New Strategies in Peripheral T-Cell Lymphoma: Understanding Tumor Biology and Developing Novel Therapies

Kieron Dunleavy¹, Richard L. Piekarz², Jasmine Zain³, John E. Janik¹, Wyndham H. Wilson¹, Owen A. O’Connor⁴, and Susan E. Bates¹

Abstract

Peripheral T-cell lymphomas (PTCL) constitute a group of heterogeneous diseases that are uncommon, representing, in Western countries, only approximately 10% of all non-Hodgkin lymphomas. They are typically associated with a poor prognosis compared with their B-cell counterparts and are much less well understood with respect to tumor biology, owing to their rarity and biologic heterogeneity, and to the fact that characteristic cytogenetic abnormalities are few compared with B-cell lymphomas. Although the outcome for patients with anaplastic large cell lymphoma (ALCL), particularly anaplastic lymphoma kinase (ALK)–positive ALCL, is good, other types of PTCLs are associated with a poor prognosis, even with aggressive anthracycline-based chemotherapy. In this respect, there is a need for new approaches in these diseases, and this review focuses on and explores recent experience with novel therapies in PTCL. Clin Cancer Res; 16(23); 5608–17. ©2010 AACR.

Background

Peripheral T-cell lymphoma (PTCL) represents a heterogeneous group of clinicopathologically defined distinct T-cell lymphomas, the most common of which are PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL; constituting anaplastic lymphoma kinase (ALK)–positive and –negative cases; Fig. 1). Rarer subtypes include extranodal natural killer cell lymphoma (NKTL), adult T-cell leukemia/lymphoma (ATLL), and enteropathy-associated T-cell lymphoma (EATL). PTCL-NOS are nodal and extranodal mature T-cell lymphomas that do not fit under any of the other specifically defined entities of mature T-cell lymphoma in the current World Health Organization (WHO) classification and will likely be further categorized as gene expression profiling and DNA sequence analysis of these diseases advances (1). The largest evaluation of PTCL to date was done by the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study in which a cohort of 1,314 patients in 22 centers worldwide was studied (Fig. 2; ref. 2). Though the study was retrospective and therapeutic approaches varied widely, it provided interesting insights into the outcome of these rare lymphomas. Although patients with ALCL (particularly ALK positive) had a good outcome with anthracycline-based therapy (ALK-positive and -negative ALCLs showed 5-year overall survivals of 70% and 49%, respectively), overall survivals for patients with PTCL-NOS and AITL were poor, and interestingly, unaffected by the use of anthracyclines in the upfront setting. The 5-year overall survival for PTCL-NOS, AITL, and all NKTLs was 32% compared with 14% for ATLL.

Biology of peripheral T-cell lymphoma

The molecular biology of these diseases is poorly understood, which is, at least partially, due to the rarity of PTCL, and this has complicated the investigation and development of new targeted therapies (3). The notable exceptions to this are ALK-positive ALCLs, most commonly characterized by a translocation t(2;5)(p23;q35) between the ALK gene on chromosome 2 and the nucleophosmin (NPM) gene on chromosome 5 (1, 4); T-cell prolymphocytic leukemia (PLL) with translocations of the T-cell leukemia (TCL-1) or mature T-cell proliferation 1 (MTCP-1) gene to chromosome 14, the site of the alpha chain of the T-cell receptor; and ATLL, the first human neoplasm associated with retroviral infection (5). Although the t(2;5) translocation is found in more than 80% of cases of ALK-positive ALCL, variant translocations involving ALK and other partner genes on various chromosomes can also occur (6, 7). The transforming NPM-ALK fusion protein that results from the t(2;5) translocation encodes a tyrosine kinase receptor, resulting in the constitutive activation of ALK and its downstream pathways (8). ALK can be detected by immunohistochemistry, and whereas in the majority of cases with the classical t(2;5)/NPM-ALK translocation, ALK staining is both cytoplasmic and nuclear, it may be membranous or cytoplasmic in variant cases (1). PLL can occur in an inherited form associated with ataxia telangiectasia or in a sporadic form. In both cases, the majority of patients

Authors’ Affiliations: ¹Center for Cancer Research, National Cancer Institute, Bethesda, Maryland; ²New York University Cancer Institute, NYU Langone Medical Center, New York, New York

