12 Standard of Care in T-Cell Lymphoma

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12.1 Introduction

Peripheral T-cell non-Hodgkin lymphoma (PTCL) is a heterogeneous group of mature T-cell neoplasms generally associated with a poor prognosis and displaying a wide geographical heterogeneity. They account for 5–10% of all aggressive lymphoma in Europe and in the United States, whereas they tend to be much more represented (up to roughly 20%) in Asia, where some peculiar forms of disease (like neoplasms of the NK-/T-cell origin) are prevalent [1–5].

PTCL have a nodal origin in most of cases, although extranodal non-cutaneous entities do exist, described by their tissue tropism. The 2016 revision of the World Health Organization classification of lymphoid neoplasms underscores several new insights into the complexity of PTCL, which emerge from molecular and genetic studies that point out many specific molecular signatures helpful in distinguishing among different entities, albeit displaying similarities in terms of morphology and immunophenotype [4, 6]. Aggressive PTCLs with nodal presentations include three main categories: nodal T-cell lymphoma with T-follicular helper (TFH) phenotype, which is a broad category which comprises the entire spectrum of nodal lymphoma displaying a TFH phenotype and includes angioimmunoblastic T-cell lymphoma (AITL), follicular T-cell lymphoma, and other nodal PTCL with a TFH phenotype; anaplastic large cell lymphoma (ALCL), either with or without the expression of the anaplastic lymphoma kinase (ALK), which clearly distinguishes two separated entities in terms of prognostic implications (ALK^- ALCL is no longer regarded as a provisional entity in the 2016 classification); and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), a category that still shows extreme cytological and phenotypic heterogeneity, in which fall all the T-cell lymphoma that cannot be further classified into any other of the existing classifiers [7]. A unique form of ALK^- ALCL, which arises in association with saline and silicone-filled breast implants and clinically presents with the accumulation of seroma fluid at the interface between the implant itself and the surrounding fibrous capsule, is now a provisional entity termed breast implant-associated ALCL [8]. Among the entities with a prevalent non-cutaneous extranodal

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involvement and an aggressive behavior are enteropathy-associated T-cell lymphoma (EATL), formerly defined as EATL type I, typically associated with celiac disease and of αβ origin, clearly distinguished by monomorphic epitheliotropic intestinal T-cell lymphoma (formerly known as EATL type II, now a separated provisional entity); hepatosplenic T-cell lymphoma of γδ origin (HSTCL); subcutaneous panniculitis-like T-cell lymphoma (SPTCL); and extranodal NK-/T-cell lymphoma (ENKL), nasal type [4].

Despite clinical, morphological, phenotypic, and molecular differences, the management of these aggressive diseases is substantially the same for all the nodal entities: an initial systemic chemotherapy and a prompt evaluation of which patient is suitable for an up-front consolidation by means of an autologous stem cell transplantation are nowadays a widely accepted standard of treatment. Peculiar entities—like low International Prognostic Index (IPI, see below) ALK^+ ALCL, ALK^- breast implant-associated ALCL, EATL, SPTCL, or ENKL—may take advantage of specifically designed strategies, based on their clinical course and their reduced tendency to spread to distant organs or nodes and which take into account the specific tropism to an organ or tissue and their sensitivity to some specific cytostatic drugs [9].

The aim of this chapter is to review the current clinical management of aggressive T-cell lymphoma, moving from disease diagnosis, initial staging, and available prognostic tools up to the discussion of the first-line therapy and the adopted strategies for relapsed and refractory disease, with a focus on newly available single agents and innovative combinations.

12.2 Clinical Presentation of Aggressive T-Cell Lymphoma

Subtypes with a prevalent nodal expression—PTCL-NOS, ALCL (either in the ALK^+ or ALK^- forms), and nodal T-cell lymphoma with T-follicular helper (TFH) phenotype (including AITL)—involve adult patients (median age at presentation variable between 60 and 65 years) with male predominance. The key feature of these diseases is generalized lymphadenopathy, with the involvement of both superficial and abdominal nodal stations, although any extranodal organ or tissue may be concomitantly affected: the skin (particularly in AITL), the liver, the spleen, and the gastrointestinal tract are among the most involved sites of disease. Hepatic and splenic enlargements are clinical hallmarks of HSTCL, which is characterized by parenchymal infiltration (including bone marrow involvement in more than 70% of cases) without forming growing and coalescent nodal masses.

Advanced stage (Ann Arbor stage III/IV) at presentation is a constant for these disease entities; B symptoms are reported in 50–70% of cases, and bone marrow infiltration is documented in 10–30% of patients. A significant proportion of patients display poor performance status at disease onset, and many of them have their clinical conditions worsening during treatment, thus being unable to undergo intensive chemotherapy or myeloablative conditioning: this is one of the major determinants of the dismal prognosis of this category of lymphoma.

Autoimmune phenomena may be associated with certain disease entities. Autoimmune markers, such as rheumatoid factor, circulating immunocomplexes, and anti-smooth muscle antibodies, may be detected in 30–50% of AITL patients, and Coombs-positive hemolytic anemia may complicate up to one-third of cases [10]. Autoimmune or immune-mediated disease, such as Crohn's disease, is concomitantly observed with HSTCL, which also correlates with the immunosuppressive regimens chronically administered after solid organ transplantation.

Signs and symptoms of PTCL with extranodal manifestations strictly depend on the involved organ or tissue. EATL may be associated with abdominal discomfort and pain at onset, along with fatigue and anorexia. Reappearance of malabsorption in a patient with a history of celiac disease favorably responding to a gluten-free diet or, alternatively, the sudden onset of gluten-insensitive severe malabsorption in an otherwise healthy individual can be key symptoms of

disease at its onset. Acute abdominal symptoms, like perforation, obstruction, and hemorrhage, require an urgent treatment and surgical intervention with bowel resection in most of cases, as a result of disease penetration into the intestinal wall. The jejunum is the mostly affected site, although any segment can be involved. When multiple segments of the small intestine have been involved, it is likely that the disease has disseminated to nearby and distant organs (mesenteric nodes, liver, spleen, lungs, and bone marrow).

