Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Pharmacotherapy of peripheral T-cell lymphoma: review of the latest clinical data

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The peripheral T-cell lymphomas (PTCL) are a disparate group of diseases with varying clinical and pathological features and heterogeneous natural histories. All of the PTCL histologies are uncommon in North America and western Europe. Even the most common PTCL histology, PTCL-not otherwise specified, accounts for only a small fraction of all cases of non-Hodgkin's lymphoma. The relative rarity and clinical heterogeneity of these diseases has hampered basic science and clinical research and, until recently, made PTCL a neglected area of drug development. This has partly contributed to lower success rates in treating PTCL relative to the more common B-cell non-Hodgkin's lymphomas. The roles of many therapies utilized to treat PTCL, including stem cell transplantation, remain undefined. Thankfully, several therapies have been approved in recent years and large scale studies are evaluating the comparative efficacy of various therapeutic approaches. This review describes the common PTCL subtypes and delineates recent advances.

Keywords: brentuximab vedotin • mogamulizumab • peripheral T-cell lymphoma • pralatrexate • romidepsin

Peripheral T-cell lymphoma

■ Epidemiology

Peripheral T-cell lymphoma (PTCL) accounts for approximately 10% of all cases of non-Hodgkin's lymphoma (NHL) diagnosed in North America and Western Europe. Approximately 6000–9000 new cases are diagnosed every year in the USA. Table 1 shows the relative frequency of various PTCL histologies [1].

There are few defined risk factors for developing PTCL. Most patients are older, with a median age at diagnosis of approximately 60 years, although some histologies have a propensity to affect young adults [2]. Infectious agents such as Epstein–Barr virus (EBV) and human T-lymphotropic virus-1 are important in the pathogenesis of several PTCL subtypes [3].

■ Presenting features

Patients frequently present with signs and symptoms common to other aggressive lymphoid malignancies, such as fever, night sweats, poor appetite and weight loss. Extranodal, particularly cutaneous, involvement is common [4]. Although the most common PTCL histology is PTCL-not otherwise specified (NOS), several other common PTCL subtypes warrant discussion due to their unique clinical and pathological features and, in some cases, unique treatment paradigms.

■ Anaplastic T-/null-large cell lymphoma

Anaplastic T-/null-large cell lymphoma (ALCL) is characterized by almost universal expression of CD30 (Ki-1) [5], and in 40–60% of cases a translocation between

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Table 1. Relative frequency of peripheral T-cell lymphoma histologies.

PTCL subtype	Relative frequency compared with all diagnoses of NHL (%)
PTCL-NOS	3.7
Anaplastic T-/null-large cell lymphoma	2.4
Extranodal NK-/T-cell lymphoma, nasal type	1.4
Angioimmunoblastic T-cell lymphoma with dysproteinemia	1.2
Others	<1

NHL: Non-Hodgkin's lymphoma; NOS: Not otherwise specified; PTCL: Peripheral T-cell lymphoma.

chromosomes 2 and 5 (t [2;5][p23;q35]), resulting in fusion of the *NPM* gene with the cytoplasmic domain of ALK (although other variants have also been described) [6]. ALK is a member of the insulin receptor superfamily and is important in neurologic development of embryos. The mechanism by which ALK promotes lymphomagenesis is not completely defined but seems to involve both the Ras/Raf/MEK/ERK1/2 cell proliferation pathways and the JAK/STAT cell survival pathway [7]. The advent of clinically available ALK inhibitors may allow for exploitation of this pathogenic mechanism.

ALCL commonly affects younger patients and there is a male predominance [8]. ALCL generally exhibits an aggressive clinical behavior and most patients present with stage III or IV disease [9]. Extranodal disease occurs in 40–60% of patients, with skin, bone, soft tissue and lung commonly involved [8]. Several reports suggested that EBV is important in the pathogenesis of ALCL; however, the weight of evidence suggests that this is not the case [10].

Patients with ALK-positive ALCL have a more favorable prognosis than patients with ALK-negative ALCL or other subtypes of PTCL, and are generally excluded from most upfront treatment trials. Table 2 lists several series examining the outcome of ALCL treated with anthracycline-based chemotherapy [11]. ALCL also occurs as a primary cutaneous-ALCL. Primary cutaneous-ALCL is an indolent disease with a 10-year survival of ≥85% and should not be treated with the aggressive modalities used to treat systemic ALCL [12].

Table 2. Overall survival of anaplastic large-cell lymphoma treated with anthracycline-based chemotherapy and based on ALK expression.

Study	5-year OS ALK+	5-year OS ALK-	Ref.
Shiota *et al.*	80	33	[92]
Nakamura *et al.*	72	30	[93]
Falini *et al.*	71	15	[94]
Gascoyne *et al.*	93	37	[95]
Savage *et al.*	70	49	[96]

OS: Overall survival.

■ Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) typically presents in older patients – often with associated rash, autoimmune hemolytic anemia and/or autoimmune thrombocytopenia, arthritis and thyroid abnormalities. The disease commonly follows a very aggressive course although there are rare reports of spontaneous remission [13].

Treatment of AITL is varied. Some patients respond to prednisone or even cyclosporine although most are treated with anthracycline-based chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). In one study comparing CHOP to prednisone the complete remission (CR) rate was 64% with CHOP compared with 29% with prednisone. The median survival rates were 19 and 11 months for patients receiving CHOP and prednisone, respectively [14].

A small proportion of AITL will have a clonal B-cell infiltrate that is usually EBV positive [15]. The finding of clonal B-cell populations in some patients generated interest in adding the anti-CD20 antibody rituximab to CHOP in this patient population. Unfortunately a trial examining R-CHOP for the initial treatment of AITL was terminated early as a result of lack of benefit [16].

Some investigators have attempted to improve the durability of responses in AITL by administering high-dose chemotherapy and performing autologous stem cell transplantation (ASCT) in first remission. A retrospective study of 146 patients yielded an overall survival (OS) of 67% at 24 months and 59% at 48 months. Patients who had achieved a CR prior to transplant had superior outcomes with a progression-free survival (PFS) of 70% at 24 months and 56% at 48 months. Those patients with chemotherapy-refractory disease at the time of transplantation had the worst outcome with a PFS of 23% at 24 and 48 months [17].

■ Adult T-cell leukemia/lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is associated with HTLV-I, a retrovirus endemic to the Caribbean, Japan, South America, and parts of West Africa but rare in the USA. Approximately 2–4% of patients infected with HTLV-I will eventually develop ATLL [18]. The mechanism of HTLV-I-induced oncogenesis is not incompletely understood [19].

