 3). As a result, various permutations of the CHOP backbone have been explored with modest improvements (Tables 1 and 2). The German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) reported a retrospective subset analysis on 320 patients with mostly nodal PTCL included in eight prospective DSHNHL trials (2). Patients under the age of 60 years with a normal lactate dehydrogenase (LDH) exhibited an improved outcome with CHOP plus etoposide (CHOEP) compared with CHOP alone (3-year EFS: 75.4% vs. 51%). A majority of the patients in that series (60%) had either ALCL, ALK− or ALK−. The greatest benefit of adding etoposide was seen in the ALCL, ALK− group (2). Another prospectively conducted phase II study from the German group demonstrated improved outcome with the addition of etoposide to the VACPE (vincristine, doxorubicin, cyclophosphamide, prednisone, etoposide) regimen. Five-year OS and event-free survival (EFS) values were 62% and 48%, respectively (4). Another retrospective analysis described the experience at MD Anderson Cancer Center (Houston, TX) with the management of treatment-naïve PTCL within the period 1996–2002. Comparison of the CHOP regimen with substantially more intensive regimens revealed no significant difference in 3-year OS (5). Sung and colleagues (6) investigated the impact of CEOP-B (cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin) on PTCL. In the first-line setting, the intensive CHOP with gemcitabine (CHOP-EG) regimen was feasible in 26 patients with PTCL. At a median follow-up of 1 year, 70% of the patients were alive; however, the median EFS was only 7 months, suggesting that remissions were not durable. A cisplatin, etoposide, gemcitabine, and solumedrol (PEGS) regimen was investigated in the period 1996–2002. Comparison of the CHOP regimen with substantially more intensive regimens revealed no significant difference in 3-year OS (5). Sung and colleagues (6) investigated the impact of CEOP-B (cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin) on PTCL. In the first-line setting, the intensive CHOP with gemcitabine (CHOP-EG) regimen was feasible in 26 patients with PTCL. At a median follow-up of 1 year, 70% of the patients were alive; however, the median EFS was only 7 months, suggesting that remissions were not durable. A cisplatin, etoposide, gemcitabine, and solumedrol (PEGS) regimen was investigated in patients with both newly diagnosed and relapsed PTCL in a recent phase II SWOG trial (36). In newly diagnosed patients, the study revealed a disappointing ORR of 38% and a 2-year PFS of only 14%. In summary, anthracycline-
sparing regimens have so far failed to demonstrate superiority to CHOP/CHOEP/EPOCH as a standard chemotherapy backbone (8, 57). With regard to entity-specific treatment strategies, the extranodal natural killer/T-cell lymphoma (ENK/TL) has a unique place in the context of PTCL. Because it seems to be unequivocally sensitive to L-asparaginase–containing regimens such as SMILE (dexamethasone, methotrexate, ifosfamide, etoposide) and AspaMetDex (L-asparaginase, methotrexate, dexamethasone; refs. 58,59). Anthracycline-based regimens (CHOP or CHOP-like) are not effective in this subtype (60), which is much more frequent in Asians than Caucasians. Addition of radiation to chemotherapy is the preferred treatment for localized disease. EBV DNA copy number from plasma or whole blood can be used as a biomarker for response. Therefore, serial monitoring of EBV DNA copy number is recommended (61). In enteropathy-associated T-cell lymphoma (EATL), recent reports indicate that for patients sufficiently fit to tolerate more aggressive chemotherapy regimens than standard CHOP, outcome can be significantly improved. For example, 26 patients treated with a regimen including ifosfamide, vincristine, etoposide, and methotrexate followed by autologous stem cell transplant (ASCT), had a 5-year OS and PFS of 60% and 52%, respectively (62).

