How I manage peripheral T-cell lymphoma, not otherwise specified and angioimmunoblastic T-cell lymphoma: current practice and a glimpse into the future

Norbert Schmitz and Laurence de Leval

Department of Haematology, Oncology and Stem Cell Transplantation, Asklepios Hospital St. Georg, Hamburg, Germany and Institute of Pathology, University Hospital Lausanne and University of Lausanne, Switzerland

Summary
Peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS) and angioimmunoblastic T-cell lymphoma (AITL) are the most frequent of more than 20 mature PTCL entities featuring a broad spectrum of morphological, immunophenotypic, molecular and clinical characteristics. Unfortunately, recent progress in understanding the (epi)genetic background of PTCL has not been met with similar advances in treatment. Thus, CHO(E)P [cyclophosphamide, doxorubicin, vincristine, and prednisone (plus etoposide)] remains standard first-line therapy. Patients without comorbidities achieving complete or partial remission proceed to autologous stem cell transplantation. With this approach about 50% of patients survive long-term. Patients relapsing after or progressing during first-line therapy have a dismal prognosis. They receive salvage gemcitabine-therapy followed by allogeneic transplantation whenever possible. After allografting, approximately half of the patients survive long-term; any other treatment is palliative. New drugs investigated in phase II studies achieved response rates between 10% and 30%; long-term remissions are the exception to the rule. While most new drugs are not licensed and not readily available, a plethora of other innovative drugs targeting (epi-)genetic abnormalities are in early development. These, together with combinations of new and old drugs, will hopefully increase response to first-line therapy, bridge more patients to transplantation, and finally improve prognosis for all patients with PTCL.

Keywords: Peripheral T-cell lymphoma, angioimmunoblastic T-cell lymphoma, pathology, personalized, treatment, stem cell transplantation.

Correspondence: Laurence de Leval, MD, PhD, Institute of Pathology, University Hospital Lausanne-CHUV, Rue de Bugnon 25, Lausanne CH-1011, Switzerland.
E-mail: Laurence.deLeval@chuv.ch

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and angioimmunoblastic T-cell lymphoma (AITL) are the most frequent of more than 20 entities of mature T- and Natural Killer (NK)-cell neoplasms listed in the 2016 revision of the world Health Organization (WHO) classification of lymphoid neoplasms (Swerdlow et al, 2016). In the Western world, T-cell lymphomas are rare, comprising approximately 10% of all lymphomas (Vose et al, 2008), while in Asia, where NK/T-cell lymphomas (and adult T-cell leukaemia/lymphoma) are more frequent, up to 20% of lymphoma patients suffer from PTCL (Kwong et al, 2009; Adams et al, 2016). PTCL-NOS and AITL make up 30–40% and 15–35%, respectively, of mature T-cell malignancies (Ellin et al, 2014; de Leval et al, 2015; Petrich et al, 2015; Swerdlow et al, 2016).

This review will focus on PTCL-NOS and AITL because of their higher frequency and because therapeutic approaches remain very similar for both entities whereas other PTCLs, particularly the anaplastic large cell lymphomas (ALCL), benefit from new treatment options including brentuximab vedotin (BV) (Fanale et al, 2014) and crizotinib, an inhibitor of the anaplastic lymphoma tyrosine kinase (ALK) (Gambacorti Passerini et al, 2014), for patients with ALK-positive ALCL.

Conventional chemotherapy, high-dose therapy and autologous stem cell transplantation (ASCT), as well as allogeneic stem cell transplantation (alloSCT), remain the cornerstones of therapy in PTCL. Because attempts to improve upon these therapies have largely failed, the unmet medical need persists. New molecules entered clinical investigation before fully understanding the functional consequences of the ever-increasing number of genetic and epigenetic changes; not surprisingly not all of them met the high expectations solicited by in vitro data. Although not many of the new drugs are licensed for the current treatment of PTCL we discuss those where phase II data are available and integration into future treatment algorithms appears possible.

Pathobiology and genetics (Table I)
Angioimmunoblastic T-cell lymphoma is defined by its cellular derivation as a neoplasm of follicular helper CD4+ T cells...
TFH cells (de Leval et al., 2007; Piccaluga et al., 2007; Swerdlow et al., 2016). TFH cells play a major role in supporting and regulating T-cell-dependent B-cell responses in the germinal centres, and their characteristics are retained in AITL neoplastic cells and probably explain the main pathological and biological traits of the disease. AITL features an important reactive cellular background and microenvironment accounted for by the secretion of various soluble factors by TFH cells promoting the recruitment, activation and differentiation of other cell types (de Leval et al., 2010; Gaulard & de Leval, 2014). For example, CXCL13 produced by TFH cells promotes B-cell expansion and plasmacytic differentiation, causing the hypergammaglobulinaemia and Coombs-positive haemolytic anaemia commonly found in AITL patients. Other factors incriminated in the pathogenesis of AITL comprise lymphotixin beta, potentially released by B cells under CXCL13 stimulation, and several angiogenic mediators.