There are four types of ATLL distinguishable by clinical presentation – acute, lymphomatous, chronic

and smoldering. The acute variant of ATLL is a fulminant disease that presents with lytic bone lesions, hypercalcemia and a prominent leukemic phase characterized by so-called 'flower cells'. The lymphomatous variant is similarly aggressive though lymphadenopathy is more prominent with less of a leukemic component. Treatment outcomes for both the acute and lymphomatous variants are poor with median survivals ranging from 6–9 months. Unfortunately these more aggressive variants represent approximately 80% of ATLL cases and account for the poor outcome of the disease [20]. The chronic and smoldering variants of ATLL can present with isolated lymphocytosis and can follow an indolent course akin to chronic lymphocytic leukemia (CLL). Survival ranges from several to many years and immediate therapy is often not warranted, especially if the patients are under 40 years of age, have a normal serum LDH, a good performance status and fewer than three sites of involvement [21].

Younger, fitter patients with aggressive variants of ATLL are treated with chemotherapy regimens modeled after those used in acute lymphoblastic leukemia. The standard treatment in Japan is alternating vincristine, cyclophosphamide, doxorubicin and prednisolone (VCAP), doxorubicin, ranimustine, prednisolone (AMP) and vindesine, etoposide, carboplatin, prednisolone (VECP), which proved superior to CHOP in a randomized trial [22]. Ranimustine and vindesine are not available in the USA and other countries. As a result, aggressive lymphoma regimens such as Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with cytarabine and methotrexate) are also frequently used in these countries. Allogeneic stem cell transplantation (alloSCT) may be of benefit in first remission in these patients [23].

Some groups have treated ATLL by targeting HTLV-I. Several studies assessing the efficacy of zidovudine (AZT) in combination with IFN-α were summarized in a recent meta-analysis. Interestingly, 70% of patients who achieved a CR with first-line AZT/IFN-α therapy survived longer than 10 years. First-line AZT/IFN-α therapy in chronic- and smoldering-type ATLL resulted in 100% OS at a median follow-up time of 5 years and is being explored further in this setting [24].

■ Extranodal NK/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma, nasal type, typically presents in an aggressive fashion in the sinonasal cavity. There is a male predominance. Extranodal NK/T-cell lymphoma, nasal type, is rare in the USA but common in Asia including Korea and Japan. The tumor cells are almost always EBV-positive and it is presumed that EBV is important in the pathogenesis of the disease [25].

Patients frequently have localized disease in which case durable long-term remissions or cure can be achieved with radiation, with or without chemotherapy. Unfortunately, disseminated disease typically responds poorly to chemotherapy. The median OS for localized sinonasal disease is approximately 3 years compared with 0.36 years for disseminated disease [26]. Recently developed regimens incorporating methotrexate and asparaginase seem to improve outcome. The poor outcome with chemotherapy has generated interest in more aggressive approaches such as alloSCT and ASCT [27].

■ Hepatosplenic T-cell lymphoma

This extremely aggressive neoplasm tends to affect young men. Patients usually present with jaundice and splenomegaly. Bone marrow involvement is very common, but lymphadenopathy is generally not prominent. While most cases of PTCL express the αβ T-cell receptor, hepatosplenic T-cell lymphoma generally expresses the γδ T-cell receptor (although αβ variants do exist). Hepatosplenic T-cell lymphoma responds very poorly to chemotherapy, and most patients will die of the disease [28]. Patients are treated with aggressive combination chemotherapy regimens such as HyperCVAD. ASCT or even alloSCT are utilized in patients who achieve remission.

■ Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a very rare entity with a female predominance. Most patients present with subcutaneous nodules mimicking infectious or autoimmune panniculitis. An associated hemophagocytic syndrome (HPS) can occur, resulting in fevers, pancytopenia, hyperferritinemia, hypertriglyceridemia and elevated soluble IL-2 receptor levels. Historically SPTCL had been classified as two variants based on the T-cell receptor type expressed on the cell surface (αβ and γδ). The γδ subtype has now been renamed as cutaneous γδ T-cell lymphoma in the most recent WHO classification of hematologic malignancies and is much more commonly associated with HPS than is αβ-SPTCL. Patients with αβ-SPTCL have more indolent disease and a favorable prognosis with a 5-year OS of 82% (91% in the absence of HPS). These patients can be managed in a similar fashion to indolent cutaneous T-cell lymphomas. In contrast, patients with γδ-SPTCL are more likely to have HPS and have a 5-year OS of only 11% [29]. These poor-risk patients require combination chemotherapy and consideration of transplantation in first remission.

■ Enteropathy type T-cell lymphoma

Enteropathy type T-cell lymphoma (EATL) is a rare condition subclassified as EATL-I and -II. EATL-I

accounts for >80% of cases and occurs almost exclusively in patients with gluten-sensitive enteropathy (celiac sprue) [30]. The tumor cells are typically CD8-negative but do express CD56 [31]. Type II EATL (also known as monomorphic EATL) is less frequently associated with gluten-sensitive enteropathy and the tumor cells do not usually express CD8 or CD56 [32]. Patients with either variant commonly present with multifocal small bowel perforation with many dying as a consequence. Adherence to a gluten-free diet in patients with sprue nearly eliminates the risk of EATL [33]. EATL is a very aggressive disease and only approximately 10% of patients are long-term survivors [34].

■ PTCL-NOS

The term PTCL-NOS is essentially reserved for cases of PTCL that cannot be classified in one of the above-mentioned categories based upon clinical presentation and/or cytogenetic findings. Although gene expression profiling and other techniques are being increasingly utilized to identify specific and reproducible subgroups of PTCL-NOS, these methods have not, as yet, resulted in any changes in clinical management or major shifts in drug development and will not be discussed further in this review [35].

■ Predictors of treatment outcome

With the exception of ALK-positive ALCL, patients with PTCL typically have worse long-term survival than patients with aggressive B-cell NHL. The International Prognostic Index (IPI) was developed to predict outcomes in diffuse large B-cell lymphoma but is also predictive in PTCL [36]. Table 3 shows the relative outcome by IPI score for aggressive B- and T-cell NHL. Unfortunately, a higher proportion of patients with PTCL present with high IPI scores relative to aggressive B-cell lymphoma patients. Recently, a separate prognostic index for PTCL (PIT) has been proposed [37]. This model includes only four factors: age >60, performance status ≥2, increased LDH and bone marrow involvement. Table 4 shows the outcome by PIT score. A modified version of the PIT, incorporating both patient and tumor characteristics, has also been proposed (Table 5) [38]. There is significant overlap between the IPI, the PIT and the modified PIT, and none of these systems has emerged as the clear standard, although at present most clinicians and authors cite the IPI.

