CLINICAL INVESTIGATION

Peripheral T-cell lymphoma: pharmacotherapy overview

Peripheral T-cell lymphomas are a heterogeneous group of aggressive diseases associated with poor outcome. The current aim in peripheral T-cell lymphoma is to enhance the understanding of the disease, in order to aid the development of more effective treatments. There has been a plethora of targeted treatments available for T-cell lymphomas. In this review article, we will present an overview of some of these novel agents, including the antifolate (pralatrexate), histone deacetylase inhibitors (vorinostat, belinostat and romidepsin), proteasome inhibitors (bortezomib and carfilzomib), mTOR inhibitors (temsirolimus and everolimus), monoclonal antibodies (alemtuzumab, brentuximab vedotin, zanolimumab, anti-CXCR4 and anti-CCR4), immunomodulatory agent (lenalidomide), nucleoside analogs (gemcitabine, clofarabine, forodesine and pentostatin), and fusion toxin (denileukin diftitox).

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Peripheral T-cell lymphomas (PTCLs) are a subtype of non-Hodgkin's lymphomas (NHLs) arising from post-thymic T cells, and account for about 12% of all NHLs [1]. The median age of PTCL diagnosis is 59 years, with 53.4 % of patients diagnosed between the age of 45 and 74 [2]. The age-adjusted incidence rate is 1.8 per 100,000 persons per year, with a male to female ratio of 1.6:1. These rates are based on cases diagnosed in 2004–2008 from 17 Surveillance Epidemiology and End Results geographic areas [2]. PTCL is divided into more than 20 different subtypes according to the 2008 WHO classification **(Box 1)** [3], which can be broadly classified according to the site of origin of the malignant T cell in the body; specifically, nodal, extranodal, leukemic or cutaneous T-cell lymphoid malignancies. Cutaneous T-cell lymphoma (CTCL) is classified as a distinct entity based on its presentation and prognosis [4]. Mycosis fungoides (MF) is the most common form of CTCL and has an indolent course and unique management strategies [5]. The leukemic variant of CTCL is known as Sezary syndrome [6] and has a poor prognosis. The most aggressive PTCLs are $\gamma\delta$ T-cell lymphoma [7], the natural killer (NK) T-cell lymphoma that compromise less than 1% of NHLs [8], hepatosplenic T-cell lymphoma associated with the treatment for inflammatory bowel disease [9], and adult T-cell leukemia/lymphoma (ATLL) associated with human T-lymphotropic virus-I infection [10,11]. The most common PTCL histology is PTCL-nos (not otherwise specified) [12], which has a prevalence of 25.9%. Other common PTCL histologies include the angioimmunoblastic T-cell lymphoma (AITL), which has a prevalence of 18.5% [13], and anaplastic large-cell lymphoma (ALCL), with an incidence of 12.1% in the International T-cell Lymphoma project study [14].

Patients with PTCL have a poor clinical outcome with overall survival (OS) differing based on each subtype. The majority have a 5-year OS between 10 and 30%, with the exception of ALK-positive ALCL, which has an excellent OS

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> **Box 1. WHO classification for peripheral T-cell lymphoma.**
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> - T-cell prolymphocytic leukemia
> - T-cell large granular lymphocytic leukemia
> - Adult T-cell leukemia/lymphoma
> - Aggressive natural killer-cell lymphoma
> - Indolent large granular natural killer-cell lymphoproliferative disorder (provisional)
> - Angioimmunoblastic T-cell lymphoma
> - Anaplastic large-cell lymphoma, ALK positive
> - Anaplastic large-cell lymphoma, ALK negative
> - Hepatosplenic T-cell lymphoma
> - Hydroa vaccineforme-like lymphoma
> - Extranodal natural killer/T-cell lymphoma, nasal type
> - Enteropathy-associated T-cell lymphoma
> - Systemic Epstein-Barr virus ± lymphoproliferative disorder of childhood
> - Subcutaneous panninculitis-like T-cell lymphoma (α/β only)
> - Primary cutaneous γ/δ T-cell lymphoma
> - Mycosis fungoides and Sezary syndrome
> - Primary cutaneous CD30-positive T-cell lymphoproliferative disorder
> - Lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma
> - Small/medium CD4-positive cutaneous lymphomas (provisional)
> - Aggressive CD8-positive epidermotropic cutaneous T-cell lymphoma (provisional)
> - Peripheral T-cell lymphoma, not otherwise specified
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> Data taken from [3].

of 70% with a failure-free survival of 64 % [15]. The International T-cell Lymphoma study showed that the 5-year OS for PTCL-nos, AITL and all NK/T-cell lymphomas as 32%, ATLL as 14%, subcutaneous panninculitis-like T-cell lymphoma as 64%, compared with enteropathy-type as 20%, and hepatosplenic PTCL as 7% [15]. Therefore, in efforts of achieving better patient outcomes in PTCL, new therapeutic options have been explored. Improved understanding of the pathways leading to lymphomagenesis have paved the way for newer targeted therapies in contrast to the classical cytotoxic agents. Some of these agents have proven to be particularly effective in the treatment of PTCL, including the antifolate pralatrexate; histone deacetylase inhibitors: vorinostat, belinostat and romidepsin; proteasome inhibitors: bortezomib and carfilzomib; mTOR inhibitors: temsirolimus and everolimus; monoclonal antibodies: alemtuzumab, brentuximab vedotin, zanolimumab, anti-CXCR4 and anti-CCR; immunomodulatory agent lenalidomide; nucleoside analogs: gemcitabine, clofarabine, forodesine and pentostatin; and fusion toxin denileukin diftitox (Table 1). These treatment options are discussed below in further detail.

