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New Strategies in Peripheral T-cell lymphoma: Understanding Tumor Biology and Developing Novel Therapies

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Abstract

Peripheral T-cell lymphomas (PTCLs) 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 to their B-cell counterparts and are much less well understood with respect to tumor biology, due to their rarity and biologic heterogeneity, and to the fact that characteristic cytogenetic abnormalities are few compared to B-cell lymphomas. While the outcome for patients with anaplastic large cell lymphoma (ALCL), particularly ALK-positive ALCL, is good, other types of peripheral T-cell lymphomas 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.

Background

Peripheral T-cell lymphoma represents a heterogeneous group of clinicopathologically defined distinct T-cell lymphomas, the most common of which are peripheral T-cell lymphoma 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)(figure 1). Rarer subtypes include extranodal natural killer T-cell lymphoma (NKTCL), 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 is performed[1]. The largest evaluation of PTCL to date was performed by the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study in which a cohort of 1314 patients in 22 centers worldwide was studied (figure 2)[2]. Though the study was retrospective and therapeutic approaches varied widely, it provided interesting insights into the outcome of these rare lymphomas. While patients with ALCL (particularly ALK-positive) had a good outcome with anthracycline-based therapy (ALK-positive and -negative ALCLs demonstrated 5-year overall survivals (OS) 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 OS for PTCL-NOS, AITL, and all NKTCLs was 32% compared to 14% for ATLL.

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Biology of PTCL

The molecular biology of these diseases is poorly understood. This is at least partially due to the rarity of PTCL and has complicated the investigation and development of new targeted therapies3. The notable exceptions to this are ALK (anaplastic lymphoma kinase)-positive anaplastic large cell lymphomas, 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 51›4; T-cell prolymphocytic leukemia (PLL) with translocations of the T-cell leukemia 1 (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 adult T cell leukemia/lymphoma (ATLL), the first human neoplasm associated with retroviral infection5. While the t(2:5) translocation is found in over 80% of cases of ALK-positive ALCL, variant translocations involving ALK and other partner genes on various chromosomes can also occur6›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 pathways8. ALK can be detected by immunohistochemistry and while 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 cases1. PLL can occur in an inherited form associated with ataxia telangiectasia or in a sporadic form. In both cases, the majority of patients 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 cells9. In ATL, cells infected with HTLV1 integrate the viral RNA and express the tax gene, which induces an autocrine growth loop through upregulation of interleukin 2 and its receptor. This immortalizes the infected T cells and presumably, over the course of decades, allows the accumulation of genetic defects that results 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 molecularly10. 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 demonstrated some overlap in expression patterns of kinases and apoptosis inhibitors, suggesting a common pathogenic mechanism. While the pathogenesis of AITL is also poorly elucidated, recent work has demonstrated overexpression of the chemokine CXCL13 by the neoplastic cells suggesting derivation from follicular helper T-cells11⁻13.

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 (figure 3). In a recent study where gene expression profiling was performed on 144 cases of PTCL, the identification of a molecular subgroup, with features of cytotoxic T lymphocytes and a poor survival compared to 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 PTCL

With the exception of ALK-positive ALCL, which is highly curable with CHOP-like therapy and has a 5 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 from their disease[2]. While 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, one and two year overall survivals were 61% and 25%, respectively. In the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study, while over 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 ICE and 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.

On the Horizon

Pralatrexate

Pralatrexate was the first drug approved specifically for use in PTCL by the Food and Drug Administration (FDA) based on its single agent activity in relapsed/refractory T-cell lymphoma[21]. It is a targeted anti-folate 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 anti-folates enter the cell), enabling the drug to be selectively accumulated in tumor cells22.

Based on preclinical modeling in both T and B cell lymphoma cell lines, which demonstrated better cytotoxicity for pralatrexate compared to 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]. While an every other week dose of 135mg/m^2 was associated with problematic stomatitis, a weekly schedule of 30mg/m^2 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 25 patients with relapsed/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, over 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 multi-center study, the principal toxicities were thrombocytopenia, mucositis, neutropenia and anemia. Shifting to a weekly schedule and treatment with folate and vitamin B12 has mitigated the risk of mucositis. The full clinical potential of pralatrexate in combination with other agents has yet to be determined. Recent studies have demonstrated synergy with agents such as gemcitabine, paving the way for combination studies26.