Table 3. Overall survival for B- and T-cell non-Hodgkin's lymphoma stratified by International Prognostic Index score.

IPI Score	B-cell NHL 5-year OS (%)	T-cell NHL 5-year OS (%)
0–1	73	74
2	51	49
3	43	21
4–5	26	6

IPI: International Prognostic Index; NHL: Non-Hodgkin's lymphoma; OS: Overall survival.

■ Current therapies

Historically, PTCL treatments have been empirically based on strategies developed for aggressive B-cell malignancies utilizing an anthracycline and alkylating agent backbone. CHOP is the most common regimen used in this setting. Depending on the histology and patient population studied, overall response rates (ORRs) with CHOP have ranged between 50 and 70%. The median PFS in PTCL following CHOP chemotherapy is 12–14 months with only approximately 30% of patients being alive and disease-free 5 years after treatment [39]. Clearly more effective therapies are needed.

Therapy intensification

A recent analysis of several German aggressive lymphoma studies suggested an event free though not OS benefit to adding etoposide to the CHOP regimen (CHOEP). This benefit was restricted to patients under the age of 60 with a normal LDH and was most evident in patients with anaplastic large cell lymphoma expressing the ALK protein. There was no benefit to intensifying the chemotherapy regimen by either increasing the doses of cytotoxics or shortening the cycle length to every 2 weeks [40]. Studies of other intensified regimens such as VIP-reinforced ABVD and HyperCVAD have also failed to demonstrate an improvement in survival [41,42].

■ High-dose therapy & stem cell transplant

The utility of ASCT in PTCL has been examined as part of the initial therapeutic regimen and as a strategy for relapsed/refractory disease. One of the largest studies of ASCT in PTCL was a prospective non-randomized analysis of 115 patients undergoing high-dose therapy and ASCT. Of these patients, 37 were in first CR, 28 were in second or subsequent CR, 44 were in partial remission (PR) and six had refractory disease. As a group, the 5-year disease-free survival was 60% with a 5-year OS of 56%. However, patients transplanted in first CR had a 5-year OS of 80%, which was statistically significantly higher than those patients transplanted in second or subsequent CR or PR [43]. Retrospective analyses from several other groups confirmed this finding [44].

Prospective trials have incorporated ASCT into the frontline treatment of PTCL. One of the largest and most recent was from the Nordic Lymphoma Group that accrued a total of 160 patients with histologically confirmed PTCL. The treatment plan consisted of six cycles of biweekly CHOP (for patients over age 60) or

CHOEP (for patients under age 60) followed by BEAM (busulfan, melphalan, cytarabine and melphalan) or BEAC (busulfan, etoposide, cytarabine and cyclophosphamide) conditioning and ASCT. On intention-to-treat analysis 115 of 160 patient completed ASCT and 90 were in CR 3 months after transplant. The 5-year OS was 51% and the 5-year PFS was 44%. Treatment-related mortality was 4%. The best outcomes were observed in patients with ALK-negative ALCL. The most common reason for not undergoing ASCT was failure to respond to induction chemotherapy, emphasizing the need for more effective therapies to induce initial remissions [45].

AlloSCT has also been studied in PTCL, primarily in the relapsed/refractory setting. One of the most widely cited trials utilized reduced intensity conditioning. This is especially important given that PTCL generally affects older patients who often cannot tolerate myeloablative conditioning. The 5-year PFS for the overall study population was 49% with a 5-year OS of 54% and non-relapse mortality risk of 20% [46]. In a similar study of 45 patients with AITL, the 5-year PFS was 57% with a 5-year OS of 64%. The non-relapse mortality was 25% [47]. Toxicity and donor availability limit the applicability of allogeneic transplantation.

Gemcitabine

Gemcitabine is a pyrimidine antimetabolite prodrug converted intracellularly to active metabolites [48]. Few studies have examined gemcitabine's role as a single agent in PTCL. In a study that included 20 patients with relapsed/refractory PTCL, gemcitabine had an ORR of 55% with a CR rate of 30% [49]. Although no data were given regarding PFS or OS, the median duration of response was 34 months. There was no grade 3 or 4 hematologic toxicity. In a second study of ten patients, two had CRs and four had PRs (ORR 60%). The median duration of response was 13.5 months [50].

The only published trial of gemcitabine as upfront therapy for PTCL was conducted in 26 patients receiving gemcitabine in addition to standard dose CHOP and etoposide. The ORR was 77% with 16 CR/CR-unconfirmed and four PR. The median OS had not been reached but the median event-free survival was 215 days [51].

Gemcitabine has been studied as part of combination chemotherapy in relapsed/refractory PTCL. One such study involved 16 patients treated with a regimen of gemcitabine, cisplatin and methylprednisolone. The majority of patients had received one to two prior regimens (range 0–4). Three patients achieved CRs and eight achieved PRs for an ORR of 69%. The median time to progression was approximately 4 months but the median OS had not been reached [52]. Gemcitabine has also been studied in combination with vinorelbine and oxaliplatin with similar results [53]. Although the clinical trial data are rather limited, gemcitabine is widely used in relapsed PTCL as a single agent and in combination chemotherapy regimens, even though it is not approved by any regulatory agency for this indication.

Table 4. Long-term survival in peripheral T-cell lymphomas stratified by Prognostic Index for T-cell Lymphoma score.

PIT score	5-year OS (%)	10-year OS (%)
0	62	55
1	53	39
2	33	18
3 or 4	18	12

OS: Overall survival; PIT: Prognostic Index for T-cell Lymphoma.

Newer agents

Pralatrexate

Antifolates have been used for decades in hematologic malignancies and elsewhere with varying degrees of success. Pralatrexate is a novel antifolate that is actively transported into malignant T-cells via the RFC-1, an oncofetoprotein important in embryogenesis and also expressed in many different tumor types [54]. Intracellularly, pralatrexate is a potent substrate for the enzyme, FPGS, which modifies pralatrexate to a polyglutamated form that effectively binds to DHFR. Binding of DHFR by pralatrexate inhibits folate metabolism and subsequently nucleotide biosynthesis resulting in cell death [55].