Corresponding Author: Kieron Dunleavy, National Cancer Institute, Building 10, Room 12N226, 10 Center Drive, Bethesda, MD 20892–1866. Phone 3014351007; Fax 3014801105; E-mail dunleavk@mail.nih.gov
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have a translocation of the TCL-1 gene into chromosome 14. TCL-1 and MTCP-1 have a similar protein structure and associate with protein kinase B (Akt) to drive proliferation of the cells (9). In ATLL, cells infected with HTLV1 integrate the viral RNA and express the tax gene, which induces an autocrine growth loop through upregulation of interleukin (IL)-2 and its receptor. This sequence immortalizes the infected T cells and, presumably, over the course of

Fig. 1. These Kaplan-Meier curves show: A, the overall survivals of patients with the most common subtypes of PTCL; B, the overall survivals of patients with the less common subtypes of PTCL; and, C, the overall survivals of patients with NKTCL. Reproduced with permission from the International T-cell Lymphoma Project, Vose et al. (2).
decades, allows the accumulation of genetic defects that result in overt malignancy. The only other molecular aberration identified in PTCL is isochromosome 7q, which is associated with hepatosplenic T-cell lymphoma. Most other T-cell lymphomas have not been defined molecularly (10). ALK-negative ALCL is poorly understood, and its inferior outcome suggests a derivation distinct from that of ALK-positive cases, although gene expression profiling has shown some overlap in expression patterns of kinases and apoptosis inhibitors, suggesting a common pathogenic mechanism. Although the pathogenesis of AITL is also poorly elucidated, recent work has shown overexpression of the chemokine CXCL13 by the neoplastic cells, suggesting derivation from follicular helper T cells (11–13).

Though gene-expression profiling studies in PTCL lag behind those in B-cell lymphomas, some recent studies, albeit with small numbers of patients due to the infrequency of these diseases, have suggested that the histopathologically defined PTCL subtypes have distinct molecular profiles (3, 14–16). Molecular classifiers have been constructed for AITL, ALK-positive ALCL, and ATLL (Fig. 3). In a recent study in which gene expression profiling was done on 144 cases of PTCL, the identification of a molecular subgroup, with features of cytotoxic T lymphocytes and a poor survival compared with the remaining PTCL-NOS cases, suggests that PTCL-NOS is a molecularly heterogeneous entity (3). This heterogeneity of lymphomagenesis makes it challenging to identify selective targets for drug development.

The biological basis for the poor treatment outcome for patients with PTCL, in contrast to patients with aggressive B-cell lymphomas, is not well understood. In the future, studies that incorporate technology such as microarray (that can interrogate the expression of thousands of genes) or deep DNA sequencing (that can identify all genetic changes) will likely help elucidate which distinct pathways are activated and transformed and provide insights into the role of epigenetic changes in these diseases.

### Treatment of peripheral T-cell lymphoma

With the exception of ALK-positive ALCL, which is highly curable with CHOP-like therapy and has a 3-year overall survival that approaches 80%, the outcome for patients with a new diagnosis of PTCL who receive anthracycline-based therapy is poor, and most patients relapse soon after initial treatment and die of their disease (2). Although historically, many studies in PTCL have included patients with ALCL, studies confined to PTCL-NOS using CHOP or CHOP-like regimens show disappointing outcomes with long-term survivals in the range of 20% (17). In one study of 36 newly diagnosed patients with PTCL-NOS who received CHOP-based chemotherapy, 1- and 2-year overall survivals were 61% and 25%, respectively. In the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study, whereas more than 85% of patients received an anthracycline-containing regimen, the 5-year overall survival for patients with PTCL-NOS, AITL, and NKTCLs was merely 32%. These results confirm the poor efficacy of current standard therapies and argue for the evaluation of new agents in these diseases. Over the past few years, a number of novel therapies with efficacy in the relapsed setting have emerged for PTCL. The suboptimal outcome for newly diagnosed patients with current standard therapeutic approaches suggests that novel agents should be investigated in clinical trials in the upfront setting in a window of opportunity approach to define their efficacy and their molecular mechanisms. Autologous bone marrow transplantation following second line therapy with regimens like ifosfamide, carboplatin and etoposide (ICE) and high-dose cytarabine, cisplatin and dexamethasone (DHAP), can be curative for patients with relapsed disease, particularly for patients with ALK-positive ALCL. (18). The experience of allogeneic transplantation in relapsed PTCL is limited to a small number of studies, and its role continues to be investigated (19, 20). Further studies to define the optimal conditioning regimens and the group of patients who would benefit most from allogeneic transplantation are necessary.
Pralatrexate was the first drug approved specifically for use in PTCL by the U.S. Food and Drug Administration (FDA) on the basis of its single agent activity in relapsed and/or refractory T-cell lymphoma (21). It is a targeted antifolate and specifically, a novel 10-deazaaminopterin, structurally similar to methotrexate, but rationally designed to have greater affinity for the reduced folate carrier (SLC19A1 or RFC-1; a fetal oncoprotein highly expressed on fetal and malignant tissue and the principal transporter through which folates and antifolates enter the cell), enabling the drug to be selectively accumulated in tumor cells (22).

