Current Therapies for T-cell Lymphomas

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Abstract Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of clinically aggressive diseases associated with poor outcome. One of the difficulties in classifying and studying treatment options in clinical trials is the rarity of these subtypes. The International T-cell Lymphoma Project has identified that the outcomes for the majority of the different subtypes of PTCL are poor using conventional lymphoma therapies. Recently, aggressive first-line strategies including consolidation with stem cell transplantation have led to improved survival in selected patients, but the majority of patients either fail to respond to therapy or are not candidates for stem cell transplantation. Novel approaches have included new classes of drug and biological agents, including antifolates, immunoconjugates, histone deacetylase (HDAC) inhibitors, monoclonal antibodies, nucleoside analogs, proteasome inhibitors, and signal transduction inhibitors. Molecular profiling has led to identification of relevant pathways for future novel approaches.

Introduction

The aggressive T-cell lymphomas are a diverse group of disorders that are associated with a poor prognosis (Fig. 1). Classification of PTCL is complex and has been further hampered by a paucity of molecular markers. The World Health Organization classification of non-Hodgkin's lymphomas includes many a number of subtypes of aggressive T-cell lymphomas (Table 1) characterized based primarily on their clinical and histopathologic features and subgroups them into the cutaneous, nodal, extranodal, and leukemic groups [1].

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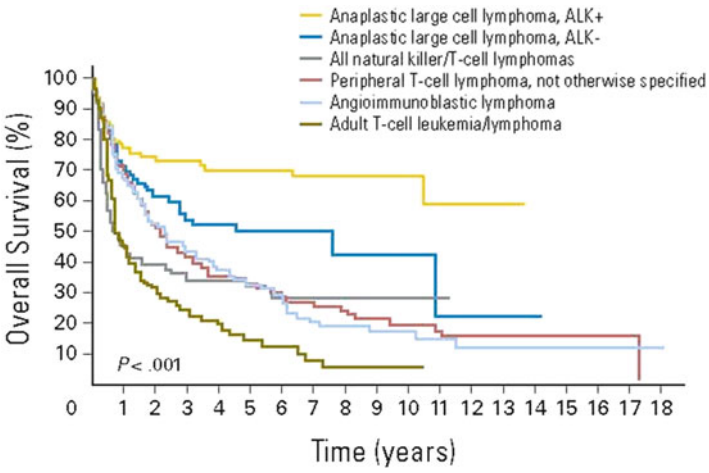

Fig. 1 Overall survival of patients with the common subtypes of PTCL. Vose et al. (International T-cell Lymphoma Project), J Clin Oncol 2008; 26:4124–4130. Figure 2A p 4127

The nodal lymphoma group includes PTCL, not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL). ALCL is further separated into the ALK^+ and ALK^- entities. According to the International PTCL study, PTCL-NOS accounts for 26% of cases, AITL accounts for 18.5%, anaplastic lymphoma kinase (ALK)-positive ALCL accounts for 6.6% and ALK-negative ALCL for 5.5% of cases [2].

The extranodal T-cell lymphomas comprise a group of less well understood diseases identified based on their tissue trophism. Hepatosplenic gamma-delta T-cell comprises 1.4% of cases and is characterized by gamma-delta T-cell infiltration of the liver, spleen, and bone marrow sinusoids. Outcomes are poor with a median survival of less than 2 years. Enteropathy-associated T-cell lymphoma (EATL) accounts for 4.7% of cases and is comprised of two morphologic variants, the pleomorphic type, associated with celiac disease and usually $CD3^+$, $CD7^+$, and $CD56^-$, and the monomorphic type, which is $CD56^+$ and often not associated with celiac disease [3]. Subcutaneous panniculitis-like T-cell lymphomas (SPTCL) constitute only 0.9% of PTCL and presents with subcutaneous nodules that are typically $CD3^+$, $CD4^-$, and $CD8^+$, with TCR-[alpha]/[beta]$^+$ expression. The cutaneous panniculitis-like T-cell lymphomas with TCR-[gamma]/[delta]$^+$ expression have now been reclassified as cutaneous gamma/delta T-cell lymphoma [21]. NK-cell lymphomas include extranodal NK/T-cell lymphoma, nasal type, blastic NK-cell lymphoma, and aggressive NK-cell leukemia account for 10.4% of PTCL cases. EBV has been implicated and found in the tumor cells of nasal/NK-cell lymphomas and aggressive NK-cell leukemia [4].

The leukemic group of T-cell lymphomas consists of adult T-cell lymphoma (ATLL) associated with human T-lymphotropic virus type I (HTLV-1), T-cell chronic large granular lymphocytic (LGL) leukemia, aggressive NK-cell leukemia, and T-cell prolymphocytic leukemia. LGL leukemia often has an indolent clinical course and is associated with neutropenia, while aggressive NK cell leukemia and

Table 1 The WHO classification for PTCLs was updated in 2008

Old WHO classification [7]	New WHO classification [9]
Precursor T-cell lymphoma	
• T-lymphoblastic lymphoma/leukemia	
Mature T-cell lymphomas	
• T-cell prolymphocytic leukemia	T-cell prolymphocytic leukemia
• T-cell granular lymphocytic leukemia	T-cell large granular lymphocytic leukemia
• Aggressive NK-cell leukemia	Aggressive NK-cell leukemia
	Indolent large granular NK-cell lymphoproliferative disorder (provisional)
• Adult T-cell lymphoma/leukemia (HTLV1+)	Adult T-cell leukemia/lymphoma
• Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma, nasal type
• Enteropathy-type T-cell lymphoma	Enteropathy-associated T-cell lymphoma
• Hepatosplenanic T-cell lymphoma	Hepatosplenic T-cell lymphoma
• Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell l ymphoma ($\alpha\beta$ only)
	Primary cutaneous $\gamma\delta$ T-cell lymphoma
• Mycosis fungoides/Sézary syndrome	Mycosis fungoides & Sézary syndrome
• Anaplastic large-cell lymphoma, systemic or cutaneous	Anaplastic large cell lymphoma—ALK$^+$
	Anaplastic large cell lymphoma—ALK$^-$ (provisional)
• Peripheral T-cell lymphoma, unspecified	Peripheral T-cell lymphoma, not otherwise specified
• Angioimmunoblastic T-cell lymphoma	Angioimmunoblastic T-cell lymphoma
	Primary cutaneous CD30$^+$ T-cell LPD
	• LYP and primary cutaneous ALC
	Primary cutaneous CD4$^+$ small/medium T-cell lymphoma (provisional)
	Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)
	Systemic EBV + T-cell LPD of childhood
	Hydroa vacciniforme-like lymphoma

The new classification expanded some existing disease types and added several new provisional diseases

ATLL often have a poor outcome even with systemic therapy. HTLV-1-associated lymphomas include acute ATLL, which presents predominantly with a leukemic component, smoldering ATLL, which is characterized by small numbers of circulating leukemia cells without nodal involvement, lymphomatous ATLL, which presents with lymphadenopathy without leukemic involvement, and chronic ATLL, which is characterized by skin lesions, leukemic, nodal, and visceral disease without hypercalcemia, gastrointestinal involvement, bone, or central nervous system (CNS) disease. HTLV-1 infection is prevalent in Japan and the Caribbean basin, but only a small proportion of patients carrying the virus develop a malignancy.