SPTCL presents with solitary or multiple nodules or plaques on the lower extremities, more rarely involving the trunk and the upper limbs. Lesions may mimic an abscess but do not resolve after surgical incision. Systemic symptoms, including fever, fatigue, and weight loss, can be present at onset. Hemophagocytic syndrome may complicate the clinical picture in some rare cases, and it is associated with a highly aggressive clinical course.

ENKL, in its nasal form, arises in the nasal cavity and invades the nasopharynx, paranasal sinus, orbits, oral cavity, and palate, usually with bone erosions, ulceration, and destructive behavior, although remaining confined to the facial district in most of cases (stages I and II). On the contrary, extranasal ENKL is an aggressive systemic disease, with the involvement of multiple anatomical sites (stages III and IV) such as skin, gastrointestinal tract, testis, lung, eye, and soft tissues (the same to which the nasal type of the disease tends to disseminate), along with systemic symptoms, lactate dehydrogenase (LDH) elevation, and poor performance status.

12.3 Diagnosis and Staging

12.3.1 Establishing the Diagnosis

The diagnosis of PTCL is always established on the biopsy of the involved tissue, which is mainly represented by a lymph node. However, virtually any extranodal site may be the target for biopsy target for biopsy: the liver, small intestine, and skin are among the mostly involved extralymphatic tissues [11, 12]. Fine needle aspiration is not sufficient to correctly establish the diagnosis. The review of all slides and of formalin-fixed paraffin-embedded tissue by a pathologist with expertise in T-cell lymphoma is always encouraged: hematopathologists are able to apply the WHO classification to diagnose a PTCL, although with heterogeneous agreement on diagnosis depending on the specific disease entity they are looking at [5]. Diagnostic accuracy is very good for ALCL, ALK-positive, but agreement is lost in case of other lymphoma subtypes, with a rate of concordance inferior to 75% for the most common subtype, PTCL-NOS.

Molecular studies may be helpful under certain circumstances to clarify or refine the diagnosis: at present, however, no molecular markers specifically dictate treatment decisions. The sole demonstration of T-cell clonality through the assessment of T-cell receptor rearrangement alone is not sufficient for diagnosis, as this may be seen also with reactive and inflammatory processes.

Physical examination, including the evaluation of the Waldeyer's ring, nasopharynx, node-bearing areas, liver, and spleen, along with thoracic auscultation and a full skin inspection, is mandatory at disease onset. Patient's evaluation is completed by full history taking, mainly focusing on lymphoma-related symptoms (recent weight loss, fever, night sweats), and by the assessment of performance status. A complete blood count with differential counts and a comprehensive metabolic panel, including LDH measurement, is also required at baseline, even for prognostic assessment. Reticulocytes and bilirubin (complete and fractionated) are useful markers in case of suspect hemolysis, which may be associated with some PTCL cases (mainly AITL). Direct Coombs test is also necessary to rule out the diagnosis of autoimmune hemolytic anemia [10].

12.3.2 Staging Procedures

Like nodal B-cell lymphoma, PTCL are staged according to the Ann Arbor staging system. Computed tomography (CT) scan of the neck, chest, abdomen, and pelvis with contrast and a

bone marrow trephine biopsy are requested to accomplish a thorough disease staging [12].

12.3.3 Role of PET Scan

^{18}F-fluorodeoxyglucose (FDG) PET scan is not mandatory for disease staging, although it has proven to be helpful in detecting FDG-avid nodal or extranodal lesions that can be missed by a CT scan evaluation. Nevertheless, PET is able to change the disease stage in no more than 5% of patients at diagnosis as compared to CT [13], and this change does not translate into any treatment modification: systemic chemotherapy in nodal PTCL, in fact, is generally used regardless of tumor extent and disease stage at presentation. It should be noted, however, that PET positivity found at the end of induction treatment and in patients who have received autologous stem cell transplantation (autoSCT) is a strong predictor of reduced survival [14]. Maximum standard uptake values in patients with PTCL are lower than in aggressive B-cell counterparts and usually less pronounced for extranodal lesions than for lymph node localizations of the disease.

12.4 Prognosis

The International Prognostic Index (IPI), although specifically designed for aggressive B-cell lymphoma, is also the mainstay of the prognostic stratification of patients with PTCL and can be determined using clinically derived variables. Similarly to B-cell counterparts, it inversely correlates with survival rates, although overall survival (OS) for each category is lower if compared to diffuse large B-cell lymphoma. Lower IPI scores (0/1 prognostic factors) correlate with a 5-year OS ranging from 90% for ALK-positive ALCL to less than 30% for EATL and extranasal NK-/T-cell lymphoma; on the contrary, patients with four/five risk factors display significantly dismal figures, with a 5-year OS of 25–33% for ALK-positive ALCL and AITL and less than 10% for all the other nodal and extranodal subtypes [5]. Newer scores have been developed to better describe the outcome of specific subtypes of T-cell lymphoma (Table 12.1): the Prognostic Index for PTCL-NOS (PIT, [15]), the modified PIT (m-PIT, [16]), and a prognostic index derived from the International T-cell Lymphoma Project (ITCLP, [17]) are descriptive of populations of PTCL-NOS patients treated with a cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) approach, whereas the prognostic index for AITL (PIA) has predicted OS more reliably than IPI in patients with AITL [18]. The stratification of patients into lower- and higher-risk categories, however, does not necessarily translate into a different management: at least 60–70% of lower-risk patients, in fact, are likely to relapse within the first 5 years; thus a less aggressive initial approach seems not to be justified (Table 12.2).