In an initial trial of 20 relapsed/refractory lymphoma patients, the four patients with T-cell lymphoma treated with single agent pralatrexate experienced CRs [56]. These encouraging results led to a subsequent expansion of the PTCL cohort with 20 additional patients enrolled. Of the 20 evaluable patients, ten responded to treatment including nine CRs. The drug was active with durable responses across histologies including acute lymphoblastic (12 months), HTLV-I-positive ATLL (18+ months), blastic NK/T (9+ months), ALK-positive ALCL (6+ months), PTCL-NOS (3 months), SPTCL (3+ months), and γδ-SPTCL (9 months).

Table 5. Survival of patients with peripheral T-cell lymphomas stratified by revised Prognostic Index for T-cell Lymphoma score.

Revised PIT score	Median OS (months)
0–1	37
2	23
3–4	6

OS: Overall survival; PIT: Prognostic Index for T-cell Lymphoma.

The maximum tolerated dose was determined to be 30 mg/m^2 intravenously for 6 of every 7 weeks with the primary toxicities being mucositis and thrombocytopenia, although these were abrogated by folic acid and vitamin B_{12} supplementation.

This promising early activity in PTCL precipitated the launch of an international, open-label Phase II trial [57]. The trial accrued 115 patients in Europe and North America. In total, 111 patients received at least one dose of pralatrexate and were evaluable for toxicity while 109 patients were evaluable for response. Pralatrexate was administered at a dose of 30 mg/m^2 weekly for 6 of every 7 weeks along with folic acid 1–1.25 mg by mouth daily and vitamin B_{12} intramuscular injections every 8–10 weeks. Responses were adjudicated by a blinded central reviewer. Patients were heavily pretreated with a median of three prior therapies (range 1–12) and 16% of patients had failed a prior ASCT. Approximately 60% of patients were refractory to the therapy they received just prior to enrolling in the trial and approximately 25% had never responded to any chemotherapy. On intention-to-treat analysis the ORR was 29% with 18% partial responses (PR) and 11% CR, while 19% of patients had stable disease. Responses were generally rapid with 63% of patients responding after one cycle. Responses were observed across all common PTCL subtypes although patients with angioimmunoblastic T-cell lymphoma seemed less likely to respond – although this was not statistically significant. Interestingly, the likelihood of response did not seem to correlate with number of prior therapies although there is no known biological predictor for response.

The most common grade 3 and 4 toxicities were thrombocytopenia (33%), neutropenia (32%), mucositis (22%) and anemia (18%). The median duration of response was 10.1 months. The median OS and PFS were 14.5 and 3.5 months, respectively. Based upon these results, the US FDA granted accelerated approval for pralatrexate for the treatment of relapsed or refractory peripheral T-cell lymphoma in September 2009. The European Medicines Agency, however, did not approve pralatrexate in a decision issued in January 2012, largely based upon concerns about the nonrandomized design of the pivotal trial.

Pralatrexate has been studied in combination with gemcitabine since both agents are active in PTCL and both can be administered to outpatients. The development of this regimen was abandoned when the combination did not offer superior efficacy over either single agent alone. This was possibly a result of overlapping toxicities that prevented administration of either agent at sufficient doses to induce optimal tumor responses [58]. A post-approval study of pralatrexate versus placebo administered as consolidation therapy after induction with CHOP chemotherapy in newly diagnosed PTCL is ongoing but no results are available.

Histone deacetylase inhibitors

Histone deacetylase (HDAC) inhibitors have been studied in a variety of malignancies, including lymphoma. The exact mechanism of action of HDAC inhibitors in a given tumor type is generally unclear. However, the agents induce the acetylation of histones and other proteins, thereby increasing tumor suppressor gene transcription, inducing growth inhibition and triggering apoptosis [59].

The first FDA-approved HDAC inhibitor was vorinostat, approved for the treatment of cutaneous T-cell lymphoma in October 2006 for patients with progressive, persistent or recurrent disease [60]. The experience with vorinostat in PTCL is very limited and it should only be used in clinical trials in this setting. A second HDAC inhibitor, romidepsin (depsipeptide), was approved by the FDA in November 2009 for patients with cutaneous T-cell lymphoma (CTCL) who had received at least one prior systemic therapy [61]. Romidepsin is a bicyclic class I HDAC inhibitor isolated from *Chromobacterium violaceum* [62]. Romidepsin was subsequently studied in PTCL based upon encouraging results from a Phase I trial and upon the success in CTCL. The initial Phase II study of romidepsin in PTCL accrued 47 patients with relapsed/refractory PTCL who had received a median of two prior therapies [63]. In total, 38% of patients failed a prior stem cell transplant. Romidepsin was administered at a dose of 14 mg/m^2 on days 1, 8 and 15 of a 21-day cycle until disease progression or unacceptable toxicity occured. The ORR was 38% (18% CR and 20% PR). The median time to response was 1.8 months and the median duration of response was 8.9 months. The median duration of CR was 29.7 months. The most frequent drug-related adverse events (AEs) were nausea, fatigue, thrombocytopenia and decreased absolute granulocyte count, although almost all were less than grade 3.

This trial also involved intensive cardiac screening as a result of ECG changes, such as T-wave flattening and ST-segment depression, observed in prior Phase I trials. There was no evidence of myocardial dysfunction or cumulative cardiac toxicity during therapy or during long-term follow up. There was a median increase of 14 ms in the corrected QT interval by automated analysis, but only a median increase of 5 ms by central cardiologist review. Patients with a history of cardiac ectopy almost universally had concomitant electrolyte abnormalities. In addition, an analysis of cases of sudden death across romidepsin protocols revealed that all patients had risk factors for sudden death, particularly antecedent cardiac disease. Thus the protocol excluded

patients with risk factors for sudden death and prohibited the administration of concomitant medications that could affect romidepsin metabolism via CYP3A4 or potentiate corrected QT (QTc) prolongation. The protocol also mandated magnesium and potassium to maintain a minimum potassium level of 4.0 mM and magnesium level of 0.85 mM. As a result of this requirement, supplementation of either electrolyte was estimated to be required during 50% of treatment administration (potassium alone: 13%; magnesium alone: 20%; both: 17%).

The encouraging findings in this initial Phase II trial lead to the launch of a larger, open-label Phase II trial of romidepsin in relapsed/refractory PTCL [64]. A total of 131 patients were enrolled and 130 had a diagnosis of PTCL confirmed by central pathology. The schedule of administration consisted of romidepsin 14 mg/m^2 by 4 h infusion on days 1, 8 and 15 of a 28-day cycle. The median number of prior therapies was two, with 38% of patients refracting to their most recent treatment and 16% of patients having undergone a prior ASCT. Patients were excluded if they had any known significant cardiac comorbidities and were required to have had a serum potassium level ≥ 3.8 mmol/l and a serum magnesium level ≥ 0.85 mmol/l before any dose of romidepsin could be administered.