The cutaneous group of T-cell lymphomas includes mycosis fungoides (MF) and the Sezary syndrome (SS) and variants of MF, which often have an indolent clinical

course. Large cell transformation may occur in patients with MF or SS and this is often associated with a poor outcome. The primary $CD30^+$ cutaneous disorders include cutaneous anaplastic large cell lymphoma, which is characteristically ALK-negative is often localized to the skin and is treated locally. The pleomorphic $CD4^+$ T-cell lymphomas are a group of disorders resembling PTCL-NOS but occurring only in the skin with no systemic manifestations and are often treated with local irradiation with no systemic recurrence in the majority of cases.

Therapeutic Approaches for Aggressive T-Cell Lymphomas

Standard First-Line Therapy

T-cell lymphomas have traditionally been treated much like the B-cell lymphomas with CHOP based regimens. Outcomes using this approach have been reviewed in a retrospective meta-analysis of 2,912 patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens which reported a 5-year overall survival (OS) of 37% [5]. Results using other more aggressive regimens have been reported in a retrospective study from MD Anderson Cancer Center including hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (HyperCVAD) and etoposide, cisplatin, cytarabine, and prednisone (ESHAP) in 135 patients with PTCL. Among those patients with non-ALCL disease, there was no significant difference in outcome between those treated with CHOP vs. the more aggressive regimens (3-year OS: 43% vs. 49%) [6].

In a prospective study by Mercadal et al., a Mega-CHOP/ESHAP regimen (cyclophosphamide 2,000 mg/m(2)/day, adriamycin 90 mg/m(2)/day, vincristine and prednisone alternating with three courses of ESHAP) was used followed by autologous stem cell transplant for patients achieving remission [7]. Of 41 patients enrolled, only 68% completed the planned treatment with 20 complete responses (CR) and four partial responses. The outcome of the 16 patients who showed primary refractoriness to Mega-CHOP/ESHAP was extremely poor, with a median OS of 8 months. Overall, the CR rate in this study (50%) was not better than with CHOP alone, suggesting no advantage to this more aggressive approach.

Recently the German High Grade Non-Hodgkin's Lymphoma Study group explored the use of dose intensive CHOP or the addition of etoposide to CHOP for aggressive lymphomas. They reported results for patients with aggressive T-cell lymphomas treated on seven trials with six to eight courses of CHOP or CHOEP (CHOP plus etoposide) [8]. Of 343 T-cell patients enrolled in these studies, 70 had PTCL-NOS, 28 had AITL, 78 had ALK-positive ALCL, and 113 had ALK-negative ALCL. As an aggregate, the younger patients demonstrated an improvement in even-free survival (EFS) for both etoposide-containing regimens (75% vs. 51%) compared to the non-etoposide regimens, but there was no OS difference. The positive effect of etoposide on EFS was seen only in the most favorable ALK-positive patients and not in patients with PTCL-NOS or AITL, in whom there was no statistically significant difference between the etoposide

and non-etoposide regimens. For the elderly patients, neither shortening of the time interval between cycles from 3 to 2 weeks (CHOP-21 vs. CHOP-14), administration of eight instead of six courses of CHOP-14, nor the addition of etoposide (CHOEP) significantly improved EFS or OS, but toxicity was increased. Patients with a favorable International Prognostic Index (IPI) score of 0–1 had a 3-year EFS above 50%, compared to 34% for those with IPI of two or greater. The conclusions from this study, which is one of the largest randomized studies of first-line regimens for aggressive lymphomas, is that younger patients may benefit from the addition of etoposide in terms of response rate and EFS, which would therefore potentially allow more patients to undergo a consolidation autologous stem cell transplant in first remission. The standard for elderly patients remains six cycles of CHOP. Finally, the excellent outcomes in patients with low IPI suggest that this group may do well and should be distinguished from the intermediate and high IPI patients.

When the German study group explored the results of a more dose intense regimen, Mega-CHOEP, results were inferior to those of standard dose CHOP or CHOEP. Of 33 patients treated, the 3-year event-free survival was only 26%, and the regimen was associated with more toxicity.

Another more intensive regimen, ACVBP (doxorubicin 75 mg/m^2 D1, cyclophosphamide 1,200 mg/m^2 D1, vindesine 2 mg/m^2 D1 and D5, bleomycin 10 mg D1 and D5 and prednisone D1 to D5), followed by a sequential consolidation consisting of methotrexate (two courses), etoposide + ifosfamide (four courses) and cytarabine (two courses) at 2 weeks intervals, was evaluated in aggressive T-cell lymphoma by the GELA. In a randomized study reported by Tilly et al., there was a benefit to the more aggressive regimen compared to CHOP [9]. Subsequently, the addition of bortezomib on days 1 and 5 of each ACVBP cycle and then days 1, 8, and 15 every 4 weeks as a consolidation showed no further benefit [10]. Of 57 patients enrolled, 46 patients responded, 28 patients completed the consolidation phase of the study, and 39% of patients died from lymphoma.

Another alternative first-line regimen, etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine (VIP-reinforced-ABVD; VIP-rABVD) was compared to CHOP-21 in 88 patients with PTCL [11]. The Groupe Ouest Est d'Etude des Leucemies et Autres Maladies du Sang (GOELAMS) treated 88 patients with this regimen and reported a 2-year EFS of 41% vs. 45% for the more aggressive regimen compared to CHOP-21 with a similar median OS of 42 months for each of the arms.

New Combination Therapies for PTCL

CHOP-Based Regimens

Based on the demonstration that 40% of PTCL cases have been shown to express CD52 by immunohistochemistry, alemtuzumab has been used as a single agent in relapsed PTCL and in combination with chemotherapy in the front line [12].

One phase II study by Kim et al. enrolled 20 patients treated with CHOP combined with intravenous alemtuzumab in 3-week cycles (cycle 1: 10 mg on day 1, 20 mg on day 2; subsequent cycles: 30 mg on day 1) as frontline therapy [13]. All patients received trimethoprim/sulfamethoxazole and acyclovir prophylaxis during the study and up to a minimum of 2 months following discontinuation of the alemtuzumab. Responses were seen in all ten patients with PTCL-NOS, 1 of 3 with extranodal NK/T cell lymphoma, 2 of 3 with AITL, and 1 of 2 with ALK-negative ALCL and SPTCL, respectively. Toxicity was high, with 90% of patients experiencing grade 4 neutropenia and 5 of 20 with cytomegalovirus (CMV) reactivation. Additionally, there were two treatment-related deaths. In another study by Gallamini et al., alemtuzumab was given subcutaneously at a dose of 30 mg on day 1 in cycles 1–4 of CHOP in the first cohort of patients and then for all eight courses in the second cohort [14]. Of 24 evaluable patients, 71% had CR, including all six with AITL, all three with ALK-negative ALCL, 7 of 14 with PTCL-NOS, and one with EATL. The incidence of neutropenia remained high at 34% of the treatment cycles, but CMV reactivation was lower at 9%. Serious infections included one patient with Jacob-Creutzfeldt virus and two with aspergillosis. The overall median duration of response was 11 months.