**Table 1. Comparative studies of first-line therapies for PTCLs (5, 62, 101)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>Histology</th>
<th>Regimen</th>
<th>( n )</th>
<th>CR</th>
<th>EFS/PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escalon 2005 Retrospective single center</td>
<td>ALCL excluded</td>
<td>PTCL-NOS, 57%</td>
<td>CHOP</td>
<td>24</td>
<td>59%</td>
<td>3 y, 43%</td>
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<tr>
<td></td>
<td></td>
<td>AITL, 14%</td>
<td>Intensive: HyperCHOP</td>
<td>52</td>
<td>58%</td>
<td>3 y, 49%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Angio-centric T/NK, 8%</td>
<td>Hyper-CVAD</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td>Simon 2010 Prospective phase III</td>
<td>PTCL-NOS, 65%</td>
<td>CHOP</td>
<td>45</td>
<td>33%</td>
<td>2 y, 41%</td>
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<tr>
<td></td>
<td></td>
<td>AITL, 17%</td>
<td>VIP-ABVD</td>
<td>43</td>
<td>44%</td>
<td>2 y, 45%</td>
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<tr>
<td></td>
<td></td>
<td>ALCL ALK+, 11%</td>
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<tr>
<td></td>
<td></td>
<td>ALCL ALK-, 3%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Schmitz 2010 Retrospective subset analysis of prospective DSHNHL studies</td>
<td>Age &lt;60 y/normal LDH</td>
<td>CHOP</td>
<td>41</td>
<td>N/A</td>
<td>3 y, 51%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>ALCL ALK+, 24%</td>
<td>CHOEP</td>
<td>42</td>
<td>N/A</td>
<td>3 y, 75%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>PTCL-NOS, 22%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AITL, 9%</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: ASHAP, doxorubicin, methotrexate, cytarabine, cisplatin; CR, complete remission; EFS, event-free survival; Hyper-CVAD, cyclophosphamide, mesna, doxorubicin, vincristine, prednisone, methotrexate, cytarabine; M-BACOS, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, methylprednisolone; MINE, mesna, ifosfamide, mitoxantrone, etoposide; VIP-rABVD, etoposide, ifosfamide, cisplatin, doxorubicin, bleomycin, vinblastine, dacarbazine.

**Upfront autologous and allogeneic stem cell transplant in PTCL**

To date, the role of upfront ASCT in PTCL has not been investigated in a randomized trial. Thus, it is hard to be too dogmatic about the value of ASCT as consolidation in this setting. However, since 2006 there have been an increasing number of phase II trials evaluating upfront ASCT in PTCL (Table 3; refs. 62–70). ALCL, ALK+ patients have characteristically been excluded from these studies due to their superior outcome with conventional regimens compared with the other PTCL subtypes (Table 3). The two studies that are most homogeneous and comparable are also the two largest (65, 70). The German study by Reimer and colleagues reported on 83 patients treated initially with four courses of CHOP-21 (every 3 weeks), restaged and treated by two additional courses if not in complete remission (CR). Patients in CR/PR received one to two courses with either Dexam-BEAM (dexamethasone, carmustine, etoposide, ara-C, and melphalan) or ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) followed by high-dose therapy (HDT)/ASCT with total body irradiation and high-dose cyclophosphamide as the conditioning regimen. After induction treatment, 32 patients were in CR and 33 in partial remission (PR; ORR 78%). Of these 65 patients, 55 (66% of the entire cohort) underwent HDT/ASCT. At a median follow-up of 33 months, 3-year OS, PFS, and DFS were 48%, 36%, and 53%, respectively. Among the 55 transplanted patients, the 3-year OS was 71%. Among the 28 not-transplanted patients, 3-year OS was only 11%. Recently, the Nordic group published the final results of a large phase II trial, in which six courses of biweekly CHOP/EPOCH were followed by ASCT in chemosensitive patients (65). The ORR rate was 82% with 51% of the patients achieving a CR. At a median follow-up of 4.5 years, the estimated 5-year OS and PFS were 70% and 61% (ALCL, ALK+), 52% and 49% (AITL), 47% and 38% (PTCL-NOS), respectively. On the basis of these experiences, a dose-dense CHOP/EPOCH-based regimen followed by
ASCT in chemosensitive and transplant eligible patients represents at present one of the most evidence-based approaches (level IIIB) adoptable outside of a clinical trial. Although there are no randomized data, it is our shared sentiment that consolidation by ASCT should be strongly considered in patients with PTCL with chemosensitive disease who are transplant eligible.