The ORR was 25% (15% CR/CR-unconfirmed) as assessed by central review. The median time to response was 1.8 months and the median duration of response was 17 months. As with pralatrexate, response rates did not vary by histology or prior therapy. Romidepsin did have a response rate of 30% in AITL, whereas pralatrexate only had an 8% response rate in PTCL. The most common grade 3 or higher AEs were thrombocytopenia (25%), neutropenia (20%) and infection (10%). ECG abnormalities occurred in 6% of patients, with 3% experiencing QTc prolongation (only one grade 3).

Based upon these results the FDA granted accelerated approval of romidepsin in June 2011 for the treatment of relapsed/refractory PTCL. The European Medicines Agency declined approval of romidepsin in July 2012 citing as a primary reason the lack of randomized trials confirming benefit. A front-line trial or romidepsin in combination with CHOP in newly diagnosed PTCL is ongoing; however, available results are limited and use of this combination cannot be recommended outside the context of a clinical trial.

Belinostat is a hydroxamic HDAC inhibitor also being studied in PTCL. Belinostat inhibits HDACs 1 and 2, although this difference in inhibitory profile compared with romidepsin is of unclear clinical significance. In total, 19% of patients with PTCL were analyzed in a Phase II trial utilizing a dose of 1000 mg/m^2 administered on days 1–5 of a 21-day cycle. The median number of prior therapies was two [65]. The ORR was 32% and the median duration of response was 9 months. There was no grade 3 prolongation of QTc. There was no grade 4 hematologic toxicity, the incidence of grade 3 neutropenia was only 4% and the incidence of grade 3 thrombocytopenia was 3%. One patient died of ventricular fibrillation 6 days after discontinuing treatment. Belinostat is currently being studied in an open-label Phase II trial under a Special Protocol Assessment agreement with the FDA, and also has orphan drug status with the European Medicines Agency. Although the final response rate is unknown, belinostat did surpass its primary end point of an ORR of 20%. Final results from this trial will hopefully be available in 2013.

At present it is not possible to assess the relative clinical utility of belinostat compared with romidepsin since the full data set for belinostat is not available and the latter agent has not yet been approved by any regulatory authority.

■ Brentuximab vedotin

Anaplastic T-cell lymphoma almost ubiquitously expresses CD30, a member of the TNF receptor family, the exact function of which is unclear but which may control apoptosis, cell activation, effector function and proliferation [66]. Unlabeled monoclonal antibodies targeting CD30 had minimal activity [67]. Brentuximab vedotin is a humanized monoclonal antibody targeting CD30 that is linked via a protease cleavable linker to monomethyl auristatin E (MMAE), a potent microtubule disrupting agent. When the antibody binds to CD30, the antibody–toxin conjugate is endocytosed and transported to the cell's lysozome where the MMAE is cleaved and released. The MMAE inhibits microtubule formation resulting in G2/M cell cycle arrest and apoptosis [68].

The pivotal trial of brentuximab vedotin in ALCL accrued 58 patients with a median of two prior treatment regimens [69]. In total, 50% of patients were refractory to their most recent therapy, 22% had not responded to any previous therapy and 26% had failed an ASCT.

The ORR by independent review was 86% (57% CR; 29% PR), the median time to response was approximately 6 weeks, and the median duration of response was 12.6 months. The median PFS was 13.3 months and the estimated 1-year survival was 70% while the median OS had not been reached. Patients with ALK-positive and -negative disease were equally likely to respond.

A total of 60% of patients experienced a grade 3 or higher AE. The most common grade 3 or 4 AEs were neutropenia (21%), thrombocytopenia (14%), peripheral sensory neuropathy (12%) and anemia (7%). There

have also been reports of rare cases of progressive multifocal leukoencephalopathy following treatment with brentuximab vedotin.

Based upon these results, the FDA approved brentuximab vedotin in August 2011 for the treatment of ALCL following at least one prior systemic therapy. Brentuximab vedotin is also approved for the treatment of Hodgkin's lymphoma after the failure of ASCT or after at least two prior systemic chemotherapies in patients who are not transplant candidates (data not shown). Brentuximab vedotin was also granted conditional marketing approval for identical indications by the European Medicines Agency in July 2012.

Brentuximab is being studied in other CD30-expressing malignancies including other histologies of T-cell NHL aside from ALCL. Approximately 30% of non-ALCL PTCL will express CD30, although the optimal cut-off to determine a true positive value is unclear [70]. In an open-label Phase II study of brentuximab vedotin in CD30-positive non-Hodgkin's lymphoma (excluding ALCL) brentuximab had a response rate of 50% in AITL and 25% in PTCL-NOS although the number of patients treated was small [71]. The toxicity profile in this population was similar to the toxicity profile described in ALCL and Hodgkin's lymphoma. Interestingly, the probability of responding to brentuximab vedotin did not correlate to the level of CD30 expression and patients whose tumors had CD30 expression as low as 1% responded to treatment while patients with much higher expression of CD30 did not respond. This finding may be a statistical anomaly due to the small number of patients treated on this trial, but does make it difficult to define the optimal patient population for study of brentuximab going forward. At present, however, the use of brentuximab outside of ALCL and Hodgkin's lymphoma cannot be recommended outside the context of a clinical trial.

Brentuximab vedotin is also being studied in the initial treatment of CD30-expressing T-cell lymphomas. In a Phase I trial presented at the 2012 meeting of the American Society of Hematology, 39 patients were treated with sequential brentuximab vedotin and standard-dose CHOP or CHP (cyclophosphamide, doxorubicin, prednisone) [72]. Vincristine was omitted in patients receiving brentuximab vedotin due to the overlapping toxicities of peripheral sensory neuropathy and the overlapping mechanism of action of tubulin inhibition. The study was composed of three arms. Patients randomized to Arm 1 received two cycles of 1.8 mg/kg brentuximab vedotin treatment administered every 3 weeks, followed by six cycles of CHOP chemotherapy. Patients randomized to Arms 2 and 3 received treatment with up to six cycles of 1.8 mg/kg brentuximab vedotin in combination with standard-dose CHP chemotherapy also administered every 3 weeks. In total, 26 patients were available for response assessment and all achieved at least a PR, while 88% achieved a CR. Febrile neutropenia occurred in 19% of patients and 8% experienced a pulmonary embolism. In total, 38% of patients developed peripheral sensory neuropathy but fewer than 5% experienced grade 3 or higher neuropathy. In total, 19% of patients discontinued therapy due to an AE. As a result of these encouraging results there is now a global randomized trial comparing standard dose CHOP with CHP combined with brentuximab vedotin. Autologous transplantation in first remission is allowed in either arm. This trial just launched and no results are available yet; however, eventually this trial should define the utility of brentuximab in combination with chemotherapy in the initial treatment of T-cell lymphoma. Until results are available, the utilization of brentuximab in combination with chemotherapy outside of a clinical trial cannot be recommended.