The 2016 update of the WHO classification recognizes two other PTCL entities related to AITL, namely follicular T-cell lymphoma (FTCL) and PTCL of TFH origin (TFH-PTCL) (Swerdlow et al., 2016). FTCL is a rare TFH neoplasm defined by a predominantly follicular growth pattern (de Leval et al., 2001, Huang et al., 2009), closely related to AITL as supported by analogies in cellular derivation, clinical presentation and documentation that patients with F-PTCL may relapse with lesions resembling AITL (Huang et al., 2009; Moroch et al., 2012). Nodal PTCL of TFH origin designates a subset of PTCL “unspecified” by morphology showing expression of a TFH phenotype. A common feature of AITL and other nodal TFH lymphomas is the presence of scattered to numerous large B-cell blasts,
Peripheral T-cell lymphoma—not otherwise specified comprises a heterogeneous group of mature T-cell neoplasms that do not qualify for any other specific entity. As mentioned above, cases with a TFH immunophenotype are now excluded from the PTCL-NOS category. Many cases are CD4⁺CD8⁻, a subset is CD4⁺CD8⁺ and, more rarely, tumours are either double-negative or -positive for CD4 and CD8. Most cases derive from T cells expressing an alpha/beta T-cell receptor (TCR), a minority are of gamma/delta derivation, or TCR-silent. Earlier studies attempted to delineate PTCL-NOS subclasses by their immunological profile (TH1 versus TH2). Gene expression profiling has identified two subgroups of PTCL-NOS characterized by high expression of either GATA3 or TBX21 transcription factors and downstream target genes, associated with different prognosis (Iqbal et al., 2014). These findings can be translated to routine immunohistochemistry: PTCL-NOS with high expression of GATA3 or TBX21/T-bet appear to be essentially non-overlapping and the high GATA3-expressing group was shown to portend a significantly worse prognosis in two independent series (Iqbal et al., 2014; de Leval & Gaulard, 2014; Wang et al., 2014).

Conventional cytogenetics and comparative genomic hybridization have shown recurrent genetic aberrations and imbalances, usually more complex in PTCL-NOS than inAITL, but have not allowed the capture of specific driver alterations (for review, (de Leval et al., 2009)). Very rare recurrent translocations involve breaks in the TCR genes. The t(6;14)(p25;q11.2) translocation involving the IRF4 locus, has been reported in clinically aggressive cytotoxic PTCL (Feldman et al., 2009; Somja et al., 2014).

With the use of classical and next-generation sequencing technologies, an increasing number of recurrent genetic aberrations have been identified inAITL and other TFH lymphomas. Besides RHOA, which is the most frequently mutated gene, highly recurrent mutations are observed in epigenetic modifier genes and in genes related to the TCR and costimulatory signalling pathways. The mutational landscape of PTCL-NOS is not fully characterised; targeted sequencing analyses have highlighted a heterogeneous pattern of alterations, including recurrent mutations in epigenetic mediators, regulators of signalling pathways and tumour suppressor genes (Schatz et al., 2015).

The RHOA gene, which encodes a small GTPase involved in regulating the actin cytoskeleton, cell adhesion and distal TCR signalling, is most frequently mutated inAITLs and TFH-PTCL (60–70% of cases). No correlation with clinical presentation or outcome has been documented. Most mutations are hotspots, generating p.Gly17Val RHOA dominant negative variant (Palomero et al., 2014; Sakata-Yanagimoto et al., 2014; Yoo et al., 2014; Vallois et al., 2016).

TET2, IDH2 and DNMT3A genes, involved in regulating DNA methylation, are mutated in 50–75%, 20–30% and 20–30% of AITLs, respectively (Cairns et al., 2012; Couronne et al., 2012; Lemonnier et al., 2012; Odejide et al., 2014). Mono- or bi-allelic TET2 and DNMT3 mutations are inactivating, and distributed along the coding sequences of the genes. Conversely, virtually all IDH2 mutations are gain-of-function missense at the R172 residue, inducing the production of an oncometabolite that inhibits various deoxygenases including TET2 and histone demethylases, resulting in global DNA and histone hypermethylation. While mutations in TET2 and DNMT3 are also found in other PTCL entities, particularly TFH-PTCLs, IDH2 mutations appear to be rather specific for AITL (Cairns et al., 2012). In AITL, DNMT3A and IDH2 mutations almost always occur in association with TET2 mutations, in contrast with myeloid neoplasms where mutations in these epigenetic modifiers are usually mutually exclusive (Couronne et al., 2012; Odejide et al., 2014; Palomero et al., 2014; Sakata-Yanagimoto et al., 2014). While RHOA and IDH2 mutations are present in tumour cells only, TET2 and DNMT3A mutations have been found also in haematopoietic progenitors (Quivoron et al., 2011; Odejide et al., 2014; Sakata-Yanagimoto et al., 2014). In most cases, RHOA mutations are observed in TET2 mutated tumours, the allelic burden for TET2 or DNMT3A mutations being higher than for RHOA, suggesting cooperation between impaired RHOA function following TET2 loss of function, contributing to AITL pathogenesis (Sakata-Yanagimoto et al., 2014).