On the basis of preclinical modeling in both T- and B-cell lymphoma cell lines, which showed better cytotoxicity for pralatrexate compared with methotrexate (in lymphoma cytotoxicity assays, pralatrexate had at least a 1-log lower 50% inhibitory concentration than methotrexate), a phase I-II study was undertaken in patients with both T- and B-cell lymphomas (23, 24). Although an every-other-week dose of 135 mg/m² was associated with problematic stomatitis, a weekly schedule of 30 mg/m² for 6 of 7 weeks, with folate and vitamin B12 supplementation, abrogated significant stomatitis that had been seen with the every-other-week schedule and reduced other toxicities (25). Though minimally effective in B-cell lymphoma, the activity in T-cell lymphoma was significant with complete and partial response rates of 28% and 24%, respectively, in

Fig. 3. Gene-expression–based molecular predictors of the major subgroups of PTCL from the International Peripheral T-Cell Lymphoma Project. A, AITL, B, ATLL, and C, ALK+ ALCL. D, The correlation between the molecular and the pathology-based diagnoses. Reproduced with permission from Iqbal et al. (3).
25 patients with relapsed and/or refractory T-cell lymphoma who received the once weekly schedule. Responses were seen across various types of PTCL, including many patients with PTCL-NOS. In responders, more than 50% achieved a durable remission of at least 6 months. Following on from the results of this study, an international phase II study in PTCL (PROPEL) was carried out (22), and was the basis for the accelerated approval granted by the FDA in 2009. In 109 evaluable patients, the overall response rate was 28% with 9% of patients achieving a complete response; the median duration of response was 9.4 months. In this multicenter study, the principal toxicities were thrombocytopenia, mucositis, neutropenia, and anemia. Shifting to a weekly schedule and treatment with folate and vitamin B12 have mitigated the risk of mucositis. The full clinical potential of palatrate in combination with other agents has yet to be determined. Recent studies have shown synergy with agents such as gemcitabine, paving the way for combination studies (26).

**Histone deacetylase inhibitors**

Acetylation of proteins is a posttranslational modification that occurs on the e-amino side chain of lysine amino acids; deacetylases are a family of enzymes that remove these acetyl groups. To date, histones have been the most characterized proteins for the posttranslational modification of acetylation. As a result, agents that block the activity of deacetylases are commonly referred to as histone deacetylase inhibitors (HDACi). Furthermore, the most commonly accepted hypothesis for the HDACi mechanism of antitumor activity is thought to be the ability of these agents to regulate gene expression. They have been shown to alter gene expression in a wide variety of tumor types and specifically have been shown to mediate increased expression of cell cycle regulators, cell type-specific differentiation genes, tumor antigens, and genes encoding proapoptotic proteins (27–30). However, with the discovery that multiple other proteins undergo posttranslational modification by acetylation, including numerous nuclear and cellular proteins, mechanisms of antitumor activity independent of regulation of gene expression through histones are potentially as important (31).