Antifolate agent

Pralatrexate (10-propargyl 10-deazaaminopterin) is a novel antifolate shown by earlier clinical trials to be efficacious in the treatment of PTCL [16]. It was the first drug to be approved by the US FDA for the treatment of relapsed/refractory PTCL, on the basis of its single agent activity in this setting [17]. Its molecular structure is similar to methotrexate except at position ten, where a carbon with a propargyl side-chain is substituted for the nitrogen with a methyl substituent. Pralatrexate was designed to have higher affinity to RFC-1, which is the principle receptor by which folates and anti-folates enter cells. RFC-1 plays an important role in the transportation of folate analogs in tumor and fetal cells but not normal cells [18]. Preclinical models utilizing lymphoma cell lines and xenograft models show improved efficacy of pralatrexate compared with methotrexate [19]. An early phase study of pralatrexate demonstrated dramatic activity in patients with relapsed/refractory aggressive T-cell lymphoma [20]. This led to a Phase I–II study, which included patients with both T- and B-cell lymphomas [21]. In this study, 25 patients with relapsed and/or refractory T-cell lymphoma received pralatrexate weekly at a dose of 30 mg/m^2 for 6 of 7 weeks, with folate and vitamin B12 supplementation. Complete response (CR) rates of 28% and partial response (PR) rates of 24% were observed, with more than 50% of responders achieving a durable remission of at least 6 months.

This was followed by the PROPEL study, a multicenter Phase II study in which 115 patients with relapsed/refractory PTCL were enrolled [22]. They had to have failed at least one line of systemic therapy, with no limit to the prior number of therapies, including autologous stem-cell transplant. A total of 111 patients received pralatrexate intravenously at 30 mg/m^2/week

for 6 weeks in 7-week cycles. The primary end point was overall response rate (ORR) and the secondary end points included duration of response, progression-free survival (PFS) and OS. The response rate in the 109 evaluable patients was 29% (32 of 109), including 12 CRs (11%) and 20 PRs (18%), with a median duration of response of 10.1 months. Median PFS and OS were 3.5 and 14.5 months, respectively. The most common grade 3/4 adverse events (AEs) were thrombocytopenia (32%), mucositis (22%), neutropenia (22%) and anemia (18%). Preclinical studies also support the presence of synergistic effects in combination with bortezomib and gemcitabine [23,24], thus establishing the platform for combination studies.

Histone deacetylase inhibitors

The opposing activities of histone acetyltransferases and histone deacetylases regulate gene expression by altering chromatin structure. Histone deacetylases inhibitors (HDACIs) may permit re-expression of proteins that promote apoptosis and cell differentiation, while inhibiting cell cycling and cell division [25]. HDACIs have been shown to have an important role in the treatment of T-cell lymphomas. HDACIs are subclassified as short-chain fatty acids, hydroxamic acids, benzamides and cyclic peptides.

■ Vorinostat

Vorinostat (Zolinza®) is a hydroxamic acid that was approved by the FDA for the treatment of CTCLs, based on two Phase II studies [26]. The first study included 33 CTCL patients with refractory/intolerant disease and compared vorinostat treatment

with conventional chemotherapy [27]. No CRs were reported but eight patients had PR and 45% of the patients had symptomatic pruritus relief. The second study was a larger Phase II study that included 74 patients with CTCL [28]. The ORR was 29.7%, and 32% of patients had pruritus relief. The most common drug-related AEs were diarrhea (49%), fatigue (46%), nausea (43%) and anorexia (26%); most were grade 2 or lower. Grade 3 or higher AEs included fatigue (5%), pulmonary embolism (5%), thrombocytopenia (5%) and nausea (4%).

■ Romidepsin

Romidepsin (Depsipeptide®, FK 228) is a cyclic peptide HDACI originally isolated from the broth culture of *Chromobacterium violaceum*. It was the second HDACI to gain FDA approval for the use in relapsed/refractory CTCL, based on a pivotal study published in 2010 [29]. This study enrolled 96 patients, the majority of which (71%) had advanced-stage disease (≥IIB) according to the updated staging criteria detailed in an article by Olsen *et al* [30]. The response rate was 34% including six patients with CR. A clinically meaningful improvement in pruritus was observed in 28 (43%) patients, including patients who did not achieve an objective response. Median duration of improvement in pruritus based on 100-mm visual analog scale (VAS) was 6 months. Drug-related AEs were generally mild and consisted mainly of GI disturbances and asthenic conditions. Nonspecific, reversible ECG changes were noted in some patients; two patients had prolonged corrected QT, leading to their discontinuation of the study drug. A recent Phase II study demonstrated