Mutation-induced activation of the TCR and costimulatory signalling pathways has recently emerged as another oncogenic mechanism in AITL, TFH-PTCL and PTCL-NOS. Activating mutations in genes encoding proximal TCR signalling elements (FYB), costimulatory receptors (CD28) or key intracellular effectors of signal transduction (PLCG1) have been discovered in AITL or cutaneous T-cell lymphomas (Manso et al., 2014; Palomero et al., 2014; Lee et al., 2015; Rohr et al., 2016) By investigating a series of 85 patients with AITL or TFH-PTCL by targeted deep sequencing of a gene panel enriched in TCR signalling elements, Vallois et al. (2016) found that half of the patients carried virtually mutually exclusive mutations in TCR-related genes other than RHOA, most frequently in PLCG1 (14-1%), CD28 (9-4%, exclusively in AITL), PIK3CA (previously termed PISK) elements (7%), CTNNB1(6%) and GTF2I (6%). CARD11 was also mutated in several patients. The vast majority of these variants could be classified as gain-of-function. Although no correlation with clinical features or a significant impact on survival was observed, the presence of TCR-related mutations correlated with early disease progression (Vallois et al., 2016). In PTCL-NOS, no such investigation has been conducted but activating PLCG1 mutations have been found in about 15% of cases (Manso et al., 2015).

Interestingly, oncogenic TCR activation may result from gene fusions. For example, the rare t(5;9)(q35;q22) translocation, found in about 20% of PTCL and occasionally in AITL (Streubel et al., 2006; Huang et al., 2009; Attygalle
et al., 2013), produces an ITK-SYK chimeric protein with tyrosine kinase activity which induces a T-cell lymphoproliferative disease in mice (Dierks et al., 2010; Pechloff et al., 2010). The recently discovered CTLA4-CD28 fusion gene, consist of the extracellular domain of CTLA4 and the cytoplasmic region of CD28, and are probably capable of transforming inhibitory signals into stimulatory signals for T-cell activation. Different fusion variants were also found in more than 50% AITL and other PTCL (Yoo et al., 2016), although this high incidence reported in cases from Asia needs to be confirmed in other cohorts (Gong et al., 2016). VAV1 rearrangements, which are recurrent in PTCL-NOS (about 10% of cases), have been shown to drive tumour cell growth (Boddicker et al., 2016).

**Diagnosis**

**Pathology**

Accurate diagnosis is a critical step in proper management, but is often challenging. Therefore, needle biopsies should be discouraged. The diagnosis is made by an expert haematopathologist on an excisional biopsy (d’Amore et al., 2015; de Leval & Gaulard, 2015). Morphological appraisal remains the cornerstone of diagnostic evaluation; immunophenotyping and, in many cases, clonality testing are essential to confirm the diagnosis.

In PTCL-NOS, lymph nodes usually are diffusely involved and cytology is typically pleomorphic (Fig 1A, B). Most cases consist predominantly of medium-sized or large cells with irregular nuclei containing prominent nucleoli and many mitoses. High endothelial venules are usually increased. Many cases comprise an admixture of small lymphocytes, eosinophils, histiocytes, B cells and plasma cells. The lymphoma cells usually express several T cell-associated antigens, but one or several of these (most commonly CD5 or CD7, more rarely CD3 or CD2) may show reduced or absent expression. CD30 is often detected in a variable proportion of tumour cells (Bossard et al., 2014)(Fig 1C, D). Up to 50% of PTCL-NOS are EBV-positive usually in a small subset of cells, probably bystander B cells, and this feature has been associated with poor survival (Dupuis et al., 2006). A subset of PTCL-NOS (15–40% of cases), most commonly CD8+, features a cytotoxic immunophenotype (Fig 1E, F). The rare lymphoepithelioid variant, comprising a proliferation of small cytotoxic CD8+ neoplastic T cells in association with

![Fig 1. Pathological heterogeneity of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). (A) PTCL-NOS composed of a monomorphic population of small to medium-sized cells; (B) PTCL-NOS featuring pleomorphic large cell morphology and marked eosinophilia; (C, D) PTCL-NOS composed of large cells showing partial CD30 expression (D); (E, F) cytotoxic PTCL-NOS characterised by diffuse positivity for TIA-1 (F). Panels A, B: original magnification ×200; Panels C, D, E and F: original magnification ×400](https://example.com/fig1)
an abundant epitheloid cell background, may have a better prognosis (Yamashita et al., 2000; Geissinger et al., 2004). All cases of CD4+ non-cytotoxic “unspecified” PTCLs should be investigated for the expression of TFH markers, as PTCL of TFH cell origin are now classified in the same group as AITL.

In AITL, lymph nodes show complete effacement of architecture, often with perinodal infiltration sparing the peripheral sinus. Less frequently, depleted follicles may be present, or the neoplastic cells infiltrate around hyperplastic germinal centres. They are typically medium-sized with clear cytoplasm and tend to form small clusters around high endothelial venules admixed with an abundant tumour microenvironment composed of small lymphocytes, histiocytes or epithelioid cells, B-cell immunoblasts, eosinophils and plasma cells (Fig 2A). The neoplastic cells are mature TCR-αβ⁺ CD4⁺CD8⁻ T-cells that frequently show aberrant loss or reduced expression of CD7, surface CD3 and/or CD4 and may show partial CD30 expression or aberrant coexpression of CD20 (Fig 2B). A population of large B-blasts, sometimes mimicking Reed-Sternberg cells, usually infected by EBV, is almost invariably present (Fig 2C). Irregular proliferation of follicular dendritic cells (FDC) is evidenced in most cases by immunohistochemistry (Fig 2D). The neoplastic cells express several markers of follicular helper T cells (T\(\text{FH}_1\)): CD10, CXCL13, CXCR5, CD154, programmed death-1 (PD-1, also termed PDCD1), inducible costimulator (ICOS), cytoplasmic SLAM-associated protein (SAP), BCL6, or c-MAF (Fig 2E–G). Monoclonal or oligoclonal rearrangement of the TCR genes is found in the vast majority of cases. Additionally, a clonal or oligoclonal rearrangement of the immunoglobulin gene(s) is found in up to one-third of patients, in relationship with increased numbers of B-cell blasts.