Table 12.1 Variables used in the calculation of relevant prognostic scores

	IPI	PIT	m-PIT	ITCLP	PIA
Age (>60 years)	•	•	•	•	•
ECOG (>1)	•	•	•	•	
ECOG (>2)					•
LDH (elevated values)	•	•	•		
Ann Arbor stage (III–IV)	•				
Extranodal involvement (≥2 sites)	•				•
Bone marrow involvement		•			
Platelet count (<150,000/mm^3)				•	•
Ki-67 (≥80%)			•		
B symptoms					•
Context	All T-cell lymphoma	PTCL-NOS			AITL

ECOG Eastern Cooperative Oncology Group, *LDH* lactate dehydrogenase

Table 12.2 Prognosis of aggressive PTCL according to the most widely used prognostic scores

Disease	Score	5-year OS (%)		5-year FFS (%)		Reference
		Low score	High score	Low score	High score	
PTCL-NOS	IPI	50	11	36	9	Weisenburger et al. [19]
	PIT	50	11	34	8	
AITL	IPI	56	25	34	16	Federico et al. [18]
	PIA	44	24	28	15	
ALK^+ ALCL	IPI	90	33	80	25	Savage et al. [20]
ALK^- ALCL		74	13	62	13	
ENKL, nasal	IPI	57	0	53	0	Au et al. [21]
ENKL, extranasal		17	20	21	20	
EATL	[a]	20		4–17		Delabie et al. [22], Ellin et al. [3][b]
HSTCL	[a]	0–43		0–20		Vose et al. [5], Ellin et al. [3][b]
SPTCL	[a]	60		30–40		Vose et al. [5], Ellin et al. [3][b]

OS overall survival, *FFS*, failure-free survival. See text for disease and prognostic score abbreviations. "Low score" means score 0/1 for IPI, score 0 (group 1) for PIT, and score 0/1 for PIA. "High score" means score 4/5 for IPI, score 3/4 (group 4) for PIT, and score ≥ 2 for PIA. Data are from the International Peripheral T-cell and Natural Killer/T-cell Lymphoma Study ([5] and related articles for specific subtypes) and mostly rely on anthracycline-treated patients during induction. Data from the Swedish Lymphoma Registry [3] integrate prognostic figures for rarer entities

[a]IPI (or any other prognostic score) not relevant for prognostic stratification of patients

[b]Data in this publication refer to progression-free rather than failure-free survival

12.5 First-Line Treatment Approach

12.5.1 Induction Regimens

The main goal of first-line treatment should be the achievement of a deep remission, which allows a timely application of a consolidative autologous stem cell transplantation (autoSCT), where appropriate, and enhances the opportunity to gain a good control of the disease in the long term.

The treatment strategies most widely adopted in aggressive PTCL are derived from the experience acquired in B-cell aggressive lymphoma: this is generally true for PTCL with a predominantly nodal presentation, whereas disease entities with an exquisitely extranodal involvement or a particular aggressiveness may be managed differently (this will be discussed separately below). It should be noted, however, that PTCL are biologically and clinically different from B-cell counterparts and this may explain the significant prognostic gap existing between lymphoma of B- and T-cell origin when the same (or at least very similar) approaches are applied.

Anthracycline-based regimens are considered the current standard of care in induction treatment of PTCL patients, as demonstrated in several reported experiences in which the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) combination was adopted in a proportion of patients variable from 60 to 85% [5, 23, 24] (Table 12.2). Patients with ALCL respond better to CHOP in comparison to other PTCL subtypes. The overall response rates (ORR) range from 70 to 80% for ALK^- ALCL patients, with complete response (CR) rates up to 50% of the cases. On the contrary, ALK^+ ALCL patients respond to first-line CHOP in up to 90% of cases. Nevertheless, nearly 40% of patients with ALK^+ disease and roughly 60% of those with ALK^- disease fail to maintain their response over time with only first-line induction [20, 25]. The role of anthracycline-containing regimens is however much more debated in patients affected by AITL and PTCL-NOS [7, 10]. On the one hand, it should be noted that according to the International Peripheral T-cell and Natural Killer/T-cell Lymphoma Study, the CR rate observed in patients receiving an anthracycline-based induction was 61% for AITL patients [18] and 56% for PTCL-NOS patients

[19], however without any significant survival advantage for those receiving anthracyclines if compared to patients treated with anthracycline-free schedules [5]. On the other, different data sets provide the evidence that anthracycline-containing regimens are associated with improved OS and PFS in all patients affected by PTCL, particularly in those with both AITL and PTCL-NOS subtypes, and that the benefit is reinforced by first-line consolidation with autoSCT, as discussed below [26]. A 30-month improvement in median OS was observed in PTCL patients treated with anthracyclines over those who were not, which was the consequence of a 13% increase in 2-year PFS documented in anthracycline-treated patients.

Much more disappointing results have been achieved in patients affected by extranodal disease subtypes, like EATL [22], HSTCL, SPTCL, and ENKL [21], which nowadays still represent a clearly unmet medical need [9]: alternative treatment strategies are urgently required.

More intensive chemotherapy regimens have not proven to be more effective than CHOP: the only phase III randomized study in which an induction schedule including etoposide, ifosfamide, cisplatin, alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine (VIP-rABVD) was tested against CHOP (given every 21 days) did not show any superiority of the former regimen in terms of event-free survival (EFS), thus confirming CHOP as the reference standard for PTCL patients [27]. There is some evidence that the addition of etoposide to CHOP can be more effective than CHOP alone, at least in PTCL-NOS and ALCL patients: the CHOEP regimen, given either every 14 or 21 days, improved response and EFS rates in young patients with normal LDH levels (3-year EFS was 70.5% after CHOEP and 51.0% after CHOP, $P = 0.004$), although 3-year OS did not significantly differ between the two groups [28]. Attempts to improve outcomes in younger patients by escalating doses of any of the drugs included in CHOEP have failed. In addition, CHOEP failed to enhance clinical outcomes in patients older than 60 years, for whom CHOP should remain the standard first-line approach.

12.5.2 Frontline Consolidation with Autologous Transplantation

Patients responding to first-line treatment generally display a short duration of remission and a high risk of relapse: for this reason, a frontline consolidation with autoSCT has been considered a valid therapeutic opportunity for patients achieving at least a partial response (PR) to induction, in particular for those with intermediate to high IPI score and with histologies other than ALK$^+$ ALCL. However, no randomized trials have specifically clarified whether up-front autoSCT should be regarded superior to conventional chemotherapy [23].