Table 1. Therapeutic agents in peripheral T-cell lymphomas.			
Class	**Agent**	**Diseases**	**US FDA**
Antifolate	Pralatrexate	PTCL	Approved for PTCL
Histone deacetylase inhibitors	Vorinostat, belinostat and romidepsin	PTCL, CTCL, ALCL, AITL, ETL	Romidepsin is approved for CTCL and PTCL
Proteasome inhibitors	Bortezomib and carfilzomib	PTCL, CTCL	Not approved
mTOR inhibitors	Temsirolimus and everolimus	T-ALL, ALCL, ATLL, NK/T-cell, CTCL, T-LGL	Not approved
Monoclonal antibodies	Alemtuzumab, brentuximab vedotin, zanolimumab, anti-CXCR4 and anti-CCR4	PTCL, CTCL, ALCL, AITL, ATLL	Brentuximab vedotin is approved for ALCL
Immunomodulatory agents	Lenalidomide	PTCL, CTCL, AITL, ALCL	Not approved
Nucleoside analogs	Gemcitabine, clofarabine, forodesine and pentostatin	PTCL, CTCL	Not approved
Fusion toxins	Denileukin diftitox	PTCL, CTCL	Approved for CTCL
AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large-cell lymphoma; ATLL: Adult T-cell leukemia/lymphoma; CTCL: Cutaneous T-cell lymphoma; ETL: Enteropathy-type lymphoma; NK: Natural killer; PTCL: Peripheral T-cell lymphoma; T-ALL: T-cell acute lymphocytic leukemia; T-LGL: T-cell large granular lymphocytic leukemia.			

disease response in PTCL patients receiving romidepsin [31]. In this study, 45 patients with PTCL of various subtypes, including PTCL-nos, AITL, ALK-negative ALCL and enteropathy-associated T-cell lymphoma, were enrolled. All patients in this study had received a median of three prior treatment regimens and 18 (38%) patients had undergone a stem-cell transplant. CR was seen in eight (18%) patients, and PR was seen in nine (20%) patients. Overall response was 38%, medium OR was 8.9 months. Six responses were seen in the 18 patients with prior stem-cell transplant. Common toxicities were nausea, fatigue, transient thrombocytopenia and granulocytopenia.

■ Belinostat
Belinostat (PXD 101) is an HDACI that belongs to the hydroxamic acid class and has potent antiproliferation and pan-HDACI activity *in vitro* and *in vivo* [32]. Belinostat has growth-inhibitory and proapoptotic activity in a variety of human tumor-cell lines, including myeloma, lymphoma and leukemia lines [33]. It has also been studied in solid tumors [34]. Ongoing clinical trials are being conducted to evaluate the efficacy of both oral and intravenous formulation of belinostat in PTCL [35]. Table 2 lists the current status of the ongoing trials of HDACIs in NHL.

Synergistic activity based on mechanistic rationale using combinations of HDACI with a number of other biologic agents is under investigation. Based on preclinical data, combinations of proteosome inhibitors such as bortezomib [36], topoisomerase inhibitors [37], and hypomethylation agents [38], with HDACIs seem promising. Clinical trials are underway to explore the activity of these combinations in T-cell lymphomas.

Protesome inhibitors
■ Bortezomib
Bortezomib, an inhibitor of the large protein complex 26S proteasome, was the first proteasome inhibitor to be tested in humans. It is approved for the treatment of relapsed multiple myeloma [39] and mantle-cell lymphoma [40]. Bortezomib is a modified dipeptidyl boronic acid with different antitumor effects, including disruption of the cell cycle, induction of

apoptosis and inhibition of NFκB [41]. It has been shown to induce apoptosis in cell lines from mature T-cell lymphoma partially by upregulation of the proapoptotic protein NOXA, which inactivates the antiapoptotic protein McL-1, thus promoting mitochondrial membrane injury and activating the intrinsic apoptotic pathway [42]. In a Phase II study, 15 patients with relapsed CTCL or PTCL received bortezomib on day 1, 4, 8 and 11 of a 21-day cycle. They had an ORR of 67%, CR of 17% and no grade-4 toxicity [43]. Bortezomib has been studied in combination with other chemotherapy regimens in T-cell lymphomas. A Phase I study of bortezomib in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was conducted in 13 newly diagnosed PTCL or NK/T-cell patients and showed a response rate of 61%, with main toxicities being neuropathy, fatigue and diarrhea [44]. Another combination Phase II study was conducted with doxorubicin, bleomycin, cyclophosphamide, vindesine and prednisone (ABCVP), which included 57 untreated PTCL patients [45]. A total of 29 patients were withdrawn prematurely from the study due to toxicity. There were no observed differences in the ORRs between the ABCVP arm and ABCVP with bortezomib combination arm. More combination regimens with bortezomib are being started and there is preliminary evidence of synergetic activity of bortezomib with pralatrexate [46].

■ Carfilzomib
Carfilzomib is a novel epoxyketone-based irreversible proteasome inhibitor, formerly known as PR-171, which initially showed preclinical activity against multiple myeloma [47]. Carfilzomib exhibits equal potency to bortezomib, but it selectively inhibits the chymotrypsin-like activity of the 20S proteasome and has minimal crossreactivity with other protease classes [48]. In a Phase I study to assess safety and tolerability, carfilzomib demonstrated clinical activity in multiple hematological malignancies [49] and was shown to have antilymphoma activity. Combinations of carfilzomib with vorinostat [50], has shown increased activity of carfilzomib in cells sensitive

Table 2. Histone deacetylases inhibitors in open clinical trials.			
Histone deacetylases inhibitors	Clinical trial design	Study status	Ref.
Belinostat/hydroxamic acid	Relapsed/refractory PTCL	Recruiting	[35]
Vorinostat/hydroxamic acid	Combination with lenalidomide and dexamethasone for PTCL	Recruiting	[205]
Panobinostat/hydroxamic acid	Combination with bortezomib for PTCL and NK/T-cell	Recruiting	[114]
Mocetinostat (MGCD0103)/benzamides	Relapsed/refractory lymphoma	Recruiting	[206]
NK: Natural killer; PTCL: Peripheral T-cell lymphoma.			