Romidepsin (FK228 or depsipeptide) was the first HDACi to show efficacy in patients with PTCL or cutaneous T-cell lymphoma (CTCL). In a report of four patients treated in a phase I study, one patient with PTCL-NOS had a complete response, and three patients with CTCL a partial response, prompting a phase II trial to assess its efficacy in patients with CTCL or PTCL (29, 32). Romidepsin is administered at a dose of 14 mg/m² given on days 1, 8, and 15 of an every-28-day cycle. An overall response rate of 34% and a complete response rate of 6% (with a median duration of response of 13.7 months) in 71 patients with CTCL was reported from a multi-institutional study, and in a separate registration trial of 96 patients, a similar overall response rate of 34% and complete response rate of 6% was observed (33, 34). The pooled data from these two trials were the basis of the FDA approval of this agent for patients with CTCL. Romidepsin was also studied in patients with PTCL in a multicenter study; of 46 evaluable patients, the overall response rate was 33% with a complete response rate of 11%; the median duration of response was 9 months (35). On the basis of these results, a confirmatory international study of romidepsin in PTCL is ongoing. The principal drug-related toxicities were fatigue, nausea, and thrombocytopenia. EKG changes consisting of T-wave flattening are noted in a majority of patients but have not been associated with cardiac damage (36). Electrolyte replacement to maintain high-normal potassium and magnesium and concurrent administration of antielectrolytes integral to ongoing studies, have made romidepsin well tolerated in both the CTCL and PTCL patient populations (33). Future clinical trials that will combine romidepsin with other agents in PTCL are important to improve efficacy and outcome.

Belinostat (PXD101) is another pan-HDAC inhibitor that has shown activity in both CTCL and PTCL. Recently, its activity in PTCL was reported (37). Patients received a dose of 1,000 mg/m² intravenously on days 1 to 5 of a 3-week cycle, and in 20 patients, the overall response rate was 25% with a complete response rate of 10%.

At this point in time, no data are available on the efficacy of the other HDACis in patients with PTCL, but it is very possible that these data will also show efficacy given the apparent activity of the entire class of agents in T-cell lymphomas. These agents include vorinostat, already FDA approved for the treatment of refractory CTCL, panobinostat, and entinostat (38, 39).

**Denileukin diftitox**

Denileukin diftitox (Ontak), a recombinant fusion protein, consists of IL-2 genetically fused with diptheria toxin. It binds to the IL-2 receptor (IL-2R), and the fusion toxin is endocytosed and cleaved, resulting in the release of the active diptheria toxin. This release leads to ADP ribosylation of the eukaryotic translation factor, elongation factor 2, with subsequent inhibition of protein synthesis and cell death. The limited expression of the IL-2R on activated T cells and T-regulatory cells and its high level of expression on many hematologic malignancies make it an attractive agent for clinical evaluation.

Denileukin diftitox was approved by the FDA for patients with refractory or relapsed CD25-positive CTCL on the basis of its activity in this disease (40, 41). It has also shown some efficacy in PTCL (42) and is currently being tested in combination with CHOP chemotherapy. A phase II trial that evaluated a dose of 18 μg/kg daily for 5 days every 3 weeks preliminarily reported an overall response rate of 48% and a complete response rate of 22% with minimal toxicity (42). A higher response rate was observed in patients with CD25+ tumors (61.5% versus 45.4%), and the median progression-free survival was 6 months. At present, denileukin diftitox administration in the setting of autologous transplantation is also being investigated in PTCL.
Novel monoclonal antibodies

Alemtuzumab. Alemtuzumab (Campath) is a humanized anti-CD52 monoclonal antibody that is approved by the FDA for relapsed and untreated B-cell chronic lymphocytic leukemia (B-CLL), but also has efficacy in T-cell lymphomas, particularly T-cell PLL. Alemtuzumab was evaluated in 39 patients with PLL and produced responses in 76% (60% complete response and 16% partial response; ref. 43). The median survival of patients was 10 months, but reached 16 months for patients who achieved a complete response. In a pilot study, it was investigated in 14 patients with heavily pretreated relapsed or refractory PTCL (44). Patients received a rapidly escalating dose during the first week followed by 30 mg, three times per week, for a maximum of 12 weeks. Though associated with significant hematologic toxicity and infectious complications (these included bacterial tuberculosis, herpes zoster, and pulmonary aspergillosis), the overall response rate was 36%, with 21% of patients achieving a complete response. This study showed that alemtuzumab has antitumor activity in PTCL, but the toxicity suggests that lower doses and/or different schedules should be explored. Sustained remissions with alemtuzumab have been reported in patients with ATL (45). Though its spectrum of activity and mechanism of action have not yet been elucidated, it likely works through a combination of different pathways that include complement-dependent cytosis, antibody-dependent cellular cytotoxicity (ADCC), and apoptosis. Alemtuzumab has been combined with doxorubicin-based chemotherapy, and although associated with a high response rate, treatment-related toxicity has been problematic over several studies (46). Intravenously administered alemtuzumab appears to be associated with a higher mortality rate than subcutaneous administration, again cautioning that dose and schedule need to be optimized (47–49). A phase III trial of CHOP-14 with or without subcutaneous alemtuzumab is currently ongoing.