Two prospective Italian phase II studies, involving 62 patients with advanced stage PTCL, demonstrated a high CR rate (89%) after frontline autoSCT, with a 12-year OS and disease-free survival (DFS) of 34% and 55%, respectively [29]. A Spanish study enrolling 41 PTCL treated up-front with intensified CHOP alternated with an etoposide, cisplatin, cytarabine, and prednisone (ESHAP) regimen documented that 51% of the 24 transplanted patients were in CR after autoSCT, with 4-year OS and PFS of 39% and 30%, respectively, for the intention-to-treat population [30]. These more disappointing results may be due to the fact that this study excluded ALK$^+$ ALCL patients, whereas the former Italian studies did not.

Reimer et al. reported the results of a prospective multicenter trial in which 83 patients were treated with 6–8 CHOP cycles followed by mobilizing chemotherapy and total body irradiation + cyclophosphamide myeloablative conditioning, with the rescue of autologous stem cells: 55 patients were transplanted, with an intention-to-treat CR rate of 58% and an estimated 3-year OS of 48%, which increased to 71% if the only cohort of transplanted patient was considered [31]. ALK$^+$ ALCL patients were again excluded from the study. Recently published results regarding an extension and update of this trial (involving 111 patients, 68% of whom received autoSCT) confirmed a 59% of CR after myeloablative conditioning, with 5-year OS, DFS, and

PFS rates of 44%, 54%, and 39%, respectively, for the entire patient population [32].

The Nordic Lymphoma Group applied a CHOEP induction strategy (given every 14 days), although omitting etoposide in patients over 60 years, in 160 PTCL patients (again excluding ALK$^+$ ALCL). The fifth or sixth cycle was used as a mobilizing therapy, while the upfront autoSCT was conditioned by carmustine, etoposide, cytarabine, and melphalan (or high-dose cyclophosphamide). The reported CR rate was 51%; the 5-year OS and PFS were 51% and 44% for the entire patient population, respectively [33].

These trials indicate that autoSCT consolidation is able to offer a chance of long-term survival in PTCL patients: nevertheless, it should be noted that a substantial proportion of patients (16–41%) had evidence of disease progression during induction or immediately before transplantation, thus precluding an effective consolidation in a relevant proportion of cases.

12.5.3 Management of Peculiar Disease Subtypes

If on the one hand the management of the most frequent nodal entities relies on a multiagent-based induction followed by autologous stem cell transplantation, if possible and indicated, some specific entities may be managed differently, based on their overall prognosis and on their tendency to disseminate. The management of some peculiar disease subtypes is briefly discussed.

Low-risk ALK$^+$ ALCL (IPI 0/1). Given the overall better prognosis of this disease entity, stem cell transplant is not often considered as part of initial therapy in this category of patients [25]. In particular, those with low IPI score (and more in general those whose IPI score is lower than 3, according to some authors, [11]) may take advantage of an anthracycline-containing induction (either CHOP or CHOEP, as discussed above), without the need of consolidation with autoSCT. Of note, the most relevant trials of autoSCT in PTCL have excluded ALK$^+$ ALCL patients; therefore no definitive conclusions may be drawn for this category of patients regarding the role of autoSCT.

ALK$^-$ breast implant-associated ALCL. Complete surgical excision, which consists of removal of the implant, total capsulectomy, and complete removal of any associated mass with negative margins upon pathological evaluation, is recommended in any patients presenting both with effusion and with tumor masses [34]. Systemic chemotherapy alone is regarded as an insufficient treatment strategy, unless applied after surgical resection: at least 30% of patients undergoing chemotherapy showed unsatisfactory responses or progressed in a recently published series of 87 patients with breast implant-associated ALCL, whereas only 4% of patients had recurrence or progression when treated by complete resection of the implant, tumor tissue, and fibrous capsule [34]. Better OS and PFS rates were described for patients undergoing complete surgical excision if compared to those who received chemotherapy, radiotherapy, or just a limited surgical approach (partial capsulectomy, implant removal or replacement, excisional biopsy of capsule or tumor mass). Multiagent chemotherapy is justified in patients with a tumor mass presentation at onset rather than with effusion only, as they are thought to display a more aggressive clinical behavior, as well as in those whose disease disseminates to nearby and distant nodes; however, any systemic approach should be necessarily preceded by a radical surgical resection [35].

EATL. Patients with EATL display one of the poorest prognoses among all patients with PTCL, with a 5-year OS and progression-free survival (PFS) of only 20% and 4%, respectively, even in case of favorable IPI score. An initial surgical approach is rather common in EATL patients, as many of them show acute abdominal symptoms (bowel perforation, hemorrhage, obstruction) requiring prompt intervention. An intensified induction with ifosfamide, vincristine, etoposide, and methotrexate (IVE/MTX), followed by autologous stem cell transplantation, has demonstrated better outcomes in terms of OS and PFS (60% and 52% at 5 years, respectively) if compared with historical controls receiving standard

anthracycline-containing inductions [36]. Nevertheless, overall toxicity is not negligible, and most of patients are unable to tolerate this aggressive approach or fail to proceed to autoSCT consolidation because of poor performance status after surgery, rapid disease progression, or clinical decay.

SPTCL. Radiation therapy (20–30 Gy), possibly preceded by reductive surgery, should be recommended in patients with localized lesions. Multiple, noncontiguous lesions may be treated with pulse steroids (prednisone or equivalents), at the dose of 0.6–0.7 mg/kg/day × 10 days/month [37]. Systemic chemotherapy with gemcitabine or multiagent chemotherapy (CHOP, CHOP-like) is advisable in case of systemic dissemination or progressive disease [38].

ENKL, nasal type. Management strictly depends on stage at presentation and local versus distant disease spread. Patients with localized ENKL, which indicates a lymphoma that involves the nose and nasal sinuses, may benefit of external radiation therapy (at a dose of at least 50 Gy), which is sometimes the only required treatment. In a recently published cooperative study from Japan [39], concurrent systemic chemotherapy has also been administered in nearly three-quarters of patients, with the dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC) regimen being the most widely used. Patients with primary disease localization other than nose and nasal sinuses rarely show localized disease and require systemic multiagent approaches. ENKL has proved to be particularly sensitive to L-asparaginase, which has been incorporated in several induction schemes, like SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide), which produced higher response rates (79% of ORR, with 45% of CR) if compared to standard anthracycline-containing inductions [40]. Toxicity is however severe, and this regimen should be applied with a careful supportive treatment. An asparaginase-containing regimen, the GELOX (gemcitabine, L-asparaginase, oxaliplatin), has also been applied with concomitant radiotherapy in localized stage ENKL, yielding an ORR of 96%, with at least 74% of patients achieving a CR [41].