Another phase I study evaluated alemtuzumab combined with dose-adjusted EPOCH (infusional etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in patients with aggressive T-cell lymphomas [15]. In this study, alemtuzumab was administered at doses of 30, 60, or 90 mg prior to each EPOCH cycle. Significant bone marrow aplasia occurred in two of three patients at both the 60 and 90 mg dose groups; therefore, phase II study accrual is continuing at the 30 mg dose of alemtuzumab. Infections were reported in 11 of 14 patients from bacterial, fungal, and viral pathogens.

Based on these results, the alemtuzumab-CHOP combination is being compared to CHOP-21 in by the Nordic Lymphoma Group and the German High Grade Lymphoma Groups (the ACT Trial). Patients over age 60 are randomized and followed until progression. Patients under age 60 are randomized to either six cycles of CHOP-14 or four cycles of alemtuzumab-CHOP-14 and two cycles of CHOP-14 without alemtuzumab vs. six cycles of CHOP-14. Patients in remission will then undergo an autologous stem cell transplant.

Another targeted agent that has been combined with CHOP in first-line therapy for PTCL is denileukin diftitox, a fusion protein which combines the interleukin-2 gene with diphtheria toxin, thereby delivering the active toxin moiety to lymphoma cells expressing the interleukin-2 receptor. Denileukin diftitox has shown activity in relapsed aggressive T-cell lymphomas, with a response rate of 48% in 27 heavily pretreated patients [16]. A multicenter prospective phase II trial was conducted to combine denileukin diftitox with CHOP in 49 untreated patients with aggressive PTCL subtypes [17]. In this study, denileukin diftitox was administered at a dose of 18 μg/kg/day on days 1 and 2 and CHOP was given on day 3; this was followed by growth factor support on day 4 every 21 days. Histologic subtypes included: ALCL 8, AILT 10, PTCL-NOS 19, EATL 3, SPTCL 5, NK/T 1, hepatosplenic TCL 1. The median cycles was six with seven patients completing

only one cycle of therapy; three patients died with progressive disease (PD) after cycle 1, and four patients were taken off study for toxicity. The overall response rate (ORR) in 47 patients was 68% with 57% CR. In the efficacy-evaluable patients (≥2 cycles completed) the ORR was 86% (CR 75%). The median progression-free survival (PFS) was 12 months and 2-year estimated OS was 60%. The median response duration for the 33 responders was 29 months. The most frequent grade 3 or 4 adverse events were bone marrow suppression and febrile neutropenia. There was no prolonged immunosuppression, and no opportunistic infections were observed.

The combination of CHOP with rituximab was explored by the GELA group in elderly patients (age 59–79) with AITL in an attempt to target non-neoplastic B-lymphocytes which may provide paracrine growth factors to the malignant T-cells. Twenty-five patients aged 59–79 years with newly diagnosed AITL received eight cycles of rituximab (375 mg/m^2 at day 1 of each cycle) and CHOP (R-CHOP21). Most of the patients had advanced disease (stage IV: 92% and B symptoms: 68%). Twenty-one patients completed all eight cycles. The overall response rate was 80%, with 44% achieving a complete response. With a median follow up of 24 months, the progression free survival was 42% and the 2-year-OS was 62%, which was no different than with CHOP alone in this population.

The anti-VEGF receptor monoclonal antibody, bevacizumab has also been combined with CHOP as first-line therapy for PTCL. Several PTCL subytpes, especially AITL and PTCL-NOS demonstrate overexpression of angiogenic factors, such as vascular endothelial growth factor (VEGF). At least one relapsed AITL patient has achieved a CR following treatment with bevacizumab [18]. A combination of CHOP and bevacizumab has been studied in patients with PTCL or NK-cell neoplasms by the Eastern Cooperative Oncology Group. Patients received bevacizumab at a dose of 15 mg/kg on day 1 followed by maintenance bevacizumab. However, this trial has been suspended when a preliminary analysis reported a high incidence of cardiac events related to the therapy, including four cases of congestive heart failure [19].

Gemcitabine-Based Regimens

Because results with CHOP and traditional anthracycline regimens have overall been inferior, other non-anthracycline regimens have been used in first-line therapy. Gemcitabine is an agent which is not metabolized by the multidrug resistance p-glycoprotein pathway and which has demonstrated efficacy in T-cell lymphomas as a single agent [20]. Zinzani reported results from 19 patients with cutaneous T-cell lymphoma (CTCL) and 20 patients with PTCL who received gemcitabine at a dose of 1,200 mg/m^2 on days 1, 8, and 15 every 28 days. The overall response rate was 51%; MF patients had a CR rate of 16% and a PR rate of 32%, while PTCL patients had a CR rate of 30% and a PR rate of 25%. Gemcitabine combined with cisplatin (GEM-P, gemcitabine 1,000 mg/m^2 days 1, 8, and 15, cisplatin 100 mg/m^2 on day 8) was reported to demonstrate a response rate of 73% and

grade 3 or 4 neutropenia in 41% of patients [21]. The combination of vinorelbine 25 mg/m^2 and gemcitabine 1,000 mg/m^2 on days 1 and 8 of each 21-day cycle was also found to be active, with a 70% response rate in a pilot study [22]. The incorporation of gemcitabine into a CHOP-based regimen (CHOP-EG, CHOP plus etoposide and gemcitabine) was also explored [23]. The regimen consisted of CHOP plus etoposide 100 mg/m^2 day 1 and gemcitabine 600 mg/m^2 every 21 days. Of 26 enrolled patients, the overall response rate was 76.9% and median event free survival was 7 months. The most severe adverse event was grade 4 neutropenia in 14 patients (53.8%) and febrile neutropenia in four patients (15.4%). While active, this regimen did not appear to be superior to studies with CHOEP and incidence of myelosuppression was higher.

The Southwest Oncology Group has recently completed a study of gemcitabine, cisplatin, etoposide, and methylprednisolone (PEGS) for patients with untreated or relapsed PTCL. The majority of the patients (79%) were untreated at the time of study entry. The 1 year event-free survival was reported to be 38%. Another regimen incorporating gemcitabine was the GIVOX regimen (gemcitabine, ifosfamide, and oxaliplatin). In a group of high risk PTCL patients, the response rate was 86% with 67% CR and the 5-year EFS was 49%. Toxicities were primarily hematologic, with grade 4 thrombocytopenia and anemia occurring in 38% and 24% of patients respectively. Overall, gemcitabine based regimens have not been shown to have superior outcomes when compared to CHOP-based therapies but there are no randomized trials comparing these two approaches.