Mogamulizumab

CCR4 is a high-affinity receptor for the CC chemokines thymus and activation-regulated chemokine and macrophage-derived chemokine [73]. CCR4 is expressed in circulating T cells, particularly T-helper type 2 cells. CCR4 is expressed in the majority of cases of adult T-cell leukemia/lymphoma [74].

Unfortunately, ATLL is frequently refractory to even these aggressive chemotherapy regimens (or patients are too old and/or infirm to tolerate such aggressive regimens) and the majority of patients will die of the disease. Mogamulizumab (KW-0761) is a humanized anti-CCR4 immunoglobulin G1 monoclonal antibody with a defucosylated Fc region intended to enhance antibody-dependent cellular cytotoxicity [75]. Mogamulizumab was developed to improve outcomes in ATLL.

An open-label Phase II trial of mogamulizumab enrolled 28 patients with relapsed/refractory ATLL. Mogamulizumab was administered weekly for 8 weeks at a dose of 1 mg/kg [76]. The ORR was 50% including a 30% CR rate. The median PFS was 5.2 months and the median OS was 13.7 months. The most common AEs were infusion reactions, occurring in 89% of patients, and skin rash, occurring in 63%; although all patients recovered completely from both. Interestingly, 13 of the 14 patients who developed grade 2 or higher skin rashes responded to treatment including eight CRs, while none of the 12 patients who developed no or grade 1 skin rashes responded to treatment. Lymphopenia occurred in 96% of patients while 25% of patients developed grade 3 neutropenia and 19% developed grade 3 or 4 neutropenia. Based upon these results, the Japanese Ministry of Health, Labour and

Welfare approved mogamulizumab in April 2012 for patients with relapsed or refractory CCR4-positive adult T-cell leukemia-lymphoma. A randomized study of VCAP/AMP/VECP plus mogamulizumab versus placebo in previously untreated ATLL is ongoing.

CCR4 is also expressed in some cases of CTCL and other PTCL histologies and mogamulizumab is being studied in these diseases. In a Phase II study presented at the American Society of Hematology meeting in 2012, 37 patients (29 PTCL, eight CTCL) with relapsed/refractory disease received mogamulizumab 1 mg/kg weekly for up to 8 weeks. The median number of prior therapies was two [77]. The ORR in PTCL was 34% including a 17% CR rate. When examining different histologies, the ORR was 19% in PTCL-NOS and 50% in AITL. The ORR in CTCL was 38% with no CR. Grade 3 or 4 lymphopenia occurred in 70% of patients, grades 3 or 4 neutropenia occurred in 16%, and grade 3 or 4 thrombocytopenia in 3%. In regards to non-hematologic toxicity, grade 3 or 4 ALT increase occurred in 3% and skin eruptions of any grade occurred in 49% (8% grade 3 or 4). Infusion-related toxicities occurred in 22%, although none were greater than grade 2. It is unclear why the incidence of infusion reactions was lower than in patients with ATLL. One explanation could be that reactions with monoclonal antibodies, such as rituximab, occur at a higher rate in patients with a significant amount of circulating disease and ATLL has a much more prevalent leukemic phase than CTCL or other PTCL histologies, although this has not been substantiated. Other notable AEs included one case of grade 3 polymyositis and two cases of cytomegalovirus retinitis. These results are certainly very encouraging and warrant further development of mogamulizumab in both CTCL and PTCL. A larger multinational open-label Phase II trial in relapsed/refractory PTCL is ongoing and a randomized trial of mogamulizumab versus vorinostat is also accruing. The antibody has been granted orphan drug status by the European Medicines Agency and FDA in PTCL.

Choosing available agents

The lack of randomized trials makes selection of currently approved agents for relapsed/refractory T-cell lymphoma challenging. All patients should be strongly encouraged to participate in clinical trials. Traditional lymphoma salvage therapies such as ICE (ifosfamide, carboplatin, etoposide) and GemOx (gemcitabine and oxaliplatin) remain viable options, particularly for patients who are candidates for autologous or allogeneic transplantation. Given the high response rate of brentuximab vedotin in anaplastic T-cell lymphoma, the author favors this as the initial single agent of choice in the relapsed/refractory setting for this histology. For patients with ATLL that is relapsed or refractory following chemotherapy, mogamulizumab is a very reasonable selection, although unfortunately the agent is not currently commercially available in the USA or Europe.

For patients who have histologies other than ALCL, or who have ALCL and have failed brentuximab, the choice amongst pralatrexate and romidepsin is largely based upon anticipated side-effect profile. Both agents have a fairly similar schedule of administration (6 of 7 weeks for pralatrexate, 3 of 4 weeks for romidepsin), although romidepsin is a 4 h infusion rather than the 5 min push with pralatrexate. Both drugs also require supplementation – folic acid and vitamin B12 with pralatrexate and potassium and/or magnesium in a significant proportion of patients receiving romidepsin. Although the numbers are small and there are no randomized data, pralatrexate appears to be less active in AITL than romidepsin and the author prefers to start with romidepsin in this histology, although it is reasonable to utilize pralatrexate as well. The author prefers to start with pralatrexate in patients with a history of significant cardiac disease, particularly arrhythmia or prolonged QTc, and in patients who are on concomitant medications that can prolong QTc and who cannot be safely held or switched to alternative non-QTc prolonging agents during chemotherapy. The author prefers to start with romidepsin in patients at high risk for mucositis (such as prior radiation to the neck and/or chest) and in patients with borderline nutritional status who may not tolerate a prolonged period of mucositis and decreased nutritional intake.

Aside from these specific populations, the choice between romidepsin and pralatrexate is largely based upon physician experience with both agents and patient preference following a discussion of the potential adverse effects. There is no evidence that either agent is curative. Therefore in reality many patients will cycle through both therapies in the relapsed/refractory setting.