12.6 Relapsed and Refractory PTCL

The survival outcome of patients with PTCL who experience relapse or progression following first-line treatment is generally very poor. British Columbia Cancer Agency (BCCA) analyzed 153 patients with relapsed/refractory PTCL diagnosed between 1976 and 2010 and showed that the median PFS and OS after the first recurrence or disease progression were only 3.1 and 5.5 months, respectively, without stem cell transplant [42]. Among patients who relapsed, 91 patients (59%) received systemic chemotherapy, and patients who received chemotherapy after progression/relapse did not have significantly improved survival compared to whom did not with a median PFS and OS of only 3.7 and 6.5 months, respectively. Although the survival outcome was generally very poor, small amounts of patients survived relatively long period without transplant with 3-year OS of 18%. In patients who responded to first-line therapy, normal LDH, good performance status, and one or less extranodal involvement upon relapse were good prognostic factors [42]. There was no significant difference in PFS and OS after first recurrence or disease progression by PTCL subtypes.

The MD Anderson Cancer Center has also assessed the survival outcome of patients with PTCL-NOS and AITL diagnosed between 1999 and 2015 who experienced disease progression or relapse after first-line and subsequent therapy [43]. Within 321 patients who were newly diagnosed with PTCL-NOS (n = 180) or AITL (n = 141), 240 patients (135 PTCL-NOS, 105 AITL) experienced progression/relapse with a median follow-up duration of 52 months. The median PFS and OS after first progression/relapse for patients who did not proceed to stem cell transplantation were 4.0 months (95%CI, 3.1–4.7 months) and 9.2 months (95%CI, 6.9–11.8 months), respectively. With the subsequent relapses, PFS and OS became shorter and shorter, and PFS after second relapse were only 2.5 months and 2.9 months in PTCL-NOS and AITL, respectively. Although with approvals of new drugs for relapsed/refractory PTCL such as

pralatrexate and romidepsin, there was no improvement in PFS and OS by the time of recurrence during this period (1999–2004, 2005–2009, and 2010–2015). Patients who underwent either autologous or allogeneic transplant had longer survival with 5-year OS rates after salvage autologous and allogeneic transplant of 32% and 52%, respectively; the 5-year OS rate for patients who did not undergo transplant was 10%.

The patients with ALCL who experienced disease progression or relapse after first-line were analyzed separately [44]. A total of 176 patients (74 ALK$^+$ ALCL, 102 ALK$^-$ ALCL) diagnosed between 1999 and 2014 were retrospectively analyzed. With a median follow-up of 64 months, 111 patients (38 ALK$^+$ ALCL, 73 ALK$^-$ ALCL) experienced progression/relapse after the first-line therapy. The median PFS following first progression/relapse in patients with ALK$^+$ ALCL and ALK$^-$ ALCL were 5.2 and 3.0 months, respectively. The median OS following second-line therapy in patients with ALK$^+$ ALCL and ALK$^-$ ALCL were 47.3 and 10.8 months, respectively. Interestingly, there were no significant differences in PFS following second-line treatment between ALK$^+$ ALCL and ALK$^-$ ALCL. Patients who experienced recurrent or refractory disease had a poor outcome, with less than 20% long-term disease control rate; however, there seems to be an improvement by newer treatment strategies for relapsed/refractory disease.

12.7 Management of Relapsed and Refractory PTCL

12.7.1 Conventional Chemotherapy

Commonly used traditional salvage chemotherapy regimens for relapsed/refractory PTCL are platinum-containing regimens, such as ifosfamide, carboplatin, and etoposide (ICE); dexamethasone, high-dose Ara-C, and cisplatin (DHAP); and etoposide, methylprednisolone, high-dose Ara-C, and cisplatin (ESHAP), or gemcitabine-based regimens such as gemcitabine, dexamethasone, and cisplatin (GDP) and gemcitabine, dexamethasone, and oxaliplatin (GemOx). There is no big randomized trial comparing conventional salvage chemotherapy at this point, and all abovementioned regimens are considered reasonable options (https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf).

The ORR with ICE ranges from 20 to 70% with 5-year PFS rate of 29% in PTCL from the largest study [45–47]. Hematologic toxicities are the main side effects with about 30% of patients who develop grade 3/4 thrombocytopenia. The ORR with DHAP and ESHAP were 55% and 64%, respectively, in patients with different histologies [48, 49]. DHAP in combination with alemtuzumab was evaluated in relapsed/refractory PTCL and showed remarkable response in PTCL-NOS, with an ORR of 86% and 43% CR, although with very small number of patients [50]. Modified ESHAP regimen, which includes carboplatin instead of cisplatin, showed an ORR of 32% with 18% of CR in patients with relapsed/refractory PTCL [51]. Hematologic toxicities and renal toxicities were the main side effects for both DHAP and ESHAP which were observed in 30–50% and about 20% of cases, respectively.

GDP in relapsed/refractory lymphoma was first evaluated in a phase I study with 22 patients including 5 patients with PTCL [52]. Among five PTCL patients, one achieved a CR and one achieved a PR. Recently, two studies evaluated GDP in patients with relapsed/refractory PTCL. In one study, 25 patients were evaluated for response, and the ORR was 72% with 48% of CR [53]. The median PFS was 9.3 months. GDP was generally well tolerated, with grade 3/4 neutropenia and thrombocytopenia observed in 16% and 13% of cycles, respectively. The other study included 25 patients with relapsed/refractory PTCL-NOS, and the ORR was 64% with 20% of CR [54]. The median PFS was 5.4 months, but patients who responded to GDP had median duration of response of 10.3 months. GemOx was evaluated in 24 elderly (age $\geq$ 60) patients with relapsed/refractory PTCL [55]. The ORR was 38% with 8% of CR after three cycles of GemOx. The median PFS was 10 months. Grade 3/4 neutropenia and thrombocytopenia were observed in 51% and 33% of all delivered courses, respectively.