Allogeneic stem cell transplant (AlloSCT) is a potentially curative option for patients with PTCL. The first prospective phase II results demonstrated sustained responses in patients with relapsed and refractory PTCL, suggesting the existence of a possible “graft-versus-T-cell lymphoma” effect (71). In the more rare extranodal subtypes, data are anecdotal, but generally supportive of the feasibility and efficacy of AlloSCT. Ongoing clinical trials are testing the role of AlloSCT as an upfront strategy in PTCL. The first prospective trial has been recently published by Corradini and colleagues (63), following the induction phase with intensive chemoimmunotherapy, responding patients with PTCL were randomized to ASCT or AlloSCT based on the availability of a HLA identical sibling or matched unrelated donor. Although sample size did not allow declaring one approach superior to the other, allografted patients had a 4-year PFS of 69%. Recently, Voss and colleagues reported their experience in hepatosplenic T-cell lymphoma (HSTCL) with encouraging responses to the more intense regimens of ifosphamide, carboplatin, etoposide (ICE) or ifosfamide, etoposide, cytarabine (IVAC) followed by stem cell transplantation, followed by AlloSCT (72).

Combinations of conventional chemotherapy and new agents
Prospective studies have shown that early treatment failures remain an unsolved problem and novel induction strategies are needed. A recently concluded collaborative phase III study (ACT study) coordinated by the German and Nordic Lymphoma Groups evaluated the impact of the addition of the anti-CD52 antibody alemtuzumab to six courses of an intensified (biweekly) CHOP, in chemosensitive patients under the age of 60 years consolidated with ASCT. The trial, which recruited a total of 252 patients, is expected to be reported in May 2015. Other new drugs, such as brentuximab, vedotin, romidepsin, and pralatrexate, are currently being tested in upfront randomized trials comparing the new drug in combination with CHOP/

### Table 2. Prospective phase II studies in newly diagnosed PTCLs (4, 6, 56, 58, 102–104)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Histology</th>
<th>Regimen</th>
<th>ORR</th>
<th>CR</th>
<th>EFS/PFS</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>Karakas</td>
<td>1996</td>
<td>27</td>
<td>Pleomorphic, 52%</td>
<td>VACPE</td>
<td>77%</td>
<td>5</td>
<td>48%</td>
<td>5 y, 62%</td>
</tr>
<tr>
<td>Sung</td>
<td>2006</td>
<td>52</td>
<td>PTCL-NOS, 79%</td>
<td>CEOP-B</td>
<td>63%</td>
<td>17%</td>
<td>5 y, 30%</td>
<td>5 y, 49%</td>
</tr>
<tr>
<td>Kim</td>
<td>2006</td>
<td>26</td>
<td>PTCL-NOS, 54%</td>
<td>CHOP-EG</td>
<td>77%</td>
<td>58%</td>
<td>1 y, 50%</td>
<td>1 y, 70%</td>
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<tr>
<td>Gallamini</td>
<td>2007</td>
<td>24</td>
<td>PTCL-NOS, 58%</td>
<td>CHOP- Alemtuzumab</td>
<td>75%</td>
<td>71%</td>
<td>2 y, 48%</td>
<td>2 y, 53%</td>
</tr>
<tr>
<td>Kim</td>
<td>2011</td>
<td>20</td>
<td>Stage IV ENK/TL, 100%</td>
<td>SMILE</td>
<td>80%</td>
<td>40%</td>
<td>1 y, 45%</td>
<td>1 y, 45%</td>
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<tr>
<td>Kim</td>
<td>2012</td>
<td>46</td>
<td>PTCL-NOS, 35%</td>
<td>Bortezomib-CHOP</td>
<td>76%</td>
<td>65%</td>
<td>3 y, 35%</td>
<td>3 y, 47%</td>
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<tr>
<td>Mahadevan</td>
<td>2013</td>
<td>26</td>
<td>PTCL-NOS, 46%</td>
<td>PEGS</td>
<td>38%</td>
<td>23%</td>
<td>2 y, 14%</td>
<td>2 y, 36%</td>
</tr>
<tr>
<td>Foss</td>
<td>2013</td>
<td>49</td>
<td>PTCL-NOS, 39%</td>
<td>Denileukin diftitox-CHOP</td>
<td>65%</td>
<td>55%</td>
<td>2 y, 43%</td>
<td>2 y, 65%</td>
</tr>
</tbody>
</table>