or resistant to bortezomib, through JNK-dependent mechanism in association with DNA damage and inhibition of NFκB. Given these results of less neurotoxicity with carfilzomib as compared with bortezomib, multiple clinical trials are currently ongoing to evaluate carfilzomib activity in T-cell lymphomas either alone or in combination with other agents.

mTOR inhibitors

The PI3K pathway is composed of a large family of lipid kinases, which play a critical role in many cellular processes, including: cell survival, cell proliferation, differentiation and angiogenesis [51]. The PI3K pathway downstream affects the tyrosine kinases receptors and the G-protein-coupled receptors and is deregulated in a number of malignancies [52]. Among the downstream targets of PI3K pathway is AKT, a serine/threonine protein kinase that regulates a variety of transcription factors, including NFκB, known to regulate cell-cycle progression, cytokine production and programmed cell death [53]. A major negative regulator of the AKT pathway is the lipid phosphatase PTEN. mTOR is an important component of the PI3K pathway downstream of AKT and has been shown to regulate many cellular functions, which includes NFκB and protein translation. Its activation results in cap-dependent protein translation, especially the translation of cyclin-D1 and C-MYC. The mTOR pathway integrates many inputs, including signals from the PI3K/AKT pathway, growth factor signaling, the energy state of the cell (cAMP levels), nutrient and O_2 availability [54]. The PI3K/AKT signaling pathway plays an important role in normal T-cell development, differentiation, transition and survival [55]. Hyperactivation of AKT pathway has been observed in several T-cell malignancies including T-cell acute lymphocytic leukemia (T-ALL) [56], ALCL [57], ATLL [58], NK/T-cell lymphoma [59], CTCL [60] and T-cell large granular lymphocytic leukemia [61]. Thus, there is great interest in the inhibition of PI3K/AKT/mTOR axis for treatment of T-cell malignancies.

■ Temsirolimus

Temsirolimus is an inhibitor of mTOR and has been shown to be a potent inhibitor of cell proliferation through G1 cell-cycle arrest. It has shown clinical activity in NHL, especially in mantle-cell lymphoma (MCL). In a Phase III study, 162 patients with refractory MCL were randomly assigned (1:1:1) to receive one of two temsirolimus regimens: 175 mg weekly for 3 weeks followed by either 75 mg (175/75 mg) or 25 mg (175/25 mg) weekly, or investigator's choice therapy from prospectively approved options. The primary end point was PFS, which was statistically significant for the temsirolimus group with median PFS 4.8, 3.4 and 1.9 months for the temsirolimus 175/75 mg, 175/25 mg, and investigator's choice groups, respectively [62]. Accordingly, ongoing studies for its usage in PTCL patients are currently underway. A phase I study of temsirolimus and lenalidomide in patients with relapsed NHL is currently being conducted at the National Institute of Health [201].

■ Everolimus

Everolimus (RAD001), 40-O-(2-hydroxyethyl) rapamycin, is another mTOR inhibitor recently approved by the FDA for the treatment of advanced renal cell carcinoma. Everolimus has been studied in a Phase I clinical trial as a single agent in patients with relapsed/refractory aggressive NHL [63]. This Phase I study of 13 patients included the following histologies: PTCL-nos, CTCL and ALCL (n = 4), diffuse large B-cell lymphoma (n = 2), MCL (n = 2), and follicular lymphoma (n = 2). Responses were observed among patients with diffuse large B-cell lymphoma (CR: 1; PR: 1) and follicular lymphoma (CR: 1; PR: 1). One patient with MCL and another with ALCL had stable disease (SD). Grade 3 and 4 toxicities were thrombocytopenia (n = 2), lymphopenia (n = 7), anorexia (n = 1) and abnormal hepatic function (n = 1). All these toxicities were transient and reversible. Currently, an ongoing Phase I/II study combing everolimus with CHOP is being conducted and actively recruiting PTCL patients [64].

Monoclonal antibodies

■ Alemtuzumab

Alemtuzumab is a humanized anti-CD52 monoclonal antibody that is approved by the FDA for the treatment of B-cell chronic lymphocytic leukemia [65]. CD52 is expressed on most normal and neoplastic lymphocytes, monocytes and macrophages [66]. The CD52 antigen is expressed at a particularly high density (>500,000 receptors per cell) on most malignant T lymphocytes, making alemtuzumab a good candidate for novel therapy in T-cell malignancies [67]. *In vitro* studies with alemtuzumab have shown activity in both complement-mediated cell lyses and antibody-dependent cell-mediated cytotoxicity assays [68,69]. Early clinical data evaluated the treatment of 39 patients with T-cell prolymphocytic leukemia with alemtuzumab [70]. The CR rate was 60% and the PR rate was 16%. Patients experienced a median survival of 10 months, but for patients who achieved a CR the median survival reached 16 months.