Transplantation as a Consolidation Therapy

Because of the historically poor outcomes and high relapse rates after first-line chemotherapy in aggressive T-cell lymphomas, the role of autologous or allogeneic stem cell transplantation in first remission has been explored in a number of small series and more recently in prospective nonrandomized trials. The largest studies from the Nordic and German study groups report overall EFS ranging from 30 to 50% and transplant rates of 40–70% based on intent to treat analysis. The Nordic group reported results from 160 patients treated with an etoposide-based regimen (CHOEP-14) followed by carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning [24]. At a median follow up of 4 years, the OS was 50% and the PFS was 48%. Outcome results were similar for each of the nodal subtypes of PTCL. In the German study reported by Reimer et al., 83 patients were treated with CHOP×4, followed by Dexa-BEAM or ESHAP [25]. The conditioning regimen for the transplant included total body irradiation along with cyclophosphamide. In this study, the CR rate to CHOP was 39%, and only 66% of patients were able to be transplanted. At a mean follow up of 33 months, the OS was 48%, and the EFS was 53%. Comparison of these two different approaches suggests that there may be no benefit for total body irradiation in this setting, and BEAM or chemotherapy based conditioning regimens remain the standard.

Novel Therapies for T-Cell Lymphomas

A number of novel agents have been used in T-cell lymphomas and have shown efficacy (Table 2). Monoclonal antibodies and fusion toxins targeting surface epitopes have been the most successful, including alemtuzumab and denileukin difititox. Other novel classes of drugs, including the HDAC inhibitors and pralatrexate have recently been FDA-approved for patients with relapsed and refractory disease. Response rates have been similar for many of the novel agents when used in the relapsed and refractory setting (Table 3). Pathway targeted agents have recently been explored in T-cell lymphomas and studies are underway to determine their efficacy as single agents and in combination with cytotoxic therapy.

Monoclonal Antibodies and Immunoconjugates

Siplizumab, an antibody targeting CD2, has shown activity in early studies in patients with aggressive T-cell malignancies. In a phase I trial in patients with CD2-expressing hematologic malignancies, there were two CR in patients with LGL, three partial responses (PRs) in patients with ATLL, and one PR in a patient with CTCL [26, 27]. A subsequent dose escalation study produced a PR in a patient with NK-cell LGL and a CR in a PTCL patient. Several cases of EBV-associated lymphoproliferative disease occurred, so subsequent trials with siplizumab have combined the antibody with rituximab to prevent EBV emergence [27].

Another humanized antibody, zanolimumab, an anti-CD4 antibody, has been shown to be active in both cutaneous and systemic aggressive T-cell lymphomas [28]. In a study of 21 PTCL patients, there were clinical responses in 24% [29].

LMB-2 is another agent targeting the CD25 component of the interleukin-2 receptor. LMB-2 consists of a single chain antibody (anti-CD25) conjugated to *Pseudomonas* toxin. LMB-2 has shown clinical activity in phase II trials in B-cell chronic lymphocytic leukemia, CTCL, and hairy cell leukemia. ATLL is the PTCL subtype that is most sensitive to LMB-2, but clinical responses have been limited to a rapid disease progression after >95% tumor reduction and immunogenic reactions [30]. A phase II clinical trial combines LMB-2 with fludarabine and cyclophosphamide.

The CD30 receptor, which is expressed on the anaplastic large cell lymphomas as well as a subset of other aggressive T-cell lymphomas, has been targeted with both monoclonal antibodies and, more recently, with an immunoconjugate, SGN35. Two anti-CD30 MAbs, iratumumab and SGN-30, have shown efficacy as single agents in patients with relapsed and refractory $CD30^+$ ALCL [31, 32]. In vitro studies further demonstrated additive or synergistic effects when the antibodies were combined with conventional chemotherapy [33].

SGN-35 is an immunoconjugate consisting of the SGN-30 antibody and monomethyl auristatin, a microtubule inhibitor [34, 35]. In vitro studies demonstrated the efficacy of this agent in CD30 expressing anaplastic large cell lymphoma cell lines and in malignant leukemia cells from patients with HTLV-1-associated

Table 2 Novel agents in use or trials in PTCL[a]

Type of agent	Name	Description	Disease(s)
Antifolates	Pralatrexate	10-deazaminopoterin	PTCL, CTCL
Conjugates	LMB-2	Anti-Tac (anti-CD25) fused to *Pseudomonas* toxin	CTCL, PTCL (esp ATL)
	Denileukin diftitox	IL-2 targeting domain fused with diphtheria toxin	CTCL, PTCL
	Brentuximab vedotin	CD30 antibody conjugated to monomethylauristan-E	$CD30^+$ T-cell lymphoma
HDAC inhibitors	Belinostat	PXD101	CTCL, PTCL
	Panobinostat	LBH589	CTCL, ATL
	Romidepsin	Depsipeptide	CTCL, PTCL
	Vorinostat	Suberoylanilide hydroxamic acid (SAHA)	CTCL
Immunomodulatory agents	Lenalidomide	Derivative of thalidomide	PTCL, CTCL
Immunosuppressive agents	Cyclosporine	Inhibitor of the NF-AT transcription complex	AITL
Monoclonal antibodies	Alemtuzumab	Anti-CD52	PTCL
	Bevacizumab	Anti-VEGF	PTCL (esp AITL), NK-cell
	Iratumumab	Anti-CD30	$CD30^+$ ALCL
	KW-0761	Anti-CCR4	ATL, PTCL
	SGN-30	Anti-CD30	$CD30^+$ ALCL
	Siplizumab	Anti-CD2	PTCL, NK-cell, ATL
	Zanolimumab	Anti-CD4	CTCL, PTCL
Nucleoside analogs	Cladribine	Purine nucleoside analog	PTCL
	Clofarabine	Purine nucleoside analog	PTCL, NK-cell
	Fludarabine	Purine nucleoside analog	PTCL, CTCL
	Forodesine	Metabolic enzyme inhibitor	PTCL, CTCL
	Gemcitabine	Pyrimidine nucleoside analog	PTCL
	Nelarabine	Purine nucleoside analog	T-ALL, T-NHL
	Pentostatin	Metabolic enzyme inhibitor	PTCL
Proteasome inhibitors	Bortezomib	Proteasome inhibitor	CTCL
Signaling inhibitors	Enzastaurin	Selective inhibitor of protein kinase C	PTCL, CTCL
	R788	Syk inhibitor	PTCL

AITL angioimmunoblostic T-cell lymphoma, *ALL* acute lymphoblastic leukemia, *ATL* adult T-cell leukemia-lymphoma, *CTCL* cutaneous T-cell lymphoma, *esp* especially, *IL-2* interleukin-2, *MAb* monoclonal antibody, *NHL* non-Hodgkin's lymphoma, *Ph* phase, *PTCL* peripheral T-cell lymphoma