Histone deacetylase inhibitors

Acetylation of proteins is a post-translational 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 post-translational modification of acetylation. As a result, agents that block the activity of deacetylases are commonly referred to as histone deacetylase inhibitors (HDIs). Furthermore, the most commonly accepted hypothesis for their 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 pro-apoptotic proteins[27–30]. However, with the discovery that multiple other proteins undergo post-translational modification by acetylation, including numerous nuclear and cellular proteins, mechanisms of anti-tumor activity independent of regulation of gene expression through histones are potentially as important31.

Romidepin (FK228 or depsipeptide) was the first HDAC inhibitor to demonstrate efficacy in patients with PTCL or cutaneous T-cell lymphoma (CTCL). In a report of 4 patients treated on a phase 1 study, 1 patient with PTCL-NOS had a CR and 3 patients with cutaneous T-cell lymphoma (CTCL) a PR, 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/m^2 given on days 1,8 and 15 of an every 28-day cycle. An overall response rate of 34% and a CR 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 CR 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 multi-center 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 months35. Based on 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 damage36. Electrolyte replacement to maintain high-normal potassium and magnesium and concurrent administration of antiemetics, 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 demonstrated activity in both CTCL and PTCL. Recently, its activity in PTCL was reported[37]. Patients received a dose of 1000 mg/m^2 IV on days 1 to 5 of a 3-week cycle and in 20 patients, the overall response rate was 25% with a CR rate of 10%.

At this point in time, there is no data available on the efficacy of the other HDIs in patients with PTCL, but it is very possible that these will also show efficacy given the apparent activity of the entire class of agents in T cell lymphomas. These 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 interleukin-2 (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 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 based on 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 for patients with minimally treated PTCL. A phase II trial that evaluated a dose of 18μg/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 difitoxin administration in the setting of autologous transplantation is 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 prolymphocytic leukemia (PLL). Alemtuzumab was evaluated in 39 patients with PLL and produced responses in 76% (60% CR and 16% PR)[43]. The median survival of patients was 10 months, but reached 16 months for patients who achieved a CR. 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 mgs, 3 times per week, for a maximum of 12 weeks. Though associated with significant hematological toxicity and infectious complications (these included military tuberculosis, herpes zoster and pulmonary aspergillosis), the overall response rate was 36% with 21% of patients achieving a complete response. This study demonstrated that alemtuzumab has antitumor activity in PTCL but the toxicity suggests that lower doses/different schedules should be explored. Sustained remissions with alemtuzumab have been reported in patients with AITL[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 cytolysis, 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]. CD 30 ligation with monoclonal antibodies or CD30 ligand produced apoptosis of ALCL cell lines in vitro and in murine xenograft models[51–54]. Based on 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 demonstrated potent preclinical antitumor activity in both

Hodgkin lymphoma and ALCL50. In a phase I study where the drug was administered once weekly, there was modest activity in ALCL and HL55. Adverse events were mild and the maximum tolerated dose (MTD) was not reached. A subsequent phase II study (where again the drug 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 cases56. Currently, there are ongoing clinical trials 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 affinity57. It has been shown to inhibit growth of CD30 expressing tumor cells in preclinical models58. It inhibits cellular proliferation through modulation of signaling and induces ADCC58. In a phase I/II study, in patients with recurrent HL and ALCL, the drug was administered on a once weekly schedule, up to a dose of 15mg/kg - the maximum tolerated dose was not reached57. Although this study only enrolled 7 patients with ALCL, 2 (28%) of these had a complete response. Interestingly, these were patients who had predominantly skin involvement by their lymphoma.