Abbreviation: SPTCL, subcutaneous panniculitis-like T-cell lymphoma.
<table>
<thead>
<tr>
<th>Author Year</th>
<th>N</th>
<th>Histology</th>
<th>Induction</th>
<th>Pre-ASCT ORR</th>
<th>Pre-ASCT CR</th>
<th>Proceeded to ASCT Conditioning</th>
<th>EFS/PFS 12 y</th>
<th>OS 12 y</th>
<th>CR 12 y</th>
<th>CR 18 y</th>
<th>CR 36 y</th>
<th>CR 48 y</th>
<th>Conditioning 3 y</th>
<th>CR 48 y</th>
<th>Conditioning 5 y</th>
<th>CR 48 y</th>
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<th>CR 48 y</th>
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<th>CR 48 y</th>
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<tbody>
<tr>
<td>Corradini 2006</td>
<td>62</td>
<td>PTCL-NOS, 45% APO/DHAP/CCE/Ara-C or 73%</td>
<td>74%</td>
<td>56%</td>
<td>74%</td>
<td>Mitoxantrone-12 y, 30%</td>
<td>12 y, 34%</td>
<td>3 y, 30%</td>
<td>3 y, 33%</td>
<td>4 y, 39%</td>
<td>4 y, 39%</td>
<td>4 y, 39%</td>
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<td></td>
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</tr>
<tr>
<td>Rodriguez 2007</td>
<td>26</td>
<td>PTCL-NOS, 42% BACMA/BEAM</td>
<td>46%</td>
<td>65%</td>
<td>73%</td>
<td>BEAM 3 y, 53%</td>
<td>3 y, 46%</td>
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<tr>
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<td>41</td>
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<td>49%</td>
<td>41%</td>
<td>41%</td>
<td>BEAM 3 y, 53%</td>
<td>3 y, 46%</td>
<td>3 y, 46%</td>
<td>3 y, 46%</td>
<td>4 y, 49%</td>
<td>4 y, 49%</td>
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<td>Reimer 2009</td>
<td>83</td>
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<td>49%</td>
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<td>49%</td>
<td>BEAM 3 y, 53%</td>
<td>3 y, 46%</td>
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<td>Nickelsen 2009</td>
<td>33</td>
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<td>39%</td>
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<td>39%</td>
<td>BEAM 3 y, 53%</td>
<td>3 y, 46%</td>
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<td>Sieniawski 2010</td>
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<td>PTCL-NOS, 39% BACMA/BEAM</td>
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<td>BEAM 3 y, 53%</td>
<td>3 y, 46%</td>
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<td>3 y, 46%</td>
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<tr>
<td>d’Amore 2012</td>
<td>186</td>
<td>PTCL-NOS, 39% BACMA/BEAM</td>
<td>39%</td>
<td>39%</td>
<td>39%</td>
<td>BEAM 3 y, 53%</td>
<td>3 y, 46%</td>
<td>3 y, 46%</td>
<td>3 y, 46%</td>
<td>4 y, 49%</td>
<td>4 y, 49%</td>
<td>4 y, 49%</td>
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<td></td>
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<tr>
<td>Corradini 2014</td>
<td>68</td>
<td>PTCL-NOS, 39% BACMA/BEAM</td>
<td>39%</td>
<td>39%</td>
<td>39%</td>
<td>BEAM 3 y, 53%</td>
<td>3 y, 46%</td>
<td>3 y, 46%</td>
<td>3 y, 46%</td>
<td>4 y, 49%</td>
<td>4 y, 49%</td>
<td>4 y, 49%</td>
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<td>5 y, 44%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim 2014</td>
<td>27</td>
<td>PTCL-NOS, 39% BACMA/BEAM</td>
<td>39%</td>
<td>39%</td>
<td>39%</td>
<td>BEAM 3 y, 53%</td>
<td>3 y, 46%</td>
<td>3 y, 46%</td>
<td>3 y, 46%</td>
<td>4 y, 49%</td>
<td>4 y, 49%</td>
<td>4 y, 49%</td>
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<td>Conditioning 5 y, 44%</td>
<td>5 y, 44%</td>
<td>Conditioning 5 y, 44%</td>
<td>5 y, 44%</td>
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</tbody>
</table>