Fig 2. Pathology of angioimmunoblastic T-cell lymphoma. (A) Medium-power magnification of angioimmunoblastic T-cell lymphoma (AITL) showing prominent vascularity and a polymorphous infiltrate comprising aggregates of cells with clear cytoplasm; (B) the majority of the lymphoid cells are highlighted with a CD3 immunostain; (C) CD20 stains aggregates of small lymphoid cells and scattered large blastic B cells; (D) an irregular expansion of follicular dendritic cell meshworks is shown by a CD21 immunostain; (E–G) the neoplastic cells express several follicular helper CD4⁺ T-cell (TFH) markers: CXCL13 (E), ICOS (F), and PD-1 (G). Panel A: original magnification ×100; panels B, C: original magnification ×200; panels E, F, G: original magnification ×400.
Clinical

The initial clinical work-up of patients with PTCL includes physical examination, complete blood counts and chemistry including lactate dehydrogenase (LDH), a bone marrow aspirate and biopsy. Serological tests for human immunodeficiency virus, human T-lymphotropic virus type 1, hepatitis B and C are required because they can assist in rendering the diagnosis. In order to complete staging and determine the International Prognostic Index (IPI) (The International Non-Hodgkin’s Lymphoma Prognostic Factors Project, 1993), computed tomography (CT) of the neck, chest, abdomen and pelvis is obligatory. Nowadays, combined positron emission tomography (PET)/CT is the imaging procedure of choice. Retrospective analyses (Cottereau et al, 2016) (Pellergrini et al, 2014) and consensus papers (Cheson et al, 1999; Barrington et al, 2014) recommended that PET/CT should be performed at diagnosis, midtherapy, and at end of therapy in all PET-avid lymphomas, including PTCL. Because it has not been shown that interim PET predicts treatment outcome significantly better than CT scan and ensuing treatment changes would improve clinical outcome we believe that interim PET should be further evaluated in clinical studies but not necessarily in clinical routine. PET-positive lesions should be biopsied and histological confirmation of active disease should be sought before implementing therapeutic changes. Further diagnostic procedures will be needed if involvement of a specific organ is suspected.

Staging and prognostic indices

Most patients with PTCL-NOS or AITL present with advanced (stage III or IV) disease at the time of diagnosis (Mourad et al, 2008; Weisenburger et al, 2011; Federico et al, 2013). Several prognostic indices that take laboratory and clinical features into account have been proposed (Cheson et al, 1999; Gallamini et al, 2004; Sonnen et al, 2005). We prefer to stay with the IPI for now. This well-established scoring system is effective in separating groups of patients with low, intermediate, and high risk of treatment failure (Ansell et al, 1997; Went et al, 2006; Gutierrez-Garcia et al, 2011). The practical consequences of staging and IPI scoring seem limited because local radiotherapy has not systematically been investigated in PTCL and advising for local radiotherapy potentially preceded by (abbreviated) chemotherapy, even in localised disease, is not supported by data.

First-line therapy

Conventional therapy

For both AITL and PTCL-NOS CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy remains the standard of care. The International T-cell Lymphoma Project (Vose et al, 2008), retrospective analyses of prospective studies (Schmitz et al, 2010) and smaller prospective studies (Simon et al, 2010) reported overall survival (OS) and progression-free survival (PFS) rates of between 30–45% and 20–30%, respectively. A registry study from Sweden in which 84% of patients had been treated with CHOP or CHOP plus etoposide (CHOP-E) reported OS and PFS rates of 28.1% and 21.3% for patients with PTCL-NOS, and 31.6% and 20.4% for patients with AITL, respectively (Ellin et al, 2014). Patients with low IPI do significantly better; however, treatment results overall remain poor because most patients present with advanced disease.