As described, survival outcome of patients with relapsed/refractory PTCL is usually dismal if stem cell transplant is not an option. Thus, these combination salvage chemotherapies are commonly offered for patients who are to undergo stem cell transplant after such salvage therapy considering higher toxicities. For those who are not transplant candidates, single-agent chemotherapy such as gemcitabine or other novel therapeutic options can be good options.

Phase II studies have evaluated single-agent gemcitabine in T-cell lymphoma, including mycosis fungoides [56–58]. Gemcitabine, given at the dose of 1200 mg/m^2, was administered on days 1, 8, and 15 of a 28-day schedule for 3–6 cycles. In the largest trial evaluating 20 patients with relapsed/refractory PTCL-NOS, ORR was 55% with 30% of CR [58]. Treatment was fairly well tolerated with no grade 3/4 hematologic toxicities observed.

12.7.2 New Approaches

Since 2009, the US Food and Drug Administration (FDA) approved four drugs with novel mechanisms of action for the treatment of patients with recurrent PTCL, including pralatrexate in 2009, brentuximab vedotin (BV) for anaplastic large cell lymphoma in 2011, romidepsin in 2011, and belinostat in 2014.

Pralatrexate, the first drug approved for patients with relapsed/refractory PTCL, is an inhibitor of dihydrofolate reductase, showing more than tenfold higher cytotoxic effect than methotrexate. A pivotal phase II study (PROPEL trial) enrolled 115 patients with relapsed/refractory PTCL. Pralatrexate was given intravenously at 30 mg/m^2/week for 6 weeks followed by 1 week rest (7-week cycles). The ORR was 29% with CR rate of 11%, and 63% of response were observed during first cycle [59]. Of note, 25% of patients who were refractory to prior treatment responded to pralatrexate. When response rates were analyzed based on histology, the ORR of patients with PTCL-NOS ($n = 59$), AITL ($n = 13$), and ALCL ($n = 17$) were 31%, 8%, and 29%, respectively, showing a very low response rate to AITL. The median PFS was 3.5 months in all patients and 10.1 months in responding patients. Severe mucositis (grade 3/4 in 22%) often led to dose delays or interruption. Grade 3/4 thrombocytopenia was observed in 33% of patients.

Histone deacetylase (HDAC) inhibitors are epigenetic modulating agents that keep histones acetylated, leading to differentiation and/or apoptosis in transformed cells. Studies have shown that epigenetic regulation plays an important role in the pathogenesis of PTCL [60], and epigenetic therapies using HDAC inhibitors have shown activity in PTCL. There are two FDA-approved HDAC inhibitors for relapsed/refractory PTCL which are romidepsin and belinostat.

Romidepsin was approved for the treatment of cutaneous T-cell lymphoma in 2009 and for the treatment of relapsed/refractory PTCL in 2011, supported by two phase II trials. The first trial enrolled 47 patients with relapsed/refractory PTCL, and romidepsin was administered intravenously on days 1, 8, and 15 of a 28-day cycle with a starting dose of 14 mg/m^2 [61]. Median number of cycles given was 3 (range, 1–57). The ORR was 38% with CR rate of 18%. Responses were seen even after prior stem cell transplant, and the median duration of response was 8.9 month. Next larger phase II study ($n = 130$) in relapsed/refractory PTCL showed ORR of 25% with CR rate of 15% [62]. Even in patients who were refractory to prior treatment, CR was seen in 18% of patients. There was no significant difference in response by histologic subtypes. The median PFS was 4 months; however, it should be noted that responses were frequently durable and the median duration of response was 28 months [63]. Hematologic toxicities were the most common adverse events, with grade 3/4 thrombocytopenia and neutropenia observed in 24 and 20%, respectively. Several clinical trials are ongoing to evaluate romidepsin combination regimens with chemotherapy or new drugs. A phase I study of romidepsin in combination with ICE was started at the MD Anderson Cancer Center, and preliminary results were reported [64]. Within the 14 patients available for the response evaluation at

the time of analysis, the ORR was 78% with a CR rate of 64%. However, this treatment was also associated with higher rate of hematologic toxicities, and grade 3/4 thrombocytopenia, grade 3/4 neutropenia, and grade 3 anemia occurred in 95%, 84%, and 73% of the cycles, respectively.

Belinostat was the second FDA-approved HDAC inhibitor for treatment of relapsed/refractory PTCL, based on the result of a phase II study (BELIEF trial) [65]. Belinostat 1000 mg/m^2 was administered intravenously on days 1–5 every 21 days. The study enrolled patients with PTCL after a failure of one or more prior systemic therapies. Among the 129 patients enrolled, the ORR was 26% with a CR rate of 10%. The median PFS was only 1.6 months; however the median duration of response was 13.6 months, and the median duration of response was not reached in patients who achieved a CR. Compared to romidepsin, belinostat had less hematologic toxicities, with grade 3/4 thrombocytopenia and neutropenia observed in 7% and 6% of cases, respectively.