SGN-30. CD30 is a cell membrane protein of the tumor necrosis factor receptor family and a regulator of cell growth and apoptosis (50). CD30 ligation with monoclonal antibodies or CD30 ligand produced apoptosis of ALCL cell lines in vitro and in murine xenograft models (51–54). On the basis of activity in animal models, anti-CD30 monoclonal antibodies were tested in CD30-positive hematologic malignancies. SGN-30 (anti-CD30 mAB) is a chimeric anti-CD30 monoclonal antibody that showed potent preclinical antitumor activity in both Hodgkin lymphoma and ALCL (50). In a phase I study in which the drug was administered once weekly, there was modest activity in ALCL and Hodgkin lymphoma (55). Adverse events were mild, and the maximum tolerated dose was not reached. A subsequent phase II study (in which the drug, again, was administered according to a weekly schedule) treated 41 patients with ALCL. The objective response rate in this group was 17.1%, and, interestingly, all the responses were in patients with ALK-negative disease, who typically have a worse prognosis than ALK-positive cases (56). Currently, clinical trials are ongoing combining SGN-30 with combination chemotherapy.

MDX-060. MDX-060 is a fully human anti-CD30 immunoglobulin (Ig) G1 κ monoclonal antibody that binds to the CD30 ligand with nanomolar affinity (57). It has been shown to inhibit growth of CD30-expressing tumor cells in preclinical models (58). It inhibits cellular proliferation through modulation of signaling and induces ADCC (58). In a phase I-II study, in patients with recurrent Hodgkin lymphoma and ALCL, the drug was administered on a once weekly schedule, up to a dose of 15 mg/kg, and the maximum tolerated dose was not reached (57). Although this study only enrolled seven patients with ALCL, two (28%) of these had a complete response. Interestingly, these patients predominantly had skin involvement with their lymphoma.

SGN-35. SGN-35 (brentuximab vedotin) is an antibody-drug conjugate in which anti-CD30 antibody is attached by an enzyme-cleavable linker to a potent, synthetic drug payload: monomethyl auristatin E, which inhibits microtubule polymerization. Preliminary results from a phase I weekly dosing study of SGN-35 suggested good efficacy in systemic ALCL (59).

Zanolimumab. Zanolimumab is a fully human monoclonal antibody that targets the CD4 antigen present on T-helper lymphocytes (60). The antibody prevents interaction between the CD4 receptor and the major histocompatibility complex II molecules and in this way interferes with T-cell activation. It is very effective in refractory CTCL, and preliminary results in a study in patients with PTCL showed encouraging activity with an overall response rate of 23%; there were two complete responses, one in a patient with PTCL-NOS and another in ATL (61). The development of zanolimumab was recently discontinued by Genmab because of slow patient recruitment into its pivotal study for zanolimumab in CTCL.

Siplizumab. Siplizumab is a humanized monoclonal antibody that targets the CD2 antigen present on most T and NK cells. Siplizumab showed activity in an animal model of ATLL with 50% of tumor-bearing animals cured with four weekly administrations of the antibody, and complete elimination of disease with a 6-month course of treatment. Two separate phase I trials of siplizumab showed promising activity in T-cell malignancies with partial and complete responses observed in patients with PTCL, ATLL, and large granular lymphocyte leukemia, but the development of Epstein-Barr virus–related lymphoproliferative disease (EBV-LPD) in 5 of 51 patients prompted closure of the single agent trials (62). Siplizumab is under evaluation in combination with rituximab in an attempt to prevent EBV-LPD. Downregulation of the CD2 receptor in response to antibody administration represents another potential problem in the use of this antibody.