Other multi-agent chemotherapy has been used. A smaller phase III study randomising patients to CHOP or VIP-rABVD (etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine) did not report improvement with the experimental regimen (Simon et al, 2010). Otherwise, only phase II studies or retrospective comparisons of different first-line chemotherapy regimens are available (Table II). In a retrospective analysis of 343 patients with T-cell lymphoma treated on several German protocols, CHOEP improved EFS from 51% to 75% in younger patients with normal LDH (P = 0.003) (Schmitz et al, 2010). The Swedish study (Ellin et al, 2014) also found a superior PFS for CHOEP (HR 0.49, P = 0.008) in patients younger than 60 years; OS was not significantly improved in both studies. Based on these analyses, phase II/III studies investigating the role of ASCT and alloSCT started treatment with 4–6 courses of CHOEP (d’Amore et al, 2012), and recent reviews (Moskowitz et al, 2014) as well as current National Comprehensive Cancer Network NHL guidelines (https://www.nccn.org/professionals/physician_gls/f_guidelines_nojava.asp), European Society for Medical Oncology (d’Amore et al, 2015) and German/Austrian guidelines (Hopfinger et al, 2016) mention CHOEP as a (preferable) alternative to CHOP in younger patients treated with curative intent. Chemotherapy consisting of CHOP plus etoposide and gemcitabine (CHOP-EG) (Kim et al, 2006), cisplatin, etoposide, gemcitabine and methylprednisolone (PEG-S) (Mahadevan et al, 2013), cyclophosphamide, etoposide, vincristine and prednisone (CEOP) alternating with pralatrexate (P) (Advani et al, 2016) as well as intense regimens like hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (Hyper-CVAD) (Escalon et al, 2005) failed to convincingly improve outcomes (Table II). Phase III studies combining CHOP with antibodies, antibody-drug conjugates (BV), or histone deacetylase (HDAC)-inhibitors (Ro-CHOP) and comparing the experimental arm to CHOP are ongoing (NCT 01796002). Results of a prospective randomised study investigating the addition of alemtuzumab to CHOP have recently been presented (Truemper et al, 2016). In 116 older patients (61–80 years) randomised to 6 courses of CHOP plus alemtuzumab or CHOP alone, the addition of alemtuzumab failed to show significant improvement in the 3-year PFS (26% vs. 29%) or OS (38% vs. 56%).

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Consolidation by autologous transplantation

Given that conventional chemotherapy alone fails to induce long-term remissions in the majority of patients with PTCL, consolidation with ASCT and, more recently, alloSCT has been used in younger patient achieving remission after 4–6 courses of chemotherapy. Quite a number of retrospective studies and a comprehensive systematic review (El-Asmar et al, 2016) of ASCT for consolidation or treatment of relapsed patients have been presented. These results must be treated with caution because only patients who could proceed to transplantation were considered, whereas prospective phase II/III studies repeatedly demonstrated that up to 40% of candidates cannot receive a transplant because of early progression or relapse (Corradini et al, 2004, 2014; Reimer et al, 2009; d’Amore et al, 2012; Schmitz et al, 2015). Prospective phase II studies on ASCT were reported by the Spanish Groups, Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea (GEL/TAMO) and Grup per l’Estudi dels Limfomes de Catalunya i Balears (GEL/CAB) (Rodríguez et al, 2001) (Mercadal et al, 2008), a German consortium (Reimer et al, 2009), and the Nordic Lymphoma Group (NLG) (d’Amore et al, 2012). In the latter study, 5-year OS and PFS were 51% and 44%, respectively. Patients with PTCL-NOS had an OS of 47% and PFS of 38%; OS and PFS for patients withAITL was 52% and 49%, respectively. The German study has recently been updated (Wilhelm et al, 2016). With now 111 patients and extended follow-up, 5-year OS and PFS rates were 44% and 39%, respectively. Entity-specific differences in survival were not found. Specifically for patients withAITL, an early (Schetelig et al, 2003) and a more recent, larger European Group for Blood and Marrow Transplantation (EBMT) study on 146 patients (Nickelsen et al, 2008a) reported OS rates of 50% and 44% at 4 and 5 years respectively. Overall, data indicate that between 40% and 50% of younger, medically fit patients undergoing ASCT with chemosensitive disease (complete response [CR] or partial response [PR] after conventional chemotherapy), survive long-term. Patients not achieving PR (or PET-negativity) after conventional chemotherapy (with few exceptions) do not benefit from ASCT. With approximately one-third of patients progressing or relapsing before ASCT, it becomes clear that PTCL patients surviving progression-free after ASCT represent a highly selected group of patients with a substantially better prognosis than PTCL patients in general. A prospective study comparing ASCT with observation in patients with PET-negative CR after 4–6 courses of chemotherapy seems highly warranted.

Consolidation by allogeneic transplantation

Transplant-related mortality (TRM) after alloSCT in patients with relapsed/refractory PTCL has been reported to be between 10% and 40% (Table III). Understandably, investigators therefore hesitated to consider alloSCT as part of first-line therapy. On the other hand, many patients never achieve a remission and about a quarter of patients relapse after ASCT, and become candidates for alloSCT at that stage. Taking into account the dismal prognosis of patients relapsing...
Table III. Outcome of allogeneic transplantation in patients with PTCL beyond first complete remission.