BV is an intravenously administered antibody-drug conjugate that consists of the CD30-specific monoclonal antibody conjugated with monomethyl auristatin E by a linker peptide. Binding of the antibody-drug conjugate to CD30 on the cell surface causes internalization of the drug by endocytosis. The drug subsequently travels to the lysosome, causing cell cycle arrest and apoptotic death. BV was studied for the treatment of relapsed/refractory systemic ALCL. In a pivotal phase II study in patients with relapsed/refractory systemic ALCL, BV 1.8 mg/kg was administered intravenously every 3 weeks [66]. The ORR was 86% with a CR rate of 57%, and median time to response was 5.9 weeks. Grade $\geq$ 3 adverse events included neutropenia (21%), thrombocytopenia (14%), peripheral sensory neuropathy (12%), and anemia (7%). Long-term follow-up data were presented in December 2016 and showed durable remission in majority of patients [67]. With a median follow-up of 71.4 months, the 5-year OS and PFS for all the enrolled patients were 60% and 39%, respectively. Median duration of response in patients who achieved a CR was not reached, and 16 patients (8 of them received consolidation transplant) remained in remission without starting any new therapy. In a retrospective study from the MD Anderson Cancer Center [44], patients who received BV at some point during treatment after first-line therapy had significantly longer OS than those who did not (median OS after first progression or relapse: 49.9 vs. 9.6 months). In patients with ALCL who had previously responded to BV and experienced a recurrence after discontinuation of this therapy, retreatment with BV was very frequently effective [68]. In the reported study, response was observed in seven of eight patients (88%) with a CR in five patients (63%) by retreatment. Median duration of response was 12.3 months (range, 6.6–28.0+ months). BV has also been evaluated as a bridging agent to allogeneic transplantation in 24 patients with CD30$^+$ lymphoma refractory to at least two lines of chemotherapy or to autoSCT [69]. In this study, among the five enrolled patients with ALCL, three achieved a CR after four doses of BV and two of them had undergone allogeneic stem cell transplantation (alloSCT). BV is a very effective treatment for relapsed/refractory ALCL; however, once disease progresses on BV, the reported median OS after BV failure was only 3 months with a 2-year OS of 30% [70], indicating a high unmet need for new treatment strategies for patients with BV refractory ALCL disease.

Based on this high efficacy, BV was evaluated in first-line treatment in patients with CD30-positive PTCL [71]. The phase I study of BV (sequential or in combination) in combination of CHOP or CHP (CHOP without vincristine) showed very promising results with manageable toxicities. Of note, the ORR was 100% with CR rate of 84% in 19 patients with ALCL who received BV plus CHP as combination therapy. Long-term follow-up data with a median follow-up of 52 months showed high durable remission, with 4-year PFS and OS rates of 52% and 80%, respectively [72]. Given these very promising results, a phase III study comparing BV plus CHP vs. CHOP for first-line treatment in patients with CD30-positive PTCL (ECHELON-2) is

ongoing and has completed enrolment, awaiting for final results (NCT 01777152, [73]).

BV was also investigated in a rather small number of patients with other PTCL expressing CD30 [74]. In PTCL-NOS, the ORR was 33% with a CR rate of 14%, and median PFS was 7.6 months. The ORR in AITL patients was 54% with a CR rate of 38%, and median PFS was 5.5 months. Interestingly, there was no correlation between immunohistochemical CD30 expression and clinical response.

Several other agents are also evaluated in patients with relapsed refractory PTCL. Bendamustine is nitrogen mustard, consisting of chloroethylamine, an alkylating group, attached to a benzimidazole ring, a purine analog. In a phase II study (BENTLY trial) of 60 patients with relapsed PTCL or cutaneous T-cell lymphoma, bendamustine at the dose of 120 mg/m^2 was administered on days 1 through 2 every 3 weeks for six cycles. Although 33% of patients could not receive more than 3 cycles mainly due to disease progression, the ORR was 50% with a CR rate of 28% [75]. Median PFS was 3.6 months. The median duration of response was 3.5 months, with 30% of responses lasting greater than 6 months. Grade 3/4 neutropenia and thrombocytopenia were seen in 30% and 24% of patients, respectively.

Lenalidomide is an immunomodulatory drug and showed activity to relapsed/refractory PTCL [76–78]. Lenalidomide, at the dose of 25 mg, was given on days 1–21 of each 28-days cycle. A phase II study evaluating lenalidomide monotherapy to PTCL enrolled 29 patients with relapsed/refractory disease: the ORR was 29% with median duration of response of 5 months [77]. Another phase II study focusing on patients with PTCL-NOS showed an ORR of 30% [78]. In a multicenter phase II trial with 54 patients conducted in France, the ORR was 22% with CR rate of 11% [76]. Nonsignificant slightly higher response was seen in patients with AITL with the ORR of 31%. The median PFS and the median duration of response were 2.5 and 3.6 months, respectively. The most common side effects were hematologic toxicities, with grade 3/4 thrombocytopenia and neutropenia observed in 20% and 15% of patients, respectively.

Mogamulizumab is a defucosylated anti-CC chemokine receptor 4 (CCR4) antibody which was initially developed for the treatment of adult T-cell leukemia/lymphoma (ATLL). In a phase II study of 28 patients with relapsed CCR4$^+$ ATLL, single-agent mogamulizumab showed an ORR of 50% with a CR rate of 31%. Median PFS was 5.2 months [79]. Since CCR4 is also expressed in various proportions of PTCL, mogamulizumab was evaluated in patient with CCR4$^+$ relapsed PTCL or cutaneous T-cell lymphoma: among the 38 patient treated, the ORR was 35% with a CR rate of 14%. Median PFS in responders was 5.5 months [80].

Alisertib is an Aurora A kinase inhibitor, which functions as a serine/threonine kinase regulating G2-M transition and centrosome separation during mitosis. Alisertib showed promising response in PTCL in a phase II study including aggressive lymphoma. In this trial, patients received alisertib 50 mg twice daily for 7 days every 21 days. Within 48 patients with relapsed/refractory non-Hodgkin lymphoma treated with alisertib in this trial, 8 had PTCL, and the ORR was 50% [81]. The treatment was associated with substantial hematologic toxicities with grade 3/4 neutropenia and thrombocytopenia seen in 63% and 33% of patients, respectively. In another phase II trial focused on PTCL and mycosis fungoides which enrolled 37 patients, alisertib showed an ORR of 33% in PTCL [82]. Based on these promising results, a phase III multicentre trial (LUMIERE trial) was conducted comparing alisertib to investigator's choice single-agent drug (pralatrexate, gemcitabine, or romidepsin) in relapsed/refractory PTCL. Overall, 238 pts were randomized across 27 countries (120 received alisertib, 118 comparator). ORR with alisertib versus comparator was 33% versus 43%, including 16% versus 25% CR, with no significant differences between the two arms. With a median follow-up of around 9 months, median PFS was 3.7 months and 3.4 months in alisertib and comparator, respectively, and again without significant difference [83]. Based on these results, the trial was discontinued, however, still waiting for final results.