[a]There are several other experimental agents in various stages of clinical trials for T-cell lymphoma

ATLL [36, 37]. In phase I studies, SGN-35 demonstrated significant clinical activity in relapsed/refractory systemic ALCL [38, 39]. In these trials, 86% of patients (6/7) had documented CR. Subsequently, a phase II multicenter registration trial of brentuximab vedotin was conducted in patients with relapsed or refractory ALCL. The overall response rate was 86% (50 of 58 patients), with CR in 53%. Pts received

Table 3 Response rates for new therapies in T-cell lymphoma

Drug	Author, year	No of PTCL pts	Response duration	ORR
Alemtuzumab	Enblad *Blood 2004*	14	2, 6, 12 months	5/14
	Zinzani *2005*	10	7 months	6/10
Gemcitabine	Zinzani *Ann Oncol 2010*	20	15–60 months (only CCRs)	55%
Zanolimumab	D'amore *BJH 2010*	21		27%
Lenalidomide	Dueck *Cancer* 2010	23	OS: 241 days	7/23
Denileukin	Dang *Br J Haematol 2004*	27	PFS: 6 months	13/27
Pentostatin	Tsimberidiou *Cancer 2004*	42	4.5 months	55%
Brentuximab vedotin	Shustov *ASH 2010*	58 (ALCL)	EFS: 1.2 months	1/8
Pralatrexate	O'Connor *JCO 2011*	115 (109)	DOR: 10.1 months PFS: 3.5 months	32/109
Romidepsin	Piekarz *Blood 2011*	45	DOR 8.9 months (CR:29.7 months)	17/45
	Coiffier et al., *ICML 2011*	130	DOR: 17 months	34/130

brentuximab vedotin 1.8 mg/kg q3 weeks for up to 16 cycles. Pts had received a median of two (range 1–6) prior systemic therapies, 62% of pts had primary refractory disease, 50% were refractory to their most recent prior therapy, and 22% had never responded to any prior therapy. Peripheral sensory neuropathy was the most frequent side effect and occurred in 36% of patients. Baed on these findings, brentixumab vedotin has been recently approved in patients with relapsed $CD30^+$ systemic ALCL. The use of brentuximab vedotin along with chemotherapy as first-line treatment for systemic ALCL is under investigation.

Histone Deacetylase Inhibitors

HDAC inhibitors are potent inducers of protein and histone acetylation and modulate expression of a number of cellular genes and pathways. HDAC and histone acetyltransferases regulate chromatin structure and function by removal and addition, respectively, of the acetyl group from the lysine residues of core nucleosomal histones, thus regulating gene expression [40]. HDAC inhibitors increase the acetylation of histones, as well as other nuclear factors. A number of clinical pathways have been shown to be modulated by HDAC agents, including apoptosis and cell survival pathways, angiogenesis pathways, and cell cycle genes. HDAC inhibitors have demonstrated significant clinical activity in T cell lymphomas and two of these agents, vorinostat and romidepsin, are FDA approved. The first agent in clinical trials was vorinostat (SAHA). Early studies with vorinostat

demonstrated activity in patients with CTCL. A Phase II study in relapsed and refractory CTCL patients showed that a dose of 400 mg daily was well tolerated [41]. A subsequent study of oral vorinostat capsules at a dose of 400 mg daily demonstrated an ORR of 30% with one CR in a patient with advanced tumor stage CTCL [42].

Romidepsin is an intravenous HDAC inhibitor which is administered at a dose of 14 mg/m^2 weekly for 3 weeks on a 4 week cycle. In a Phase II study of relapsed and refractory CTCL patients, an overall response rate of 34% was reported [43]. The median response duration was 15 months (range 1–20+) and median time to progression was 8.3 months in early and 6.4 months in more advanced disease.

Romidepsin was subsequently explored in patients with relapsed and refractory PTCL. A multicenter phase II study was initiated by the group at the NCI, which enrolled 43 heavily pretreated patients (mean of 3.9 prior therapies). The ORR was 39% [44]. The median response duration was 8.3 months (range 1.6 months to 4.8+ years). A multicenter, multinational phase IIB registration study of romidepsin at the same dose and schedule in relapsed and refractory PTCL enrolled 130 patients with a median of two prior therapies. The ORR in this trial was 26% with 15% CR by radiographic documentation. Twenty-one patients (16%) had received a prior transplant and 49 patients (38%) were refractory to their most recent therapy. ORR and median DOR were similar across subtypes. The median duration of response for all responders was 28 months. Disease control rate including stable disease was 46%. Toxicities included gastrointestinal and constitutional events and thrombocytopenia.

Belinostat, a hydroxamic acid-derived HDACi, has been studied in both intravenous and oral formulations. Belinostat was administered intravenously at 1,000 mg/m^2/daily for 5 days every 3 weeks in 53 patients including 19 with refractory PTCL and 29 with refractory CTCL [45]. The ORR in PTCL was 32% with two CR and a median response duration of 8.9+ months, and 14% in CTCL, with a response duration of 9.1 months. A multicenter phase II registration trial of belinostat in relapsed PTCL patients has been completed.

Additive and synergistic activity has been demonstrated in vitro for combinations of HDAC inhibitors with a number of agents, including topoisomerase inhibitors, bortezomib, and cytotoxic chemotherapy drugs and clinical trials are underway to explore the activity of these combinations in T-cell lymphomas. In one study, the combination of HDAC inhibitors and hypomethylating agents has been shown to be synergistic in vitro [46].

Pralatrexate

Pralatrexate is a novel folate antagonist whose activity is associated with binding to the reduced folate carrier. In a phase I/II dose escalation trial of pralatrexate in refractory lymphoma patients, the response rate was 54% for patients with T-cell lymphomas [47, 48]. These encouraging results led to the PROPEL trial, a multicenter phase II trial of pralatrexate in relapsed and refractory PTCL. The trial

enrolled 111 patients who were treated with pralatrexate weekly for 6 weeks on a 7-week cycle. The median prior to therapies was three, and 63% of patients had no response to their last line of therapy. The ORR was 29% and the median response duration was 10.1 months [49]. Five patients with relapsed/refractory PTCL who responded to single-agent pralatrexate were able to undergo a curative stem cell transplant. Drug-related adverse events included mucositis in 70% of patients and thrombocytopenia in 40%. The incidence of mucositis with pralatrexate is ameliorated to some degree by the administration of cobalamin and folic acid during the course of therapy [50]. A number of recent studies have explored the potential synergy between pralatrexate and other active agents in T-cell lymphoma.

Immunomodulators and Immunosuppressants

Cyclosporine is an immunosuppressive agent that inhibits the NF-AT transcription complex, which activates the genes encoding cytokines and cell surface molecules involved in cell-to-cell communication and death. An early study exploring the activity of cyclosporine in CTCL and aggressive T-cell lymphomas demonstrated only modest activity [51]. A more recent study of cyclosporine was conducted in patients with AITL because this subtype of T-cell lymphoma is characterized by immune dysregulation, Cyclosporine was administered to 12 patients [52]. Two-thirds (thee CRs, five PRs) of the patients responded, but there were four deaths. A phase II trial of cyclosporine in AITL was conducted by the Eastern Cooperative Oncology Group but closed early due to slow accrual.