A pilot study of alemtuzumab in 14 patients with heavily pretreated advanced-stage PTCL showed an

ORR of 36%, with three patients achieving a CR and two patients a PR [71]. CRs lasted 2, 6 and 12 months. Cytomegalovirus (CMV) reactivation was seen in six patients. In an attempt to improve treatment options in PTCL, combinations of alemtuzumab with cytotoxic chemotherapy have been investigated. In a Phase II trial, 27 patients with newly diagnosed PTCL and 11 patients with refractory/relapsed PTCL received a combination of alemtuzumab, fludarabine, cyclophosphamide and doxorubicin (Campath-FCD) [72]. The ORR was 61% with a CR rate of 39%. In newly diagnosed patients, the ORR was 63%, the median OS was 25.9 months and PFS was 11.8 months. In relapsed/refractory patients the median OS was 6.1 months. CMV reactivation occurred in 12 patients, but only two had CMV disease. Treatment-related deaths occurred in six newly diagnosed patients and one with relapsed/refractory disease. This study showed that Campath-FCD is active in PTCL but is associated with significant toxicity. Another study enrolled 13 patients, newly diagnosed with PTCL (extranodal nasal NK/T-cell lymphoma [n = 5], subcutaneous panniculitis-like T cell lymphoma [n = 4], PTCL-nos [n = 3], enteropathy type T-cell lymphoma [n = 1]) [73]. Patients were treated with alemtuzumab and CHOP, which was given on cycles 1, 3 and 5, alternating with etoposide, methylprednisolone, cisplatin and cytarabine (ESHAP), on cycles 2, 4 and 6 at 28-day intervals. Of the ten evaluable patients, eight patients achieved CR, one patient had PR and one patient had CNS progression while on treatment. Infection was a major AE; 54% had CMV reactivation, 54% had febrile neutropenia and 15% had TB. In an attempt to reduce the infectious complications of this agent, trials have been conducted using a subcutaneous route of administration. A recent study was conducted with subcutaneous alemtuzumab plus CHOP (CHOP-C) [74] in 25 patients with newly diagnosed PTCL. Out of a total of 24 evaluable patients, 17 (71%) patients had a CR, one patient had a PR and the median duration of response was 11 months. At a 16-month follow-up, nine patients had died from progressive disease, and one patient had died from pneumonia after a CR lasting 6 months. Toxicity was evaluated for all 25 patients who were treated with CHOP-C for a total of 176 courses. Of the 176 courses, AEs included: neutropenia in 59 (34%), thrombocytopenia in 4 (2%) and CMV reactivation detected in 15 (9%). This trial suggests that subcutaneous administration of alemtuzumab in combination with chemotherapy is an effective regiment with manageable toxicity. A randomized trial is underway in Denmark to evaluate subcutaneous alemtuzumab plus CHOP followed by high-dose therapy with autologous stem cell transplant in younger patients with T-cell lymphomas [202].

■ Brentuximab vedotin

Brentuximab vedotin (SGN-35) is an anticancer antibody–drug conjugate [75] directed against CD30, which has shown promising results in CD30-expressing PTCL. The antibody–drug conjugate comprises the anti-CD30 monoclonal antibody cAC10 conjugated to the cytotoxic agent monomethyl auristatin E, a synthetic analog of the tubulin polymerization inhibitor. Brentuximab vedotin is designed to release monomethyl auristatin E upon internalization into CD30-expressing tumor cells, resulting in a targeted cell-killing effect. The CD30 antigen is highly expressed by a variety of hematologic malignancies, including Hodgkin's lymphoma and some T-cell NHLs, specifically ALCL. Phase I data from two studies involving mainly relapsed/refractory Hodgkin's lymphoma patients also demonstrated activity of brentuximab vedotin against a smaller population of T-cell lymphomas, including ALCL, AITL and PTCL patients, with ORRs of 46% in both studies [76,77]. A Phase II, single-armed, multicentered study that enrolled 58 refractory/relapsed ALCL patients treated with brentuximab vedotin also studied the effectiveness of this medication [78]. Interim analysis of the first 30 patients treated showed the majority of patients enrolled to be ALK-1 negative (70 %; n = 21). The medium number of prior regimens were two and showed CR in 57% (n = 17), PR in 30% (n = 9) and SD in 10% (n = 3).

■ Zanolimumab

Zanolimumab (HuMax-CD4) is a fully human monoclonal antibody that targets the CD4 antigen present on helper lymphocytes and malignant T-lymphocytes [79], and has also been studied as a treatment for T-cell lymphoma. Zanolimumab prevents interaction between the CD4 receptor and the major histocompatibility complex class II molecules, thus inhibiting T-cell receptor signal transduction that induces antibody-dependent cell-mediated cytotoxicity of T-lymphocytes and downregulates CD4 expression [79]. Clinical data was encouraging in CTCL, especially MF, with an ORR of 34% and a median duration of response of approximately 20 months [80]. A further Phase II trial of zanolimumab in 21 patients with relapsed/refractory PTCL showed good tolerability, with a ORR of 23.8%, including three PRs and two CRs [81].

■ Anti-CXCR4

CXCR4 is a chemokine receptor that is encoded by

the *CXCR4* gene in humans [82]. Chemokines are essential for tissue localization and migration of various lymphocytes subpopulations expressing specific chemokine receptors. SDF-1, also known as CXCL12, induces intracellular actin polymerization in lymphocytes, a process that is thought to be a prerequisite for cell motility [83], via binding to its major receptor CXCR4; thus plays a major role in stem-cell mobility and development [84]. The CXCR4/SDF-1 axis was shown also to be involved in lymph-node metastasis in solid tumors [85]. A Japanese study showed that inhibition of the CXCR4/SDF-1 axis by the CXCR4 antagonist AMD3100 suppresses the migration of culture cells from ATLL patients and murine lymphoblastoid cells from human T-lymphotropic virus-I infection Tax transgenic mice [86]. Currently, multiple ant-CXCR4 trials are recruiting patients to assess their safety, including MDX-1338 [203] and ALX-0651 [204].