KW-0761. KW-0761 is a defucosylated humanized anti-CCR4 antibody that has been evaluated in a phase I trial in patients with ATL or PTCL. The antibody is unique in that defucosylation enhances ADCC and permits a lower dose of antibody to be effective. Responses were observed in patients treated at doses ranging from 0.01 to 1 mg/kg, with the latter dose being evaluated in phase II trials (63).
Interestingly, this antibody also depletes T-regulatory cells and may exert some of its antitumor effect through this mechanism.

**Daclizumab.** Daclizumab is a humanized monoclonal antibody that inhibits IL-2 binding to its receptor IL-2R and is approved by the FDA for the prevention of renal transplant rejection (64). Basiliximab, a chimeric antibody that binds to the same receptor, would be anticipated to have similar activity. Neither antibody depletes CD25-expressing T cells, but daclizumab has activity in patients with smoldering and chronic ATLL, in which it interferes with the autocrine growth loop stimulated by tax (64).

A major difficulty in the use of most monoclonal antibodies directed at T-cell antigens to treat lymphoma resides in the necessary depletion of normal T cells that accompanies their use. T-cell depletion predisposes to the development of opportunistic infections and secondary malignancies and these combinations appear to be greater with the combination of monoclonal antibodies and chemotherapy. The addition of rituximab may prevent the development of EBV-LPD and the use of antiviral and antifungal prophylaxis may help reduce the incidence of opportunistic infections.

**Immunosuppressants and immunomodulatory agents**

Cyclosporine A is an antifungal metabolite with immunosuppressive effects. It has a suppressive effect on T cells at the early stages of activation and a direct cytotoxic effect on lymphocytes. This rationale led investigators to examine its role in ATLL, a disease that is characterized by complex immune dysregulation. Cyclosporine was administered twice daily for 6 to 8 weeks, with gradual tapering over several weeks and responding patients received maintenance therapy (65). Considering the poor outcome with standard therapy in this disease, the results with this drug were noteworthy. Eight of 12 (67%) patients with ATLL experienced a response, with 2 patients achieving a complete response; the median duration of response was 13 months (65). The investigators proposed that cyclosporine may act by inhibiting deregulated T-cell activation through the calcineurin-nuclear factor of activated T-cell (NF-AT) signaling pathway.

Lenalidomide, a derivative of thalidomide, has shown interesting efficacy across a broad range of lymphoid diseases (66–68). Its mechanism of action is poorly understood; in vitro it has direct antitumor effects, inhibits angiogenesis, and results in increased NK cells in tumor tissue. Recently, it was tested in patients with relapsed or refractory PTCL and administered at a dose of 25 mg once daily on days 1 to 21 of a 28-day cycle (69). In a preliminary report, the overall response rate was 30% in 23 evaluable patients, suggesting that further investigation of this drug in PTCL is warranted (69). Thalidomide, in a case report, showed efficacy in ATLL (70).

**Other agents in peripheral T-cell lymphoma**

Gemcitabine is a novel nucleoside analog that competes with the natural nucleotide deoxyctydine, arresting tumor growth and causing apoptosis. It also causes cell apoptosis through inhibition of ribonucleotide reductase. It has shown activity in relapsed T-cell lymphomas (71, 72). One study investigated its activity in patients with relapsed PTCL; gemcitabine was administered at a dose of 1,200 mg/m² on days 1, 8, and 15 of a 28-day cycle for a total of three to six cycles (71, 73). Albeit a small study, 55% of patients with PTCL had a response, with 30% achieving a complete response. Response duration ranged from 15 to 60 months (71, 73).

Pentostatin was tested at a dose of 3.75 or 5 mg/m² by intravenous bolus administration daily for 3 days on an every-3-weeks schedule in patients with relapsed T-cell lymphoma (74). Forty-two patients were evaluable for response, with an overall response rate of 54.8% observed. The median duration of remission was short at 4.3 months, but some responses were prolonged to more than 5 years. The major toxicities included nausea, neutropenia, and CD4 T-cell depletion.