Investigational agents

The last decade has resulted in a significant improvement in the therapeutic armamentarium for PTCL, with the approvals of pralatrexate, romidepsin, brentuximab vedotin and mogamulizumab. Unfortunately, however, PTCL remains a difficult disease to treat and a greater array of treatment options is needed. Some of the agents in development are discussed in this section.

Alemtuzumab

CD52 is a phosphatidylinositolglycan-anchored glycoprotein with an exact function that is unknown but that is widely expressed in many immune cells including a high proportion of PTCL cases. Alemtuzumab is a humanized monoclonal antibody that targets CD52

and is FDA approved to treat CLL. CD52 is expressed in almost all cases of ATLL, approximately 35% of cases of PTCL-NOS, and 40% of cases of AITL but with very low or absent expression in ALCL [78]. As a result of expression of CD52 on various PTCL subtypes and the activity of alemtuzumab in CLL, various investigators studied alemtuzumab in the treatment of relapsed and refractory PTCL expressing CD52. Small studies in patients with relapsed/refractory PTCL yielded response rates of 36–50% [79]. Based upon this single agent activity, alemtuzumab has been combined with a variety of chemotherapy regimens, in particular CHOP. A representative study of alemtuzumab in combination with CHOP in previously untreated PTCL yielded a CR rate of 71% and a 1-year failure-free survival of 48% [80]. A second study yielded an ORR of 80%, with 65% CRs and a 1-year event-free survival of 43% [81]. However, this trial was closed early as a result of a 55% incidence of febrile neutropenia and two treatment-related deaths. Infectious toxicity – including unusual infections such as aspergillosis, mycobacteriosis, CMV retinitis and EBV-driven secondary lymphoma – have plagued other trials studying the combination of CHOP and alemtuzumab and raise substantial concerns about the viability of the regimen moving forward.

Two randomized, prospective Phase III trials should definitively assess the utility of adding alemtuzumab. The German/Nordic cooperative study (ACT-2) is enrolling patients aged 60–80 years. The treatment plan utilizes CHOP-14 for six cycles with or without alemtuzumab. The trial was amended due to the occurrence of opportunistic infections in the alemtuzumab arm. Granulocyte growth factors and prophylactic antibiotics are now used routinely and the dose was reduced from 60 to 30 mg/cycle. In the Nordic study (ACT-1), patients aged 18–60 years are randomized to CHOP-14 ± alemtuzumab followed by consolidation with ASCT. The dose of alemtuzumab was also reduced in this trial due to a high incidence of invasive fungal infections. Preliminary results from this trial were presented at the 2012 meeting of the American Society of Hematology [82]. The number of serious AEs per patient was 0.86 for patients treated at the lower alemtuzumab dose levels compared with 3.25 at the higher dose level of alemtuzumab. Notably, however, the incidence of serious AEs in the lower dose alemtuzumab cohort was still significantly greater than the rate of 0.46 for patients treated with CHOP alone ($p = 0.002$). The frequency of grade 3 or higher bacterial and fungal infections, however, was similar in the low dose alemtuzumab and control arms. Alemtuzumab-treated patients had more viral events, particularly asymptomatic cytomegalovirus reactivations. The authors reported that the final efficacy results from this trial are anticipated in the second quarter of 2015.

Last, in a prospective Italian study, CHOP–alemtuzumab is given for two cycles followed by two cycles of high-dose methotrexate–cytarabine and cyclophosphamide. Patients then undergo consolidation with alloSCT or ASCT based on 'biological randomization'. Patients with an available matched donor will undergo allogeneic transplantation while those without a donor will undergo autologous transplantation. This trial will do more to address the relative utility of autologous transplantation versus allogeneic transplantation as consolidation in PTCL than it will the role of alemtuzumab since all patients receive alemtuzumab.

In summary, alemtuzumab has demonstrated single agent activity in PTCL, although is not approved by regulatory agencies for this purpose and its use as a single agent should be reserved for clinical trials. Various combinations of alemtuzumab with chemotherapy in previously untreated PTCL have been afflicted by substantial treatment-related morbidity, particularly infections. This raises significant concern regarding the viability of these regimens going forward. Patients treated in such a fashion should only be treated on clinical trials and require G-CSF support, antimicrobial prophylaxis and intensive monitoring for cytomegalovirus reactivation or primary infection. Fortunately, there are several ongoing, well-designed, randomized trials that will eventually define whether or not alemtuzumab in combination with chemotherapy has a role in the treatment of PTCL.

■ Bendamustine

Bendamustine is a bifunctional alkylating agent currently approved by the FDA for the initial treatment of CLL and for the treatment of relapsed/refractory follicular lymphoma. Bendamustine is currently undergoing evaluation in a variety of other lymphoproliferative disorders including PTCL. Results of a Phase II trial of bendamustine in relapsed/refractory PTCL and CTCL was presented at the American Society of Clinical Oncology meeting in 2012 [83]. Bendamustine was administered at a dose of 120 mg/m^2 intravenously on days 1 and 2 every 3 weeks, for six cycles. In total, 60 patients with a median age of 66 and a median of one prior therapy were treated. Most patients had PTCL-NOS or AITL. On an intention-to-treat analysis the ORR was 50% with a CR rate of 28%. The median duration of response was 3.5 months. The median PFS was 4 months and the median OS was 6 months. The toxicity profile was consistent with the known toxicities of bendamustine and the most frequent grade 3 or 4 AEs were neutropenia (30%), thrombocytopenia (24%) and infections (20%). Although these patients were less heavily pretreated than patients included in the registration trials of romidepsin and pralatrexate, these results are certainly very encouraging.

Alisertib

Aurora kinases are oncogenic serine/threonine kinases that regulate multiple phases of mitotic signaling. Inhibition of AAK leads to mitotic errors that trigger aneuploidy and eventually apoptosis [84]. Alisertib is an ATP-competitive, orally available inhibitor of AAK that induces apoptosis of PTCL cell lines *in vitro* [85]. In a Phase II study, alisertib was administered at a dose of 50 mg twice daily for 7 days of a 21-day cycle [86]. The trial enrolled a variety of lymphoma subtypes including eight patients with PTCL. The ORR rate in the PTCL cohort was 57%. Interestingly, there was no correlation between AAK expression and response. The grade 3 or 4 AEs were neutropenia (63%), thrombocytopenia (31%), stomatitis (15%) and febrile neutropenia (13%). Alisertib has a benzodiazepine-like structure and 6% of patients did experience grade 3 or 4 fatigue. Although this activity was observed in a small number of patients it was nonetheless encouraging. The results of this Phase II trial precipitated the launch of a global, randomized Phase III trial comparing alisertib with investigator's choice of gemcitabine, romidepsin or pralatrexate. This trial just started and results will probably not be available for several years.