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Histology (%)</th>
<th>NRM (%)</th>
<th>Relapse (%)</th>
<th>PFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al (2013)</td>
<td>74 MAC</td>
<td>PTCL-NOS: 50</td>
<td>30 @ 1 year</td>
<td>37 @ 3 years</td>
<td>29 @ 3 years</td>
<td>31 @ 3 years</td>
</tr>
<tr>
<td></td>
<td>45 RIC</td>
<td>AITL: 10</td>
<td>27 @ 1 year</td>
<td>42 @ 3 years</td>
<td>32 @ 3 years</td>
<td>50 @ 3 years</td>
</tr>
<tr>
<td>Dodero et al (2012)</td>
<td>52 RIC</td>
<td>PTCL-NOS: 45</td>
<td>12 @ 5 years</td>
<td>49 @ 5 years</td>
<td>40 @ 5 years</td>
<td>50 @ 5 years</td>
</tr>
<tr>
<td>Jacobsen et al (2011)</td>
<td>31 MAC</td>
<td>PTCL-NOS: 38</td>
<td>36 @ 3 years</td>
<td>33 @ 3 years</td>
<td>45 @ 3 years</td>
<td>52 @ 3 years</td>
</tr>
<tr>
<td></td>
<td>21 RIC</td>
<td>AITL: 10</td>
<td>14 @ 3 years</td>
<td>57 @ 3 years</td>
<td>nodal PTCL</td>
<td>nodal PTCL</td>
</tr>
<tr>
<td>Le Gouill et al (2008)</td>
<td>57 MAC</td>
<td>PTCL-NOS: 35</td>
<td>34 @ 5 years</td>
<td>NR</td>
<td>53 @ 5 years*</td>
<td>57 @ 5 years†</td>
</tr>
<tr>
<td>Kyriakou et al (2009)</td>
<td>25 MAC</td>
<td>AITL: 100</td>
<td>29 @ 3 years</td>
<td>17 @ 3 years</td>
<td>54 @ 3 years</td>
<td>58 @ 3 years</td>
</tr>
<tr>
<td></td>
<td>20 RIC</td>
<td>AITL: 14</td>
<td>24 @ 3 years</td>
<td>24 @ 3 years</td>
<td>51 @ 3 years</td>
<td>71 @ 3 years</td>
</tr>
<tr>
<td>Glass et al (2011)</td>
<td>95 MAC</td>
<td>PTCL-NOS: 32</td>
<td>43 @ 5 years</td>
<td>14 @ 5 years</td>
<td>43 @ 5 years</td>
<td>46 @ 5 years</td>
</tr>
</tbody>
</table>

AITL, angioimmunoblastic T-cell lymphoma; MAC, myeloablative conditioning; NOS, not otherwise specified; NR, not reported; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma; RIC, reduced intensity conditioning.

*80% for AITL, 58% for PTCL-NOS; †80% for AITL, 63% for PTCL-NOS.

after first-line therapy (Mak et al, 2013) and the general decrease of TRM after alloSCT over time, two recent studies integrated alloSCT into first-line therapy. The first study by Corradini et al (2014) used 2 courses of CHOP plus alemtuzumab (CHOP-A) and 2 courses of high-dose methotrexate, cyclophosphamide and high-dose cytarabine to induce remission. Patients that achieved a CR or PR and had a human leucocyte antigen (HLA)-identical donor were to receive alloSCT after reduced-intensity conditioning (thiotepa, fludarabine and cyclophosphamide). Patients without a suitable donor were to proceed to BEAM (carmustine, etoposide, cytarabine and melphalan) high-dose therapy and ASCT. After induction chemotherapy, 40 patients (66%) achieved CR/PR; the other patients relapsed early or progressed (n = 18), died of toxicity (n = 5), or refused further therapy (n = 1). Only 37 of 61 patients (61%) were transplanted, 23 of whom received alloSCT. Four-year OS was 92% after ASCT and 69% after alloSCT (P = 0.10); PFS was 70% and 69% (P = 0.92), respectively. We recently presented the interim results of a prospective phase III study, which randomised upfront younger patients (<60 years) with PTCL to alloSCT or ASCT (Schmitz et al, 2015). Treatment started with 4 courses of CHOP-E14 followed by 1 course of DHAP (dexamethasone, high dose cytarabine, cisplatin). Patients randomised to alloSCT who had a suitable donor received myeloablative conditioning (MAC) with fludarabine, busulfan and cyclophosphamide; patients randomised to ASCT proceeded to ASCT if stem cell collection was successful. At the time of the analysis, 58 patients had been randomised to ASCT (n = 30) or alloSCT (n = 28). Very similar to the Italian experience, only 62% of patients were able to complete treatment as per protocol. Sixteen patients unable to proceed to transplantation had experienced early progression or relapse, six patients died after alloSCT, mostly of graft-versus-host disease, 3 patients died of salvage therapy and its toxicity, and one patient developed post-transplant lymphoproliferative disease after alloSCT. There was no significant difference in OS or PFS between treatment arms. The Italian and the German study demonstrate that despite aggressive therapy more than one-third of PTCL patients were unable to reach transplantation. While TRM after ASCT was low and relapse remained the major problem, patients who underwent alloSCT have experienced no relapse to date; however, TRM was relatively high, counterbalancing the graft-versus-lymphoma effect provided by allogeneic T cells. More efficient first-line therapy bringing more patients to transplantation as well as decreasing TRM are needed.

**Relapsed and refractory disease**

**Conventional therapy**

Single agent gemcitabine (Zinzani et al, 2010), gemcitabine-based combination chemotherapy (Arkenau et al, 2007) (Park et al, 2015) or salvage protocols originally developed for patients with relapsed DLBCL [ICE (ifosfamide, carboplatin, etoposide), DHAP or ESHAP (etoposide, methotrexate, cisplatin)] are frequently used in patients with PTCL failing first-line therapy. Outcome after any conventional chemotherapy is dismal; patients who cannot proceed to transplantation have no realistic chance to survive long-term. In an analysis of 153 patients from British Columbia (PTCL-NOS 52%, AITL 25%) OS and PFS after relapse or progression were 5.5 and 3.1 months, respectively (Mak et al, 2013).