Forodesine is a potent purine nucleoside phosphorylase inhibitor, which leads to T-cell selective intracellular dGTP accumulation, causing apoptosis. It has in vitro activity against a wide range of B- and T-cell diseases and has shown moderate efficacy in patients with CTCL in a preliminary analysis (75). Clofarabine is a deoxyadenosine analog that has increased stability compared with cladribine or fludarabine, and is under investigation in PTCL.

Bortezomib, a proteasome inhibitor, was initially approved for use in relapsed and/or refractory multiple myeloma and, subsequently, was also found to be very effective in mantle-cell lymphoma (76–78). It has also shown activity in T-cell lymphoma, mostly in CTCL but also in PTCL-NOS, with skin involvement (79). In previously untreated patients with PTCL and NKTL, it has been combined with CHOP and was well tolerated and an active combination (80).

A recently published study that evaluated the first clinically available spleen tyrosine kinase (Syk) inhibitor in recurrent B-cell lymphoma showed high objective response rates, particularly in patients with CLL and small lymphocytic leukemia (81). Overexpression of Syk has been shown in PTCL, and inhibition of Syk induces apoptosis and blocks proliferation in T-cell non-Hodgkin lymphoma cell lines (82, 83). Therefore, Syk inhibition is an interesting therapeutic strategy, and fostamatinib disodium is being investigated in PTCL.

**Bone marrow transplantation**

Although autologous transplantation has an established role in relapsed ALK-positive ALCL, as discussed earlier, the role of this strategy in the setting of other relapsed PTCLs or as frontline consolidation in PTCL has not been well established (84, 85). Allogeneic transplantation is a potentially effective therapy for some patients with relapsed T-cell lymphoma and is under investigation in prospective studies (86). For histologies like EATL and hepatosplenic γ-δ T-cell lymphoma, in which outcomes with conventional approaches are extremely poor and survivals short,
consolidation allogeneic transplantation following induction therapy should be investigated in clinical trials.

Conclusions

With the exception of ALK-positive ALCL, the outcome for most patients with PTCL is poor and significantly inferior to that of patients with aggressive B-cell lymphomas. Therapeutic advancement in T-cell lymphoma has been curtailed, at least in part, by the rarity of these tumors, which has made instituting large-scale clinical trials challenging. Additionally, there is a lack of reagents to do preclinical studies. While cell lines are limited from patients with T-cell neoplasms, efforts to develop these lines have the potential to increase our understanding of these diseases. Whereas the biology of many B-cell lymphomas has been well elucidated, the pathogenesis and pivotal pathways that characterize distinct T-cell lymphomas remain poorly understood at present. Recent gene-expression profiling studies, albeit in small numbers of patients, have shown that certain key signatures are associated with PTCL subtypes and suggest that more extensive and expansive molecular analyses are critical to advancement of the field. It is likely that defining the molecular abnormalities in T-cell lymphomas will provide an opportunity to develop specifically targeted agents.

In the preceding paragraphs, we have discussed a long list of agents with potential utility in PTCL: novel agents that are under study prior to registration and previously FDA-approved agents in which PTCL would represent an expanded indication. These agents include small molecules, monoclonal antibodies, immunomodulators, and conjugates, and represent a pipeline that is one of the most extensive in oncology. The fundamental question is how to move these compounds forward. At the present time, only one of these (pralatrexate) is FDA approved for PTCL. The approval was accelerated, indicating that further studies are required to confirm clinical benefit. Trials with HDACIs are completed, and submission to the FDA expected. For these therapeutic advances to be translated into long-term clinical benefit for patients with PTCL, it is imperative that a systematic clinical trial effort is instituted in this disease. Given its rarity and generally poor prognosis, most patients with PTCL should be considered for enrollment in clinical trials. In the context of these trials, it is critical to further develop international consortiums, and attempt to pair molecular characterization of tumors with drug development and investigation. Novel agents with activity in the relapsed setting need to be incorporated into upfront clinical trials, given the aggressiveness and frequently poor outcome of PTCL subtypes other than ALK-positive ALCL. Novel clinical trial designs, including adaptive designs, also need to be considered to increase efficiency. Window of opportunity trials offer the opportunity to test agents in newly diagnosed patients. The goal is to move agents from the long list of potential agents either off the list, or into their appropriate places in the armamentarium, and to bring the outcome for patients with PTCL up to that expected for patients with more curable types of lymphoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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