Abbreviations: APO, doxorubicin, prednisolone, vincristine; Ara-C, cytarabine; BEAM, cytarabine, etoposide, melphalan, prednisone, bleomycin; DHAP, dexamethasone, cytarabine, cisplatin; IFEMA, ifosfamide, etoposide, melphalan, prednisone, vincristine; MACOP-B, cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin; TBI, total body irradiation; TBIC, TBI-cyclophosphamide, doxorubicin, etoposide; TBI-Mel, TBI-melphalan; TBI-VCT, TBI-etoposide, cyclophosphamide, vincristine, prednisone; AITL, anaplastic large cell lymphoma; ALCL, anaplastic large cell lymphoma; ENK/TL, enteropathy-type T cell lymphoma; NK, natural killer cell lymphoma; eTCL, enteropathy-associated T cell lymphoma; PTCL-NOS, peripheral T cell lymphoma, not otherwise specified; Reactivation of known gene expression in lymphoid tissues (REELIT); POET, peripheral T cell lymphoma, not otherwise specified; SMILE, ifosfamide, etoposide, melphalan, prednisone; Hyper-EFS, hyperemic, early failure syndrome; Phase I, phase I clinical trial; Phase II, phase II clinical trial; Phase III, phase III clinical trial; N/A, not available.
CHOP–like regimens versus CHOP alone. These efforts are likely to reduce the fraction of primary refractory or early relapses and thereby improve the overall outcome in PTCL.

Management of Relapsed and Refractory Disease

One of the areas where substantial progress has been made in managing patients with PTCL has been in the relapsed/refractory setting. As we discuss below and present in Table 4, a number of new agents have been recently approved for patients with PTCL, and select subtypes.

Pralatrexate

The first drug ever approved for the treatment of patients with relapsed or refractory PTCL was pralatrexate (Folynt) in 2009. Pralatrexate is an antifolate designed to have high affinity for the reduced folate carrier (RFC). The RFC is a unique oncofetal protein highly expressed on fetal and malignant tissue, which shuttles folates into the cell for purine and pyrimidine biosynthesis. It also coincidentally transports fraudulent mimics of folic acid, such as methotrexate, pralatrexate, and other antifols. After preclinical studies documented the marked activity of pralatrexate in lymphoma, an early phase II–I–II study demonstrated that among 48 assessable patients, the ORR was 31%, including 17% of patients who attained a CR (73, 74). Interestingly, all 8 patients who achieved a CR had T-cell lymphoma, and 4 of 6 patients with PTCL who achieved a PR were PET-scan negative. The activity was seen across all subtypes, in patients with chemotherapy refractory disease, and was found to be durable in the majority of patients.

On the basis of these data, the PROPEL study was launched. PROPEL was a registration-directed international phase II study of pralatrexate in patients with relapsed or refractory PTCL (75). The study enrolled 115 patients, of which 111 were treated with pralatrexate. Among this heavily treated patient population that included all aggressive subtypes of PTCL, the ORR was 29%, including 11% of patients who attained a CR. The duration of response was approximately 12 months. Interestingly, of the 15 patients who received pralatrexate as second-line therapy, the ORR by independent central review was 47%, with 20% of patients achieving a CR.

One of the major toxicities associated with pralatrexate has been mucositis. Although in the phase I experience the incidence of grade 3–4 mucositis was 21%, a substantial fraction of patients also experienced grade 2 toxicity (73). Recently, strategies to mitigate some of the mucositis risk have evolved around a dose titration approach and the use of leucovorin. On the basis of an extensive population pharmacokinetic model published by Mould and colleagues (76), both idiosyncratic area under the curve and pretreatment methylmalonic acid (and to a lesser extent homocystein) levels predicted the risk of mucositis. On the basis of these data, a gradual dose escalation of pralatrexate is recommended.