At least two chemotherapeutic agents previously not available or not used in PTCL, pralatrexate (O’Connor et al, 2011) and bendamustine (Damaj et al, 2013) have recently been investigated. In 111 patients (median age 58 years) with relapsed/refractory PTCL (53% PTCL-NOS; 12% AITL) the pralatrexate study reported a median OS of 14.5 months; PFS, however, was only 3.5 months indicating the limited...
potential of pralatrexate to induce long-term remissions (O’Connor et al, 2011). The phase II study of bendamustine in 60 patients (median age 66 years) with relapsed/refractory PTCL-NOS (38%) or AITL (53%) confirmed the poor outcome with chemotherapy. The median OS and PFS reported were 6-2 and 3-6 months, respectively (Damaj et al, 2013). Overall, it is difficult to recommend a specific regimen for relapsed/refractory disease. More aggressive regimens probably should be reserved for patients where the final goal is bridging to transplantation. For all other patients, palliation is the primary goal and quality of life considerations should prevail when deciding on the most suitable treatment.

Autologous transplantation

Many investigators consider ASCT an integral part of salvage therapy for patients with relapsed/refractory PTCL. Larger series from the EBMT (n = 484) and Center for International Blood and Marrow Transplant Research (CIBMTR; n = 115) including all PTCL entities (Nickelsen et al, 2008b; Smith et al, 2013) and an EBMT study of 146 AITL patients (Kyrriakou et al, 2008) reported OS rates of 50% at 3 years, 53% at 3 years and 67% at 2 years. The EBMT report confirmed the favourable outcome of patients with chemosensitive disease (3-year PFS 47%) but also demonstrated that ASCT is much less effective in patients with refractory disease (3-year PFS 15%). All series, including the recent meta-analysis (El-Asmar et al, 2016), do not present intent-to-treat analyses and therefore largely overestimate the benefit of ASCT. Taken together, patients with PET-negative CR/PR have a fair chance of long-term survival with ASCT. For all other patients, alloSCT should be strongly considered (Lunning et al, 2013).

Allogeneic transplantation

Allogeneic transplantation after reduced intensity conditioning or MAC induces a graft-versus-lymphoma effect, translating into the low relapse rates seen after successful alloSCT (Nickelsen et al, 2008a; Smith et al, 2013). After the first prospective study of alloSCT in T-cell lymphoma had been published (Corradini et al, 2004) further reports from different institutions confirmed that alloSCT may cure around 50% of relapsed/refractory patients (Table III). Studies large enough to look into different T-cell entities did not find statistically different survival between entities. An important advantage of alloSCT is that not only CR and PR patients but also patients with stable disease or early progression can benefit from alloSCT (Glass et al, 2014). Unfortunately, even recent publications report high TRM (Glass et al, 2014), calling for careful selection and counselling of transplant candidates. However, many patients do not have a choice. First reports using haplo-identical donors also in lymphoma patients have been published (Kanate et al, 2016). Early results seem comparable to those of matched unrelated donor transplants.

New targets—new drugs

Progress in understanding the molecular lesions underlying PTCL has opened new avenues by designing molecules that specifically target genetic/epigenetic abnormalities. Here, we focus on drugs with substantial pre-clinical activity for which at least phase I/II data have been published (Table IV).

Epigenetic modifiers

A large variety of mutations in chromatin-modifying genes occur across virtually all PTCLs, suggesting that epigenetic changes contribute to lymphomagenesis and drug resistance. Different histone deacetylase inhibitors have been tested, with heterogeneous results; determinants of response are poorly understood and correlations between genotype and clinical success have not been reported. The results of phase II studies with romidepsin and belinostat are summarised in Table IV. The combination of romidepsin and CHOP has

Table IV. Results of phase II studies using new drugs.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Patients (n)</th>
<th>Median age (years)</th>
<th>PTCL-NOS or AITL (%)</th>
<th>IPI high or high/intermediate (%)</th>
<th>PFS (median)</th>
<th>OS (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coiffier et al (2012)</td>
<td>Romidepsin</td>
<td>130</td>
<td>61</td>
<td>74</td>
<td>76 (≥2)</td>
<td>4 months</td>
<td>NR</td>
</tr>
<tr>
<td>O’Connor et al (2015)</td>
<td>Belinostat</td>
<td>120</td>
<td>64</td>
<td>83</td>
<td>1-6 months</td>
<td>7-9 months</td>
<td>NR</td>
</tr>
<tr>
<td>Horwitz et al (2014a)</td>
<td>Brentuximab</td>
<td>35*</td>
<td>64</td>
<td>100</td>
<td>2-6 months</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Ogura et al (2014)</td>
<td>Mogamulizumab</td>
<td>37</td>
<td>67</td>
<td>96</td>
<td>NR</td>
<td>2-0 months</td>
<td>14-2 months</td>
</tr>
<tr>
<td>Barr et al (2015)</td>
<td>Alisertib</td>
<td>37</td>
<td>62</td>
<td>59</td>
<td>NR</td>
<td>3-0 months</td>
<td>8-0 months</td>
</tr>
<tr>
<td>Toumishey et al (2015)</td>
<td>Lenalidomide</td>
<td>39</td>
<td>65</td>
<td>59</td>
<td>NR</td>
<td>4-0 months</td>
<td>12-0 months</td>
</tr>
<tr>
<td>Ribrag et al (2013)</td>
<td>Platidepsin</td>
<td>34</td>
<td>58</td>
<td>59</td>
<td>NR</td>
<td>1-6 months</td>
<td>10-2 months</td>
</tr>
</tbody>
</table>