Other immune modulating and antiangiogenic agents, including bevacizumab, rituximab, lenalidomide, and thalidomide, are also being explored as single agents and in combination with chemotherapy. A phase II study of lenalidomide at a dose of 25 mg/m^2 daily for 21 days of a 28 day cycle was conducted in 24 relapsed PTCL patients [53]. The ORR was 30% with a PFS of 95 days. Toxicities included neutropenia and thrombocytopenia in 20% and 33% of patients, respectively. Combinations with lenalidomide are currently being planned.

Nucleoside Analogs

Deoxycoformycin (pentostatin) and forodesine are nucleoside analogs which have shown activity in both cutaneous and aggressive T-cell malignancies. Deoxycoformycin is an inhibitor of adenosine deaminase and as such it does not incorporate into DNA, unlike the other nucleoside analogs. Pentostatin increases the deoxyadenosine triphosphate pool, which leads to apoptosis in T-cells. A study conducted at MD Anderson Cancer Center reported an ORR of 71% in 24 patients with cutaneous T-cell lymphoma [54]. In the largest reported experience with pentostatin reported from the Royal Marsden, 145 patients with postthymic T-cell malignancies were given pentostatin intravenously at 4 mg/m^2/week for the first

4 weeks and then every 2 weeks until maximal response. The ORR was 32%, with marked variation according to diagnosis. The best responses occurred in patients with SS (62%) and T-PLL (45%), with CRs in three of 16 patients with SS and five of 55 patients with T-PLL. In contrast, no responses were documented in 13 patients with other types of cutaneous T-cell lymphoma, including five MF. Two of five patients with LGL had a CR and two of four with SS had a PR. A low response rate was observed in 27 patients with PTCL (19%) and in 25 with ATLL (12%) [55, 56].

Forodesine (BCX-1777, Immucillin H, 1-(9-deazahypoxanthin)-1,4-dideoxy-1,4-imino-D-ribitol) is another novel nucleoside [57]. Forodesine blocks purine nucleoside phosphorylase (PNP), preventing plasma dGuo from being cleaved to Gu, leading to accumulation of dGTP, which leads to inhibition of ribonucleotide reductase and apoptosis. A phase I/II study of oral forodesine in relapsed and refractory CTCL patients reported a 53% overall response rate, and a phase II trial has been completed [58].

Proteasome Inhibitors

Bortezomib, a proteasome inhibitor, has been well tolerated and active as a single agent in relapsed or refractory CTCL patients [59]. In a phase II study of bortezomib in relapsed CTCL or PTCL patients, the ORR was 67% with two CR and no grade 4 toxicity [59]. Bortezomib was also shown to potentially synergize with pralatrexate in an in-vitro system [60].

Signaling Inhibitors

Enzastaurin is a selective inhibitor of protein kinase C (PKC), which acts in part through the AKT pathway. By targeting the PI3K/AKT pathways, enzastaurin inhibits cell proliferation, induces tumor cell apoptosis, and suppresses tumor-induced angiogenesis in CTCL cell lines [61]. Enzastaurin is currently being explored in two phase II trials: one for patients with several types of lymphoma, including PTCL and CTCL, and another for relapsed CTCL patients.

The PI3 kinase inhibitors are another class of agents which may have therapeutic efficacy in T-celll malignancies. PI3K-δ has demonstrated a role in receptor and cytokine signaling and is important for T-cell function including proliferation, activation, and differentiation [62]. The PI3K-δisoform-specific inhibitor CAL-101 (GS-1101) has demonstrated clinical activity in patients with hematologic malignancies. In heavily pre-treated patients with refractory CLL and bulky lymphadenopathy, single agent CAL-101 was highly active and clinically efficacious, providing a durable clinical benefit [63]. Studies to explore the role of PI3 kinase inhibitors in T-cell lymphomas are underway.

Treatment Approaches for Individual Subtypes

NK/T Cell Lymphomas

One of the most difficult subtypes of PTCL to treat is NK/T-cell lymphoma. Patients with this subtype have responded poorly to anthracycline containing regimens. Patients with localized disease (Stage I, II) tend to do very well with a combination of chemotherapy and involved field radiation. The radiotherapy is an important component of management of localized NK/T cell lymphomas and has been administered both before and after cytotoxic chemotherapy. However, once the disease becomes more advanced, outcomes are relatively poor, with 2-year OS rates of 0% for those with disseminated disease [64]. Further, the CR rate for patients with advanced-stage NK/T-cell lymphoma treated with CHOP-like regimens is relatively low, with a 5-year OS rate of <10% [5]. A regimen of ifosfamide, methotrexate, etoposide, and prednisolone proved to be more effective with a 79% CR rate in early stage patients, but the CR rate was only 13% in advanced stage patients [65]. Furthermore, the relapse rate was high in both groups. The combination of CHOP and etoposide demonstrated a CR rate of 45% with a 3-year OS rate of 59% for nasal-type NK-cell lymphoma [66].

Recently, two groups have explored the activity of asparaginase-containing regimens. The combination of L-asparaginase with dexamethasone and methotrexate induced an overall response rate of 67% and a CR rate of 50% in a study of relapsed or refractory patients [67]. In another study, with an asparaginase, methotrexate, and dexamethasone regimen, response were seen in 14 of 18 evaluable patients after three cycles with 61% CR [68]. Based on these encouraging results, an asparaginase-containing regimen, SMILE, was studied as first-line therapy in patients with advanced NK/T-cell lymphomas by the NK Study Group. The SMILE regimen consists of methotrexate, etoposide, ifosfamide, dexamethasone, and L-asparaginase. Of 39 patients enrolled, 21 were newly diagnosed, 13 relapsed, and 5 had primary refractory disease [69]. Of 29 patients who completed the therapy, the overall response rate was 74%, with 38% CR. The incidence of myelosuppression was high, with Grade 3 or 4 infections in 41% of patients. Nevertheless, this regimen has been adopted by many centers for this group of difficult patients.

HTLV-1-Associated T-Cell Leukemia/Lymphoma

For patients with ATLL, results with conventional chemotherapy regimens have been uniformly poor. A phase III Japanese study evaluated a combination regimen of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECP (vindesine, etoposide, carboplatin, and prednisone) against CHOP-14 in ATLL [70]. The study demonstrated superiority for VCAP-AMP-VECP for newly diagnosed aggressive ATLL patients.

A phase II study is in preparation to investigate the ability of allogeneic stem cell transplant after induction with the VCAP-AMP-VECP regimen to prolong the median survival time, which is currently 13 months with the VCAP-AMP-VECP regimen.