### Table 4. Summary of activity of new agents emerging for the treatment of PTCL

<table>
<thead>
<tr>
<th>Drug</th>
<th>PTCL subtypes</th>
<th>N</th>
<th>ORR/CR</th>
<th>PFS/DOR, mo</th>
<th>Prior therapies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pralatrexate</td>
<td>PTCL, 53%</td>
<td>111</td>
<td>29%/19%</td>
<td>3.5/12.4</td>
<td>3 (1–13)</td>
<td>73, 74</td>
</tr>
<tr>
<td></td>
<td>AIL, 15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>AILT, 12%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tMF, 18%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Blastic NK</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>ATLL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romidepsin</td>
<td>PTCL, 53%</td>
<td>130</td>
<td>25%/15%</td>
<td>4/16</td>
<td>1 (1–8)</td>
<td>84–86</td>
</tr>
<tr>
<td></td>
<td>AIL, 21%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brentuximab</td>
<td>PTCL, 57%</td>
<td>35</td>
<td>41%/23%</td>
<td>6.7/2/6</td>
<td>2 (1–9)</td>
<td>98, 99</td>
</tr>
<tr>
<td></td>
<td>AIL, 37%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendamustine</td>
<td>AILT, 53%</td>
<td>60</td>
<td>50%/28%</td>
<td>3/6.6</td>
<td>1 (1–3)</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>PTCL, 38%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belinostat</td>
<td>PTCL, 64%</td>
<td>129</td>
<td>25%/10%</td>
<td>1.6/13.6</td>
<td>2 (1–8)</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>AIL, 18%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>AIL, 10%</td>
<td></td>
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<tr>
<td></td>
<td>PTCL, 10%</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>tMF, 16%</td>
<td></td>
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</tr>
<tr>
<td>Alisertib</td>
<td>PTCL, 30%</td>
<td>42</td>
<td>24%/5%</td>
<td>3/not reported</td>
<td>3 (1–18)</td>
<td>100, 101</td>
</tr>
<tr>
<td></td>
<td>AIL, 21%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>tMF, 16%</td>
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<tr>
<td></td>
<td>ATLL, 10%</td>
<td></td>
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</tbody>
</table>

Abbreviation: tMF, transformed mycosis fungoides.

1Independent central review of response.

CHOP–like regimens versus CHOP alone. These efforts are likely to reduce the fraction of primary refractory or early relapses and thereby improve the overall outcome in PTCL.
pralatrexate, starting at 10 mg/m² and gradually escalating weekly to 20 mg/m² then to 30 mg/m² has been adopted. If a patient develops mucositis, the escalation is stopped or reduced (mucositis at 10 mg/m² is rare). In addition, based on the publication of Koch and colleagues, several groups have begun to demonstrate that the addition of leucovorin (15–25 mg orally every day or twice a day) can both abrogate any mucositis, and can be used prophylactically to preempt further mucositis without compromise in efficacy. Thus, in our practice, we routinely will use leucovorin at a dose of 15 mg orally twice a day in patients who have experienced any mucositis, holding the leucovorin the day before, day of, and day after pralatrexate administration. These practices are now being integrated into a number of ongoing clinical trials of pralatrexate, both in and outside the United States.

Targeting the epigenome in PTCL

A promising area of research in T-cell lymphoma involves epigenetic therapies. We can define epigenetics as the processes that ensure that the right genes are expressed at the right time, in the right quantity, and in the right place. This process is ensured by an expanding list of genes that themselves must be expressed at the right time and right place.

Critical to the control of gene transcription are the octomer of histone proteins known as the nucleosome. How densely the DNA and nucleosomes are packed depend, at least in part, on posttranslational modifications found on the 5’ ends of the histone proteins. These modifications include acetylation, methylation, phosphorylation, and ubiquitination, each having its own signal specificity. As illustrated in Fig. 2, enzymes that add, remove, and read these posttranslational modifications have been found mutated in cancer, as have proteins that remodel chromatin, and the histone proteins themselves (77). It is interesting to note that while we generally think of oncogenesis as involving loss of a tumor suppressor or gain of an oncogenic protein, these are usually separate events involving different proteins. Epigenetic mutational events in contrast are more complex, sometimes involving the same gene deranged by loss-of-function or a gain-of-function mutation.