IPI, International Prognostic Index; NR, not reported; OS, overall survival; PFS, progression-free survival; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

*patients with any CD30 expression detectable by immunohistochemistry were eligible.
been evaluated in previously untreated PTCL patients (Dupuis et al, 2015); a study randomising patients to romidepsin-CHOP or CHOP is ongoing (NCT 01796002).

**Brentuximab vedotin**

Brentuximab vedotin (BV) is highly active in patients with relapsed ALCL (Pro et al, 2012). More recent studies looked into the activity of BV in a wider range of CD30-positive B- and T-cell lymphomas, either as a single agent or in combination with chemotherapy (Fanale et al, 2014). Although some CD30 expression is detected in a large proportion of both PTCL-NOS and AITL (Sabattini et al, 2013; Bossard et al, 2014; Onaindia et al, 2016), strong expression is uncommon in AITL; in PTCL-NOS, the extent and intensity of CD30 staining tend to correlate with larger tumour cell size, and a subset of PTCL-NOS feature high levels of CD30 expression (Bossard et al, 2014). Surprisingly, no correlation was observed between clinical response and CD30 expression in the tumour cells (Horwitz et al, 2014a). Prospective studies comparing CHOP with CHP (cyclophosphamide, doxorubicin, prednisone) plus BV in CD-30 positive PTCL including PTCL-NOS and AILT are ongoing (ECHELON-2 study, NCT01777152).

**Mogamulizumab**

Mogamulizumab is a humanized anti-CCR4 antibody with a defucosylated Fc-region that enhances antibody-dependent cell-mediated cytotoxicity. The phase II study from Japan reported an overall response rate (ORR) of 35%. Interestingly, 6/12 patients with AITL responded. PFS, however, was short and some unusual grade 3/4 toxicities (polymyositis, cytomegalovirus retinitis) were reported (Ogura et al, 2014). A phase II study conducted in Europe found only 11% ORR in 35 PTCL patients with relapsed or refractory PTCL (Zinzani et al, 2016).

**Alisertib**

Alisertib is an inhibitor of Aurora kinase A, leading to abnormal spindle formation and subsequent apoptosis. Thirty-seven patients were enrolled in a multi-centre phase II study (Barr et al, 2015). The PFS was 3 months and the 1-year PFS rate was 8%. A phase III study randomising patients to alisertib or investigator’s choice (NCT01482962) and phase II studies combining alisertib with vorinostat and romidepsin, respectively, are ongoing (NCT 01567709).

**Lenalidomide**

Lenalidomide is an immunomodulatory drug with clinical activity in a wide range of haematological malignancies. The final report on the phase II study in PTCL was recently published with results no more encouraging than with other new drugs (Toumihey et al, 2015).

**Plitidepsin**

Plitidepsin is a cyclic pepsipeptide that has activity in leukaemia and lymphoma. The phase II study in relapsed/refractory lymphoma showed promising activity in PTCL (Ribrag et al, 2013).

A plethora of other agents, including duvelisib (Horwitz et al, 2014b), selinexor (Kuruvilla et al, 2014) and AG-221 (a mutated IDH2 protein inhibitor, NCT02273739) are under review.
study; no clinical results are currently available. PD-1 and PD-L1 (also termed CD274) antibodies have shown efficacy in various lymphoma entities; very limited data on PTCL are available which do not enable the role of PD-1 or PD-L1 antibodies to be predicted in PTCL (Lesokhin et al., 2016).

**Conclusion (Fig 3)**

Standard first-line therapy of patients with PTCL, NOS andAITL consists of 4–6 courses of CHOP chemotherapy. The addition of etoposide to CHOP (CHOEP) may improve results in younger patients; the use of alternative chemotherapy, the addition of other cytotoxic agents and the addition of new drugs to CHOP are under study. The major problem of all therapy is the occurrence of early relapse or progression in up to 40% of patients starting first-line therapy. Clinicians hope that the molecular characterisation of PTCL and subsequent development of targeted therapies may alleviate this problem. ASCT is the preferred option for patients achieving CR/PR after first-line therapy, although a randomised study proving the superiority of ASCT is lacking. Initial results of alloSCT as part of first-line therapy failed to provide evidence of the superiority of alloSCT over ASCT. In patients with chemosensitive relapsed/refractory PTCL, ASCT remains a valuable option. Chemorefractory patients should proceed to alloSCT whenever possible. Several new drugs show ORRs between 10% and 30% in relapsed patients; none of them, however, resulted in long-term remissions or even cure. New drugs that have passed phase I/II studies are almost invariably investigated in combination with chemotherapy in order to bridge patients to alloSCT. Development of more effective drugs, based on the molecular characterisation of PTCL, continues to be an unmet clinical need.

**Author contributions**

Norbert Schmitz and Laurence de Leval wrote the paper.

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