SGN-35

SGN-35 (brentuximab vedotin) is an antibody-drug conjugate (ADC) 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 1 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 class 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 demonstrated encouraging activity with an overall response rate of 23% - there were 2 complete responses, one in a patient with PTCL-NOS and another in AITL[61]. The development of zanolimumab was recently discontinued by Genmab due to 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 demonstrated activity in an animal model of ATLL with 50% of tumor-bearing animals cured with 4 weekly administrations of the antibody and complete elimination of disease with a six-month course of treatment. Two separate phase I trials of siplizumab demonstrated 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 five 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. Down modulation 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 .01– 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, where 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 (CsA) 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 investigate its role in AITL, a disease that is characterized by complex immune dysregulation. Cyclosporine was administered twice daily for 6–8 weeks, with gradual tapering over several weeks and responding patients received maintenance therapy65. Considering the poor outcome with standard therapy in this disease, the results with this drug were noteworthy. Eight of 12 (67%) patients with AITL experienced a response with 2 patients achieving a complete response; the median duration of response was 13 months65. 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 anti-tumor 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 25mgs 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, demonstrated efficacy in AITL[70].

Other agents in PTCL

Gemcitabine is a novel nucleoside analog that competes with the natural nucleotide deoxycytidine, arresting tumor growth and causing apoptosis. It also causes cell apoptosis through inhibition of ribonucleotide reductase. It has demonstrated 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 1200mg/m2 on days 1,8 and 15 of a 28-day cycle for a total of 3 to 6 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/m^2 by intravenous bolus administration daily for three days on an every three week schedule in patients with relapsed T cell lymphoma[74]. There were forty-two patients 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 five years. The major toxicities included nausea, neutropenia and CD4 T cell depletion.

Forodesine is a potent purine nucleoside phosphorylase (PNP) inhibitor, that 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 demonstrated moderate efficacy in patients with CTCL in a preliminary analysis[75]. Clofarabine is a deoxyadenosine analog that has increased stability compared to cladribine or fludarabine and is under investigation in PTCL.

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

A recently published study that evaluated the first clinically available spleen tyrosine kinase (Syk) inhibitor in recurrent B-cell lymphoma demonstrated high objective response rates, particularly in patients with CLL and SLL[81]. Over expression of Syk has been demonstrated in PTCL and inhibition of SyK induces apoptosis and blocks proliferation in T-cell NHL cell lines82›83. Therefore, SyK inhibition is an interesting therapeutic strategy and fostamatinib disodium is being investigated in PTCL.

Bone marrow transplantation

While there is an established role for autologous transplantation 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 enteropathy associated T-cell lymphoma and hepatosplenic γ-δ T-cell lymphoma, where 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 perform pre-clinical studies. There are limited cell lines available from patients with T-cell neoplasms and efforts to develop these lines has 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 demonstrated 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 histone deacetylase inhibitors 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, every patient with a PTCL subtype other than ALK-positive ALCL 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 demonstrated in the relapsed setting need to be incorporated into upfront clinical trials, given the aggressiveness and frequent 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.

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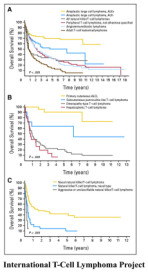

Figure 1.

These Kaplan-Meier curves show (A) the overall survivals of patients with the most common subtypes of peripheral T-cell lymphoma (PTCL); (B) the overall survivals of patients with the less common subtypes of PTCL; and (C) the overall survivals of patients with natural killer T-cell lymphoma. (Copied with permission from the International T-cell Lymphoma Project: Vose et al. JCO)

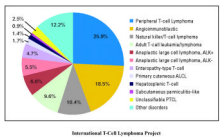

Figure 2.

Shown here is the distribution of 1314 cases by consensus diagnosis. NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; PTCL, peripheral T-cell lymphoma

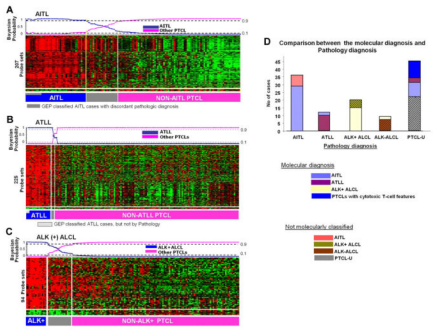

Figure 3.

Shown here are 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) illustrates the correlation between the molecular and the pathology-based diagnoses.