Two lines of evidence have developed that support a role for targeting the epigenome in T-cell lymphomas. One is the discovery of mutations in epigenetic genes in PTCL, while the other centers around the activity of histone deacetylase (HDAC) inhibitors in T-cell lymphoma. Mutations in epigenetic genes in PTCL have been found in the mature T-cell subtypes PTCL-NOS and inAITL, as described above. Systematic sequencing of the rarer subtypes of PTCL and of cutaneous T-cell lymphomas (CTCL) is needed to determine the true incidence across the disease spectrum.

The mutations in epigenetic genes in angioimmunoblastic T-cell lymphoma (AITL) and PTCL-NOS have centered on pathways that result in aberrant DNA methylation (illustrated in Fig. 3). Two recent studies have shown...
mutations in TET2, IDH2, and DNMT3A, and in some patients, lymphoma samples have shown mutations in all the three genes (32, 36, 38–40). TET2 and IDH mutations increase DNA methylation. TET serves as a DNA demethylase; inactivating mutations interfere with its conversion of methylcytosine to hydroxycytosine. IDH mutations are activating, but result in the preferential production of 2-hydroxyglutarate (2HG) rather than the metabolic intermediate α-KG. TET2 is inhibited by 2HG, thereby promoting hypermethylation. 2HG also inhibits multiple lysine-specific demethylases, thereby promoting histone methylation as well as DNA methylation, and thus gene silencing.

The second line of evidence showing a role for epigenetic therapy in T-cell lymphoma is the activity of HDAC inhibitors. As of the recent approval of belinostat for PTCL, there are three approved agents of this class. Vorinostat was approved for CTCL, then romidepsin for CTCL and PTCL, and recently belinostat (82–87). These agents inhibit HDACs (erasers in Fig. 1), leading to an increase in the expression of genes that cause cell-cycle arrest or apoptosis. Vorinostat and belinostat are hydroxamic acid derivatives that inhibit both class I and II HDACs, whereas romidepsin is a cyclic peptide that inhibits primarily the class I HDACs. The class II HDACs deacetylate a number of cytoplasmic proteins, including Hsp90 and tubulin, which may play a role in HDAC inhibitor activity in some models. The activity of all these agents in T-cell lymphoma suggests that inhibition of the class I HDACs may be the decisive factor in this disease.

It has become increasingly clear that HDAC inhibitors have a more complex mechanism of action than simply altering gene transcription induced by histone acetylation. Laboratory studies have shown that while there is a global increase in histone acetylation, this does not correlate with cell death, beyond a required concentration threshold (88). It can be argued that the effect on chromatin (i.e., global histone acetylation leading to gene transcription) should be considered separately from the events leading to cell death. Furthermore, multiple laboratories have pointed to a critical role for apoptosis in effecting cell death following HDAC inhibitor exposure (89–92). These studies suggest that HDAC inhibitor efficacy could be increased by the addition of agents increasing the propensity of cells to undergo apoptosis. Examples include the addition of MAPK pathway inhibitors to increase levels of the proapoptotic protein BIM and the addition of proapoptotic BH3 mimetics (91, 93). In addition to these studies, numerous studies in the laboratory show synergy with DNA-damaging agents, and several studies have reported the efficacy of combined HDAC inhibitor and other epigenetic targeting agents (94–97). The challenge is how these laboratory insights might be used to explain and improve the clinical results in T-cell lymphoma. About a third of patients with PTCL obtain responses to HDAC inhibitors.

The recent belinostat data demonstrate again a remarkable efficacy for the HDAC inhibitors in T-cell lymphoma, suggesting that the T-cell lymphomas may represent a disease characterized by dysregulation of broad epigenetic functions, which may account in part for the sensitivity of these diseases to epigenetic drugs such as HDAC inhibitors and hypomethylating agents. However, a waterfall plot of the maximum change from baseline from the BELIEF study shows no evidence of a unique subgroup effect, as there is a continuum of maximum shrinkage, arguing against a subset
with an epigenetic lesion explaining response to the HDAC inhibitor. What the waterfall plot also demonstrates is some activity in more than 60% of patients, suggesting that combination therapies could improve the activity of belinostat and other HDAC inhibitors in patients with PTCL. Whether improved response and duration of response will come from other epigenetic agents, DNA-damaging agents, or agents directly targeting the mitochondrial apoptotic protein milieu remains to be determined in the clinical setting. Given the rarity of this disease, novel clinical trial designs are needed to identify best combinations to move forward.