■ Anti-CCR4
KW-0761 is a defucosylated humanized monoclonal anti-CCR4 antibody with a strong antibody-dependent cellular cytotoxicity. A Phase I study was conducted to assess its safety and pharmacokinetics in patients with relapsed CCR4-positive ATLL and PTCL [87]. A total of 15 out of 16 patients completed the designed study where they received KW-0761 weekly (four-times). Two patients had CR and three patients had PR. KW-0761 was well tolerated, and only one patient developed grade 3 skin rash and one patient grade 4 neutropenia at the 1 mg/kg dose. This led to a Phase II study using KW-0761 at 1 mg/kg with 27 ATLL patients (14 acute, six lymphoid and seven chronic phase) [88]. A total of 14 patients completed the protocol treatment of eight infusions. Among the 26 patients evaluable for efficacy, the ORR was 52% (14 patients), distributed as the following: six of 14 patients in acute, three of six patients in lymphoid and five of six patients in chronic phase. Seven patients had CR and seven patients had PR. Treatment-related severe AEs were observed in five patients, including a Stevens Johnson syndrome (grade 3) and four skin rashes (grade 3). All these AEs improved with steroid treatment.

Immunomodulatory agents
■ Lenalidomide
Lenalidomide is a second-generation thalidomide analog approved for the treatment of multiple myeloma, and a member of the immunomodulatory agents. Immunomodulatory agents have anti-proliferative effects and are responsible for the modulation of crucial cytokines such as TNF-α, IL-12 and IFNδ [89]. Immunomodulatory agents also have co-stimulatory

effects on T and NK cells, which have been heralded as a unique and important property towards enhancing anti-myeloma immune activity. The first study showing activity of lenalidomide in T-cell malignancy was conducted in CTCL patients [90]. Ten CTCL patients were enrolled in this Phase II study in 2005 and three out of eight evaluable patients had OR. This was followed by a Phase II study of lenalidomide in patients with refractory and recurrent T-cell lymphomas [91]. A total of 24 patients were enrolled in this study and 23 patients were available for evaluation. The ORR was 30% with two patients having SD for ≥five cycles. Responses were seen in ALCL, AITL and PTCL-nos patients. The most common grade 4 AE was thrombocytopenia (33%) and grade 3 AEs were neutropenia (21%), febrile neutropenia (17%) and pain-nos (17%).

Nucleoside analogs
■ Gemcitabine
Nucleoside analogs are chemotherapeutic agents that primarily inhibit DNA repair and replication. Gemcitabine is the most studied pyrimidine nucleoside analog in the treatment of PTCL as a single agent and in combination with other chemotherapeutic agents. A study including 39 pretreated PTCL or MF patients who received gemcitabine as a single agent showed an ORR of 51%, CR of 23% and PR of 28% [92]. The 20 patients with PTCL in this study had a CR of 30% and PR of 25%. Gemcitabine combination studies are underway with bortezomib [93] and alemtuzumab [94] in T-cell lymphomas.

■ Clofarabine
Clofarabine is a second generation of purine nucleoside analogues designed to combine the most favorable pharmacokinetic properties of fludarabine and cladribine. Clofarabine acts by inhibiting DNA polymerases and ribonucleotide reductase as well as by inducing apoptosis in cycling and noncycling cells [95]. An ongoing study shows promising efficacy of clofarabine in the treatment of PTCL patients [96].

■ Forodesine
Forodesine is a potent inhibitor of purine nucleoside phosphorylase, which leads to elevation of plasma deoxyguanosine and intracellular accumulation of deoxyguanosine triphosphate levels, and then apoptosis mainly in T cells [97]. Forodesine was shown to have high antitumor effect by activation of p53-independent mitochondrial apoptosis through induction of p73 and proapoptotic BIM protein in chronic lymphocytic leukemia [98]. It has been shown to have activity against NHL and different T-ALL. In an interim analysis of a Phase II study [99], 34 patients with T-ALL

were enrolled and received intravenous forodesine at a dose of 40 mg/m² daily for 5 days/week, with 18 patients undergoing dose escalation to 90 mg/m² after cycle one for lack of response. The study showed an OR rate of 32.4%, with seven patients achieving CR. A subsequent Phase I/II study of 36 CTCL patients was reported a year later [100]. The 36 patients received forodesine as 80 mg/m² orally daily for 4 weeks. The study showed an ORR of 39%. Based on these data a Phase I study was conducted in Japan, which included 13 patients with recurrent/refractory T/NK malignancies to evaluate the safety profile of forodesine and check for the dose-limiting toxicities [101]. Patients received forodesine as 100, 200 or 300 mg/m². There were no dose-limiting toxicities, and toxicities of grade 3 or greater were lymphopenia (62%), anemia (15%), leukopenia (8%), thrombocytopenia (8%) and viral infection (8%). One patient with ALCL achieved CR, two patients with MF reached PR, and four patients had SD (PTCL-nos [n = 2], ALCL [n = 2]).

■ Pentostatin

Pentostatin (2′-deoxycoformycin) is a purine analog that functions as a potent inhibitor of adenosine deaminase, thus increasing the deoxyguanosine triphosphate. Adenosine deaminase levels are higher in normal circulating T cells than in B cells [102]. Inhibition of adenosine deaminase is associated with selective lymphotoxicity that correlates with the accumulation of deoxyguanosine triphosphate [103]. Pentostatin was studied in 28 patients with CTCL and PTCL [104]. A total of 24 patients were available for evaluation, three of which had PTCL. The CR was 25% and the PR was 46%, with all the patients with PTCL achieving a response (CR: 1; PR: 2).