The use of interferon and zidovudine has been shown to induce responses in up to 50% of patients with acute or lymphomatous ATLL [71] In a recent meta-analysis, 116 patients with acute ATLL, 18 patients with chronic ATLL, 11 patients with smoldering ATLL, and 100 patients with lymphomatous ATLL were evaluated [72]. Five-year OS rates were 46% for 75 patients who received first-line antiviral therapy ($P=0.004$), 20% for 77 patients who received first-line chemotherapy, and 12% for 55 patients who received first-line chemotherapy followed by antiviral therapy. Patients with acute, chronic, and smoldering ATLL significantly benefited from first-line antiviral therapy, whereas patients with lymphomatous ATLL experienced a better outcome with chemotherapy. In acute ATLL, 82% of patients were alive at 5 years with antiviral therapy, and 100% of patients with chronic and smoldering ATL were alive at 5 years. Multivariate analysis showed that first-line antiviral therapy significantly improved OS (hazard ratio, 0.47; 95% CI, 0.27–0.83; $P=0.021$). Prospective studies are underway to explore the use of zidovudine and interferon in smoldering ATLL.

Finally, a humanized anti-CCR4 antibody, KW-0761, has shown promise as a single agent in Japan for the treatment of ATLL. KW-0761 was used for relapsed patients with CCR4-positive ATL and PTCL in a phase I study [73]. The ORR was 31% (5/16; 95% CI, 11–59). There were no dose-limiting toxicities, and no anti-KW-0761 antibodies were detected. A phase II trial for relapsed ATLL patients was recently completed [74]. Of 27 enrolled patients (14 acute, 6 lymphomatous, 7 chronic ATLL), the ORR was 54% with seven CR. Toxicities included cytopenias (lymphopenia 96%, neutropenia 33%), skin rash (52%), and mild transaminitis. KW-0761 is now being combined with CHOP chemotherapy for first-line treatment of patients with ATLL.

Enteropathy-Associated T-Cell Lymphoma

EATL is a rare primary extranodal T-cell lymphoma in characterized by infiltration of malignant T-cell within the gastrointestinal epithelium. EATL represents 4.7% of cases of PTCL around the world and consists of two distinct histopathologic subtypes, EATL type 1, which is associated with a history of celiac sprue, and EATL type 2.

EATL type 1 is more frequent (80–90% of cases) and is a pleomorphic infiltate of anaplastic T-lymphocytes with a phenotype that is $CD3^+$, $CD7^+$, $CD5^-$, $CD8^-$, $CD4^-$, $CD103^+$. The tumor cells may express cytotoxic markers such as TIA-1, and a subset may express CD30. EATL Type 2 occurs sporadically and is composed of monomorphic populations of T-cells, which are characteristically $CD3^+$, $CD8^+$, and $CD56^+$. Chromosomal abnormalities found in EATL include gains at chromosome

9q33-q34 in up to 70% of cases. In the International T-cell Lymphoma Project, 69% of EATL patients had Stage III/IV disease at presentation. Bone marrow involvement was rare and occurred in only 3% of cases, and only 25% of patients had a low IPI (0–1) [75].

Most patients with EATL present with abdominal pain or perforation and are diagnosed at the time of laparotomy. With conventional CHOP chemotherapy, the 5 year OS and PFS were 20% and 4% respectively. Even for the low IPI group, 5-year survival was only 29%. Recent strategies to improve outcomes have included more aggressive treatment regimens and introduction of non-anthracycline-based regimens in the first line. The Nordic group reported results from 21 patients treated with CHOEP-14 followed by stem cell transplant. On that study, 33% of patients never made it to transplant due to progressive disease, and at 45 month follow up, 10 (45%) of patients were still alive [76]. Lennerd et al. have reported the use of CHOP×1 cycle followed by three cycles of non-cross resistant chemotherapy consisting of ifosfamide, etoposide, and epirubicin with intermediate dose methotrexate and then autologous stem cell transplantation. With this regimen, they have reported a response rate of 69% with a 5-year survival of 60%. Thus far there has been no data comparing outcomes with autologous vs. allogeneic stem cell transplantation in EATL, but patients with high IPI should be considered for clinical trials testing this approach. There is little data on efficacy of salvage therapy in EATL, so the treatment focus should be on effective first-line therapy followed by a consolidation with stem cell transplantation.

Subcutaneous Panniculitis-Like T-Cell Lymphoma

SPTCL is characterized by infiltration of malignant T-lymphocytes in subcutaneous tissue, often rimming the fat lobules. Although SPTCL has been recognized as a distinctive entity in the category of peripheral T-cell lymphoma in the WHO classification, its diagnostic criteria has been redefined by the recent WHO-European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas. The term SPTCL is now restricted to primary tumors expressing the alpha/beta T-cell receptor phenotype. These lymphomas are usually CD3(+), CD4(−), CD8(+), and CD56(−), and usually have an indolent clinical course. The tumors expressing the gamma/delta phenotype have been reclassified as primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL).

SPTCL usually presents with one or multiple subcutaneous nodules involving one or multiple areas of the body and may be associated with fevers, weight loss, and pancytopenia. The pancytopenia is often cytokine mediated, as bone marrow involvement is rare [77, 78]. The hemophagocytic syndrome may occur in up to one third of patients and in some cases may be fulminant. The clinical course for patients with SPTCL has been highly variable, due in part to the small number of cases reported and to the fact that until recently the distinction between the alpha/beta and gamma/delta subtypes had not been uniformly made at diagnosis. Kong et al. have

reviewed 22 cases of SPTCL in Asia and have identified angioinvasion as a poor prognostic marker [79].

PCGD-TCL accounts for less than 1% of all cutaneous TCL and presents as diffuse skin involvement with disseminated lesions that mainly affect the extremities and frequently are associated with ulceration and necrosis. The phenotype of PCGD patients is $CD3^+$, $CD8^-$ with expression of cytotoxic markers in most cases (TIA-1, granzyme B, perforin). Unlike alpha/beta SPTCL, dissemination to other extranodal sites is frequently, and the majority of patients present with B-symptoms.

A retrospective review by Willemze and colleagues and the EORTC Cutaneous Lymphoma Group describes clinical features and outcomes of 63 patients with SPTCL and 20 with PCGD-TCL based on careful pathological review of the cases [80]. The median age was younger (39 years vs. 59 years) for the SPTCL patients, and there was no difference in the frequency of B-symptoms or bone marrow involvement between the groups. There was a higher frequency of hemophagocytic syndrome in the PCGD-CTL group compared to the SPTCL group (45% vs. 17%). When treatment and outcomes were reviewed, it was noted that 50–70% of patients received CHOP like regimens, 10–38% had immunosuppressive therapies, and a small number were treated with radiation or local excision of the nodules. With initial therapy, 80% of patients in the SPTCL group had a response, compared to 65% in the PCGD group. The 5-year OS for the SPTCL patients was 82% vs. 11% for the PCGD patients.