Other new drugs and strategies

In addition to pralatrexate and HDAC inhibitors, a number of other drugs have emerged with promising activity in PTCL. One of these is the CD30-targeted antibody-drug conjugate brentuximab vedotin. Brentuximab vedotin was approved for the treatment of patients with ALC [both ALK (+) and (−)]. On the basis of a phase II study in patients with relapsed or refractory PTCL, brentuximab vedotin demonstrated an ORR of 84%, with 57% of patients achieving a CR (98). Interestingly, recent data have shown that when brentuximab vedotin was studied in patients with PTCL-NOS and AITL who had received a median of two lines of prior therapy, the ORR was 41%, with 24% of patients achieving a CR, with a median PFS of 2.7 months (99). Although the patient populations studied across the various clinical trials are markedly different, these data establish the notion that when normalized across the biologic and clinical heterogeneity that defines the PTCLs, many of these agents produce similar efficacy, albeit each have their own nuances with respect to toxicity and duration of benefit.

Another agent emerging as active in PTCL is the aurora A kinase inhibitor alisertib. In an early-phase II experience across all subtypes of B- and T-cell lymphomas, alisertib was shown to produce an ORR of 27% (n = 48), but among the 8 patients with heavily treated PTCL, 4 of 8 patients responded (100). What made the observation intriguing was that 3 of these patients continued treatment beyond one year, including 2 patients in CR, and 1 in PR. More recently, SWOG presented the results of a phase II study of alisertib in patients with PTCL (101). Among the 42 patients reported, representing a diverse selection of PTCL subtypes, the ORR was 24%, though surprisingly, none of the 7 patients with transformed mycosis fungoides responded. On the basis of these data, a randomized phase III clinical trial was launched comparing alisertib against deals' choice (pralatrexate/romidepsin/gemcitabine) in patients with relapsed or refractory PTCL. This study is now actively accruing around the world. Although the single-agent response rate of alisertib appears similar to that of the other agents in this setting, a biologic rationale supporting a combination study with romidepsin was advanced by Zullo and colleagues (108). In preclinical models of PTCL, these investigators demonstrated that the combination appears to exhibit profound synergy only in T-cell lymphoma and not in models of B-cell lymphomas. These findings are now being studied in a combination phase I study of alisertib and romidepsin in patients with B- and T-cell lymphoma (clinical trials at NCI, Bethesda, MD).

Conclusions

Advances in molecular and genetic analyses, especially the advent of high-throughput, next-generation sequencing technologies, are beginning to provide important and exciting insights into the molecular pathogenesis of mature T/NK-cell lymphomas (T/NK). The identification of recurrent mutations in previously well-characterized genes, as well as novel genetic aberrations deregulating as yet poorly understood signaling pathways, is creating new opportunities for better diagnosis and disease classification. Future studies are awaited to determine whether the emerging genetic abnormalities could serve as biomarkers for risk stratification and whether the pathways affected could be targeted by novel therapeutic agents. Irrespective, the approval of many new agents for this disease is creating a number of interesting paradigms for combination studies focused on novel backbones.

Disclosure of Potential Conflicts of Interest

O.A. O’Connor reports receiving commercial research grants from Acetylen Pharmaceuticals, Celgene, Mundipharma, Seattle Genetics, Spectrum Pharmaceuticals, and Takeda. F. D’Amore reports receiving commercial research grants from Amgen, Roche, and Sanofi-Aventis, and is a consultant/advisory board member for CH Life Sciences, Kyowa-Kirin, Mundipharma, and Takeda/Seattle Genetics. S.E. Bates reports receiving a commercial research grant from Celgene via CRADA with NCI. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: O.A. O’Connor, F. D’Amore, S.E. Bates
Development of methodology: O.A. O’Connor
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): O.A. O’Connor, G. Bhagat, D. Radeski
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): O.A. O’Connor
Writing, review, and/or revision of the manuscript: O.A. O’Connor, G. Bhagat, K. Ganapathi, M.B. Pedersen, F. D’Amore, D. Radeski, S.E. Bates
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): O.A. O’Connor
Study supervision: O.A. O’Connor

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