Fusion toxins

Denileukin diftitox (Ontak®) is a fusion protein that was approved by the FDA in 1999 for treatment of relapsed CTCL patients [105]. This fusion protein is composed of nucleotide sequences for the enzymatically active ADP ribosyltransferase domain and membrane translocation domains of diphtheria toxin coupled with human IL-2R [106]. The IL-2Rα consists of CD25 and p55 [107], with CD25 playing an important role in T-cell proliferation, activation of both regulatory and effector T cells and cell death [108]. Although denileukin diftitox binds to all three forms of the IL-2R (α, β and γ), only cells with the intermediate (IL-2Rβ or γ) or high affinity receptors (α, β and γ combined) will internalize the fusion protein [109].

The first large study of its clinical use was a Phase III trial where 71 patients with CTCL were enrolled [110]. After treatment, 20% of the patients had PR and 10%

had CR. AEs consisted of flu-like symptoms (fever/chills, nausea/vomiting and myalgias/arthralgias), acute infusion-related events (hypotension, dyspnea, chest pain and back pain), and vascular leak syndrome (hypotension, hypoalbuminemia and edema). In addition, 61% of the patients experienced transient elevations of hepatic transaminase levels, with 17% being grade 3 or 4. Hypoalbuminemia occurred in 79%, including 15% with grade 3 or 4 changes. The first report of its use in PTCL came from a case report of a patient with refractory/relapsed PTCL who had failed 13 standard single- and multiple-chemotherapy regimens, but showed near CR after receiving six cycles of this agent with only 1% body surface area skin involvement [111].

This led to a Phase II study of PTCL patients to be conducted at a single institution at MD Anderson Cancer Center and it included 27 patients. Denileukin diftitox was given at a dose of 18 μg/kg/day for 5 days on a 21-day cycle. A CR was achieved in six patients and PR in seven patients [112]. ORR was 48% with 30% of the patients achieving SD. Median PFS was 6 months and a higher response rate was noted in CD25-positive tumors. Based on these results, a combination of denileukin diftitox and CHOP was studied in untreated PTCL patients. A total of 49 patients were enrolled and they received denileukin diftitox 18 μg/kg/day on day 1 and 2, followed by CHOP on day 3 and growth factor (GCSF) support on day 4 of the 21-day cycle [113]. The ORR in the 49 patients was 65%, with 51% of the patients achieving CR. In the efficacy-evaluable patients (≥two cycles) the ORR was 86% (CR 73%). Response rate in subgroups were: PTCL-nos: 47%, AITL: 80% and ALCL: 87%. Medium PFS for the 49 patients was 12 months and 2-year estimated OS was 60%. Median response duration for 32 responders was 29 months. The most frequent grade 3/4 AEs (>5%) were leukopenia (20%), thrombocytopenia (12%) and neutropenia (12%). Denileukin diftitox-associated toxicities included infusion-related rigor in seven patients, hypoalbuminemia in 17 patients, and acute hypersensitivity in one patient. Denileukin diftitox remains a therapeutic option for patients with PTCL, especially if their primary tumor expresses CD25.

Conclusion & future perspective

Multiple new-targeted agents (Table 3) have been used in the treatment for PTCL with improved outcomes. However, it is very unlikely that cure will be achieved in the future by using a sole agent, but rather by the combination of some of the treatments discussed in this review. Current studies are being conducted in both the clinical and animal models to study this

Agent	Patients enrolled	Response	Major AEs	Ref.
Pralatrexate	115 patients with relapsed/refractory PTCL	CR: 12 (11%); PR: 20 (18%)	Thrombocytopenia (32%), mucositis (22%), neutropenia (22%), anemia (18%)	[22]
Vorinostat	74 patients with CTCL	ORR: 22 (29.7%); pruritis relief = 24 (32%)	Diarrhea (49%), fatigue (46%), nausea (43%), anorexia (26%)	[28]
Romidepsin	45 patients with PTCL	CR: 8 (18%); PR = 9 (20%)	Fatigue (40%), leukopenia (47%), thrombocytopenia (47%), anemia (40%)	[31]
Bortezomib	15 patients with relapsed CTCL or PTCL	CR: 2 (17%); PR: 6 (50%)	Neutropenia grade 3 (17%), thrombocytopenia grade 3 (17%), sensory neuropathy (50%)	[43]
Alemtuzumab	14 patients with refractory PTCL	CR: 3 (21.4%); PR: 2 (14.3%)	CMV reactivation (43%), pulmonary aspergillosis (14%), pancytopenia (28.6 %)	[71]
Anti-CCR4	16 patients with PTCL or ATLL	CR: 2 (12.5%); PR: 2 (12.5%)	Skin rash grade 3 (one patient), neutropenia grade 4 (one patient)	[88,89]
	27 patients with ATLL	CR: 7 (26%); PR: 7 (26%)	Skin rash grade 3 (52%), leukopenia (56%), neutropenia (33%), thrombocytopenia (26%), hypoxemia (19%), AST/ALT increase (48%)	
Lenalidomide	24 patients with recurrent/refractory T-cell lymphomas	CR: 0; PR: 7 (30%)	Thrombocytopenia grade 4 (33%), neutropenia grade 3 (21%), febrile neutropenia grade 3 (17%), pain-nos grade 3 (17%)	[91]
Gemcitabine	39 patients with MF or PTCL	CR: 9 (23%); PR: 11 (28%)	Neutropenia grade 1–2 (38.5), thrombocytopenia grade 1–2 (46%), transient increase in liver enzymes grade 1–2 (36%)	[92]
Forodesine	13 patients with recurrent/refractory T-cell/NK lymphomas	CR: 1 (7.7%); PR: 2 (15.4 %); SD: 4 (30.8%)	Lymphopenia grade 3–4 (62%), anemia grade 3–4 (15 %), leukopenia grade 3–4 (8%), thrombocytopenia grade 3–4 (8%), viral infection grade 3–4 (8%)	[101]
Pentostatin	28 patients with CTCL or PTCL	CR: 6 (25%); PR: 11 (46%)	Granulocytopenia (30%), thrombocytopenia (7%), Herpes zoster (19%), renal insufficiency (15%)	[104]
Denileukin diftitox	71 patients with CTCL	CR: 7 (10%); PR: 14 (20%)	Transient increase in liver enzymes (61%), acute infusion hypersensitivity reaction (60%), hypoalbuminemia (79%)	[110]