Treatment approaches for SPTCL and PCGD-TCL have not been clearly established. In the retrospective EORTC review, half of the patients were treated with aggressive chemotherapy and several had autologous stem cell transplantation as a consolidation. One third of the patients were treated with single agent therapies such as methotrexate, prednisone, cyclosporine, chlorambucil, or cyclophosphamide. Sixteen of 24 had a complete response, but nine of these relapsed and five subsequently had a durable response on reinstitution of the same therapy. Eight of the patients received CHOP in relapse and three had a CR. Of five patients presenting with a solitary skin relapse, all were treated with local therapy (radiotherapy or surgery) and are in remission. In the PCGD group, 14 of 20 patients received multiagent chemotherapy and only three had a CR; one patient went on to allogeneic transplant and had a CR after transplant. Seven patients developed visceral disease and at 12 months, 15 of 20 had died of hemophagocytic syndrome or progressive disease.

Other case reports and small series have described responses in SPTCL and PCGD-TCL patients. In one single institution review of ten consecutive patients, three (two SPTCL and one PCGD-TCL) were treated initially with denileukin diftitox; one each with SPTCL and PCGD- TCL disease had PR on therapy and have been maintained without PD [81]. Seven patients were treated with cytotoxic chemotherapy regimens. Four of seven achieved a remission after EPOCH (2), denileukin diftitox-CHOP (1) or pentostatin/cyclophosphamide followed by alemtuzumab (1). Four patients (one with refractory SPTCL, two with refractory PCGD- TCL and one with PCGD- TCL in first CR after denileukin diftitox-CHOP) underwent allogeneic hematopoietic stem cell transplantation (HSCT) from matched-related donors. Two patients are alive six and 13 months after HSCT with no evidence of disease; one patient died in CR from infectious complications of

HSCT, and one relapsed 6 months after HSCT and died from PD. At a median follow up of 3 years from diagnosis, eight patients (80%) are alive, including the two patients with SPTCL and six of eight patents with PCGD- TCL. In patients who were refractory to CHOP in one series, response to cyclosporine was reported in four [82]. Another report has demonstrated the efficacy of a fludarabine-based regimen in one patient with aggressive disease [83].

On the basis of these findings, the treatment approach to PCGD-TCL should be similar to that of other aggressive poor prognosis T-cell lymphomas and should include multiagent chemotherapy followed by stem cell transplantation from an allogeneic donor if one is available. Patients with SPTCL with a benign clinical behavior may be managed with single agent therapies. For those with progressive or disseminated disease or with the hemophagocytic syndrome, multiagents chemotherapy followed by autologous stem cell transplantation should be considered.

The Role of Transplantation in Aggressive T-Cell Lymphomas

Several retrospective studies suggest that there are populations of patients with PTCL that will benefit from transplantation. The National Cancer Consortium Network (NCCN) guideline includes transplant as an option for consolidation after first remission in patients with histologies other than ALK-positive ALCL with advanced stage disease. The role of autologous transplantation in relapsed or primary refractory disease is less well defined. Disease status at transplant is a major predictor of success, with inferior results reported for patients who are not chemosensitive. In several reports, only 25–30% of refractory patients benefit from this approach. In the studies where 5-year outcomes are reported, OS average 34%. The single center experience at Stanford reported only a modest benefit after autologous transplant (5-year OS of 36%) for patients with relapsed disease and a 5-year OS of 76% in patients transplanted in first remission.

A prospective study from Germany using chemotherapy and up-front autologous transplantation for PTCL has demonstrated that a significant number of patients were never able to be transplanted due to progression of disease on first-line therapy. The treatment regimen consisted of 4–6 cycles of CHOP, followed by either dexaBEAM or ESHAP. Patients in complete or partial remission then underwent myeloablative chemoradiotherapy and autologous stem cell transplant. Two thirds (66%) of the patients were chemosensitive and went on to autologous stem cell transplant. At a median follow-up time of 33 months, the estimated 3-year OS and PFS for patients in complete response were 48% and 36%, respectively. Patients who did not experience a response to chemotherapy and therefore did not undergo autologous stem cell transplant had a very poor outcome, with a median survival of less than 2 years.

There are currently no randomized studies comparing outcomes between autologous and allogeneic transplant approaches. The Nordic and German lymphoma groups are launching a large, prospective randomized trial to compare the different strategies as consolidation after first-line therapy. In a retrospective single-institution

study that compared autologous and allogeneic transplant, outcomes for autologous transplant were best when conducted in first remission, and allogeneic transplant was better for patients with resistant or relapsed disease. Further prospective studies are needed to define which subsets of PTCL patients will optimally benefit from allogeneic or autologous stem cell transplant [84–88].

Evidence-Based Treatment Approaches for PTCL

Because of the inferior outcomes with CHOP-based regimens, novel strategies are needed for patients with aggressive T-cell lymphomas. The NCCN has established evidence-based treatment approaches for T-cell lymphoma and stratifies patients based on stage. For early stage patients with localized disease, chemotherapy should be followed by involved field radiotherapy. It is recommended that all patients except for those with low IPI be consolidated with autologous stem cell transplant. ALK-positive ALCL is identified as the one subtype, which has an excellent outcome and should not be transplanted in first remission. Recent data suggest that ALK-positive patients with high IPI could be an exception to this rule. In prospective trials where up to 40% of patients do not undergo a complete remission and therefore cannot be consolidated with transplant, new approaches are necessary.

Selection of first-line therapy based on histopathologic features has not yet been widely employed but should be considered. For nodal T-cell lymphomas (PTCL-NOS, AITL, ALCL) the standard regimen used is a CHOP-based therapy. For extra-nodal subtypes, regimens may be individualized. For SPTCL, distinction should be made between the alpha-beta type and the gamma-delta type, which is now included in the category of cutaneous gamma-delta T-cell lymphoma. The alpha-beta patients may be treated with single-agent therapies or combination chemotherapy and generally have an excellent outcome. The cutaneous gamma-delta T-cell lymphomas overall do poorly and should be treated with aggressive chemotherapy followed by transplantation. Likewise, hepatosplenic and intestinal T-cell lymphomas have a poor outcome. In one study, 26 enteropathy-associated T-cell lymphoma patients were treated with CHOP then methotrexate alternating with ifosfamide, etoposide, and epirubicin.[128] Patients who achieved CR went on to transplant ($n=33$). For the transplanted EATL, the PFS and OS were 52% and 60%, respectively. NK/T-cell lymphoma patients have also had inferior outcomes with CHOP-based regimens, and consideration of alternative regimens such as SMILE and asparaginase combinations should be strongly considered for these patients.

The role of autologous vs. allogeneic stem cell transplantation in patients with poor prognosis subtypes such as NK/T cell and gamma-delta T-cell lymphomas has not been ascertained. In retrospective series, results with these subtypes are inferior to those of the more common PTCL-NOS and AITL subtypes after autologous transplantation. Therefore, consolidation with allogeneic stem cell transplantation should be considered in patients who have appropriate donors.

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