Lenalidomide

Lenalidomide is FDA approved to treat multiple myeloma and myelodysplastic syndrome. Lenalidomide is being studied in a variety of different lymphomas as well as CLL. In a Phase II trial in PTCL, lenalidomide was administered at a dose of 25 mg daily on days 1–21 of a 28-day cycle [87]. A preliminary report described the efficacy of lenalidomide in the first 24 patients on treatment. Patients had a median age of 65, with a median of one prior therapy, including four patients who were previously untreated since they were not considered to be candidates for chemotherapy. The ORR was 30%, all PRs. The median PFS was 96 days and the median OS was 241 days. The most common grade 3 AEs were neutropenia (20.8%), febrile neutropenia (16.7%) and 'pain not otherwise specified' (16.7%), which was not elaborated upon in the abstract. Overall, however, the toxicity profile is consistent with the known toxicity profile of lenalidomide.

Lenalidomide is now being studied in a number of PTCL studies including ongoing single agent studies and in combination studies with various agents such as CHOP, everolimus, temsirolimus and romidepsin, as well as in a study utilizing lenalidomide as a maintenance therapy after ASCT. At present, lenalidomide use in PTCL should be restricted to clinical trials.

ALK inhibitors

The FDA approved the ALK inhibitor crizotinib in August 2011 for patients with relapsed/refractory non-small-cell lung cancer with certain ALK mutations. Crizotinib is also being developed in relapsed/refractory ALK-positive ALCL. In a pediatric trial of ALK expressing tumors, crizotinib induced CR in seven of eight patients with ALK-positive ALCL [88]. In a study of four young adult patients with ALK-positive ALCL who had received a median of three prior therapies, crizotinib induced three CR and one PR [89]. The most common side effects included rash, diarrhea and ocular disturbances. These promising results led to the initiation of a Phase II trial of crizotinib in ALK-positive ALCL, which is ongoing.

Future perspective

Peripheral T-cell lymphomas remain a challenging group of diseases to manage. Long-term survival rates with ALCL expressing the ALK protein are generally good, but the outcomes for other histologies remain poor. Numerous studies have demonstrated the utility, but also the limitations, of escalating doses of chemotherapy. Strategies such as adding etoposide to the CHOP regimen and consolidating remissions with high-dose chemotherapy and ASCT may improve long-term survival rates but, despite this intensification of therapy, the majority of patients will still recur and will succumb to their disease. Thus, the key to future success in these diseases clearly does not lie with currently available conventional cytotoxics alone.

AlloSCT can cure a significant subset of patients with PTCL by inducing an immunologic effect against the lymphoma. This approach, however, is limited by significant toxicity from graft-versus-host disease and infection and the lack of donor availability. In addition, allogeneic transplant is generally challenging in older patients and those with significant comorbidities, which further limits the applicability of this treatment approach.

Romidepsin and pralatrexate have been important additions to the therapeutic landscape of PTCL but their response rates are modest and both have significant toxicities. Furthermore, as of yet there is no biologic indicator of response to either agent and selection of therapies remains empiric. There is no evidence that either of these agents is curative in the relapsed/refractory setting and their utility in frontline therapy remains unknown.

Brentuximab vedotin is very active in relapsed/refractory ALCL but, again, there is no evidence that the agent is curative in this setting. Brentuximab may be active in other T cell subsets but the data thus far are limited. Further complicating matters is the lack of correlation between CD30 expression and response to therapy in histologies such as PTCL and AITL, which makes patient selection for clinical trials challenging.

Also, only a minority of patients with non-ALCL PTCL histologies will have CD30 expression, which limits the applicability of brentuximab to a relatively small subset of PTCL if it proves useful at all. Brentuximab is being studied in combination with chemotherapy in the initial treatment of CD30-expressing PTCL, but overlapping toxicity and mechanism of action with vincristine requires the omission of vincristine from the standard CHOP regimen when given with brentuximab. It remains unclear what effect the omission of vincristine will have on efficacy. Hopefully, however, the addition of brentuximab to chemotherapy will result in similar success to that seen with the addition of rituximab to chemotherapy in CD20-expressing B-cell malignancies.

Alisertib, bendamustine and lenalidomide are promising agents, although, as of yet unproven in PTCL. A registration trial of alisertib is ongoing but results are likely several years away. To the author's knowledge, there are no ongoing registration trials of bendamustine or lenalidomide in PTCL. Crizotinib is a promising agent in ALK-positive ALCL, although, based upon its known mechanism of action, would not seem to be useful in other PTCL subtypes.

PDGFR-β substantially prolonged survival in NPM-ALK transgenic mice and also increased the efficacy of an ALK inhibitor in transplanted NPM-ALK tumors [90]. *In vitro* data have also suggested that PDGFR-α may be an important target in T-cell lymphoma [35]. These data are supported by clinical data demonstrating two CRs in patients with relapsed/refractory T-cell lymphoma treated with dasatinib, which amongst other targets inhibits PDGFR-α and PDGFR-β [91]. Further investigation of the therapeutic utility of PDGFR inhibitors is clearly warranted.

Clearly the path forward in PTCL does not lie solely with adding additional cytotoxics to current regimens or increasing the dose intensity of existing regimens. We must fundamentally understand the biology of these diseases better and utilize molecularly targeted and/or antibody-based therapies to improve the therapeutic outcome. Also, identifying biologic predictors of response will be critical to creating effective therapeutic regimens specifically tailored to an individual patient's disease profile.

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Executive summary

- Peripheral T-cell lymphoma (PTCL) represents a heterogeneous group of diseases with variable clinical presentations and variable responses to treatment.
- Treatment outcomes for PTCL are not as good as those for aggressive B-cell lymphomas.
- Therapy intensification, including stem cell transplantation, may improve outcome but the majority of patients still die of their disease.
- Romidepsin and pralatrexate are important advances in therapy but their long-term impact on survival remains unclear.
- Brentuximab vedotin is very active in relapsed/refractory anaplastic T-/null-large cell lymphoma but its role in upfront therapy remains to be defined.
- Mogamulizumab is an important therapeutic advance in adult T-cell leukemia/lymphoma and is now being studied in combination with chemotherapy as part of the initial treatment of adult T-cell leukemia/lymphoma.
- Alisertib, alemtuzumab, lenalidomide and crizotinib are promising agents but their exact utility in PTCL remains to be defined.

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