Table 3. Active single agents against T-cell lymphomas.

AE: Adverse effect; ATLL: Adult T-cell leukemia/lymphoma; CMV: Cytomegalovirus; CR: Complete response; CTCL: Cutaneous T-cell lymphoma MF: Mycosis fungoides; NK: Natural killer; ORR: Overall response rate; PR: Partial response; PTCL: Peripheral T-cell lymphoma; SD: Stable disease.

Executive summary

Background

■ Peripheral T-cell lymphomas (PTCLs) are rare lymphomas that comprise approximately 12% of all non-Hodgkin's lymphomas. According to the most recent WHO classification, there are over 22 different types of PTCLs. Most are aggressive diseases with the exception of some cutaneous lymphomas. Overall prognosis remains poor and there is a great need for new and improved targeted therapies based on the pathways of lymphomagenesis of these diseases.

Antifolate agents

■ Pralatrexate is a novel antifolate with increased affinity for the RFC-1. It achieves higher concentrations in the cells compared with methotrexate and has shown activity in a variety of lymphoma cell lines. In the clinical setting, it is the first agent to be approved for the treatment of relapsed/refractory PTCL, based on a trial that showed a response rate of 29% in a multicenter Phase II setting. The agent is well tolerated with its major side effects are mucositis and thrombocytopenia.

Histone deacetyalse inhibitors

■ These epigenetic agents affect the acetylation status of histone. The exact mechanism of action is unknown but they are thought to modify the expression of various proteins that regulate cell function, resulting in increased apoptosis, differentiation, as well as affecting other biologic functions, such as angiogenesis and immune response, with resultant anticancer activity that is most prominent in PTCL. There are many different types of histone deacetyalse inhibitors based on chemical structure and potency. Many agents are in clinical trials but two are approved for therapy in the USA. These include the orally administered vorinsotat (approved for relapsed cutaneous T-cell lymphoma [CTCL]) and the intravenously administered romidepsin (approved for relapsed CTCL and PTCL). The side-effect profile of all these agents is similar, with the main effects being nausea, diarrhea, asthenia, thrombocytopenia and mild effects on the corrected QT interval seen on electrocardiograms.

Proteosome inhibitors

■ These agents are designed to inhibit the protein degradation function of proteosome, thus affecting several growth pathways in the cell. Boretezomib is the first agent in this class to be approved for human use and is approved for the treatment of multiple myeloma and mantle-cell lymphoma. However, a Phase II trial has demonstrated activity in PTCL and CTCL. Combinations of this agent with other targeted therapies and chemotherapy are underway. Cafilzomab is another proteosome inhibitor currently in clinical trials for PTCL in combination with HDACIs and other targeted therapies.

m-TOR inhibitors

■ Several agents of this class are active in the treatment of lymphomas. They block the P13K/AKT pathway, which is an important pathway in cell growth and differentiation. Temsirolimus has shown activity as a single agent in PTCL. Everolimus is another mTOR inhibitor that is being investigated for the treatment of PTCL. The greater promise of these agents lies in the use of these agents in combination therapies.

Monoclonal antibodies

■ Monoclonal antibodies designed to target various T-cell markers are a promising strategy to treat PTCL. Alemtuzumab is designed to target CD52 expressed on most T cells, both in the normal and neoplastic state. Several clinical trials have been designed to look at the activity of alemtuzumab either alone or in combination with chemotherapy in PTCL. While activity has been demonstrated, there is significant immunosuppression and cytomegalovirus reactivation, as well as other opportunistic infections, which remains the main cause for concern while using this agent. Bretuximab vedotin, an antibody conjugate designed to target CD30 has recently been approved for the treatment of relapsed anaplastic T-cell lymphoma that expresses CD30. Other promising antibodies include zanolimumab and anti-CXCR4.

Immunomodualtory agents

■ These include lenalidomide and other members of the immunomodualtory agents currently in clinical trials. Moderate activity has been noted for lenalidomide as a single agent in PTCL.

Nucleoside analogues

■ Many of these have significant anti-T-cell activity and hence are active in PTCL. Most notable ones are gemcitabine, clorarabine and forodesine. Most agents are being evaluated as combination therapies.

Fusion toxins

■ The best studied agent of this class is denileukin diftitox. It is an antibody directed against CD25 conjugated to diphtheria toxin. It is approved for the treatment of CTCL, but is active as a single agent as well as in combination with chemotherapy agents in other forms of PTCL as well.

Conclusion & future perspective

■ Treatment options for PTCL are improving and given the large number of agents that are showing promising activity in PTCL, treatment paradigms will likely shift towards combined targeted therapies.

combination. PTCL is a result of the interplay of multiple different diseases, all of which need to be targeted in order to achieve effective disease response.

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