12.7.3 New Combinations

The response rate in relapsed/refractory setting is not satisfactory except for BV for ALCL, and thus currently many clinical trials are evaluating novel combinations to improve outcomes. Romidepsin in combination with alisertib was evaluated in phase I trial, and one in three patients with PTCL enrolled in the study achieved a CR (NCT01897012) [84]. Romidepsin in combination with pralatrexate showed remarkable response rates in relapsed/refractory PTCL in phase I study (NCT01947140) [85]. The ORR was 77% (10/13 patients) with a CR rate of 31%, and the median duration of response was 6.6 months. Romidepsin with lenalidomide was also evaluated in phase I/II trial, and it showed 50% response (5/10 patients) in PTCL (NCT01755975) [86]. These are early phase studies with premature data and further investigations are warranted.

12.8 Hematopoietic Stem Cell Transplant for Relapsed and Refractory Disease

The benefit of autoSCT in patients with relapsed/refractory disease was initially reported rather disappointing, with 5-year PFS after autoSCT being 10–30% [87–90]: therefore, it has been relatively discouraged to consider autoSCT in relapsed/refractory patients. However, more recent data suggest that there is no significant difference in survival outcome (at least in short term) by autoSCT and alloSCT [43]. In a retrospective analysis from the MD Anderson Cancer Center, 76 patients with PTCL underwent autoSCT ($n = 41$) or alloSCT ($n = 35$) in relapsed/refractory disease [87]. The 4-year OS rates were 50% and 36% for autoSCT and alloSCT patients with chemosensitive disease, respectively, and there was no statistical difference. Response prior to SCT is a significant factor to predict survival outcome [87, 91], and thus patients who achieve a CR to salvage chemotherapy would be good candidate for autoSCT consolidation, particularly if there is no option for alloSCT. While the most commonly used high-dose regimen is the combination of carmustine, etoposide, cytarabine, and melphalan (BEAM), alternative conditioning regimens may improve outcomes. Currently, a phase II trial to evaluate romidepsin maintenance therapy after autoSCT is ongoing (NCT01908777).

AlloSCT has shown significant graft-versus-lymphoma effect including response to donor lymphocyte infusion, and thus it may provide effective disease control in relapsed/refractory PTCL [92–97]. The French group has reported the outcome of 77 patients who received alloSCT: the 5-year transplant-related mortality (TRM) was 33%, and the 5-year OS and PFS were 57% and 53%, respectively [96]. In this study, the majority of patients received myeloablative conditioning regimen, and relatively high TRM was a concern. Recently, reduced-intensity conditioning regimen (RIC) is becoming a more standard approach. A phase II study of RIC with alloSCT in 17 patients with relapsed/refractory PTCL showed 3-year OS and PFS rates of 81% and 64%, respectively, with low TRM (6% in 2 years) [92]. The Fred Hutchinson Cancer Center has reported on 17 patients with relapsed/refractory PTCL who underwent RIC alloSCT [97]. The 3-year OS and PFS were 59% and 53%, respectively, with a 3-year TRM of 19%. In a Japanese study, 354 patients (PTCL-NOS, $n = 200$; AITL, $n = 77$; ALCL, $n = 77$) who received alloSCT were retrospectively analyzed [98]. The 3-year TRM rates and the 3-year OS rates in younger patients (16–49 years of age) who received myeloablative regimen were 22% and 43%, and those who received reduced-intensity conditioning regimen (RIC) were 14% and 56%, respectively, suggesting that RIC is a good option even for younger patients.

12.9 Conclusion

PTCL are a group of biologically and clinically heterogeneous disease, and their classification is still evolving. First-line anthracycline-containing regimens, mainly CHOP or CHOEP, are at present the accepted and most widely applied

standard of care, although the best first-line approach is yet to be defined. AutoSCT is regarded as part of the first-line approach, to be performed after induction in transplant-eligible patients. Nevertheless, only a minority of patients could receive transplantation at the right time, mainly because of disease progression during treatment or refractoriness to induction.

Several new drugs are active in relapsed and refractory patients: these drugs are able to induce high OR rates and CR rates, although response durations are limited over time, thus without a significant impact on survival rates. Whether these drugs can be safely and efficiently combined with CHOP or CHOEP in newer first-line regimens to improve the efficacy of standard induction regimens is under investigation.

Allogeneic transplantation in patients achieving a remission after salvage treatment may at present offer the possibility of long-term disease control or even a cure, due to a well-acknowledged graft-versus-lymphoma effect.

References

1. Adams SV, Newcomb PA, Shustov AR. Racial patterns of peripheral T-cell lymphoma incidence and survival in the United States. J Clin Oncol. 2016;34:963–71.
2. Chihara D, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S, et al. Differences in incidence and trends of haematological malignancies in Japan and the United States. Br J Haematol. 2014a;164:536–45.
3. Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014;124:1570–7.
4. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–90.
5. Vose J, Armitage J, Weisenburger D. International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26:4124–30.
6. Iqbal J, Wright G, Wang C, Rosenwald A, Gascoyne RD, Weisenburger DD, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood. 2014;123:2915–23.
7. Broccoli A, Zinzani PL. Peripheral T-cell lymphoma, not otherwise specified. Blood. 2017a;129:1103–12.
8. Thompson PA, Lade S, Webster H, Ryan G, Prince HM. Effusion-associated anaplastic large cell lymphoma of the breast: time for it to be defined as a distinct clinico-pathological entity. Haematologica. 2010;95:1977–9.
9. Ansell S. How to select the frontline treatment for a patient with peripheral T-cell lymphoma. Leuk Lymphoma. 2016;57:783–8.
10. Broccoli A, Zinzani PL. Angioimmunoblastic T-cell lymphoma. Hematol Oncol Clin North Am. 2017b;31:223–38.
11. Corradini P, Marchetti M, Barosi G, Billio A, Gallamini A, Pileri S, et al. SIE-SIES-GITMO guidelines for the management of adult peripheral T- and NK-cell lymphomas, excluding mature T-cell leukaemias. Ann Oncol. 2014;25:2339–50.
12. d'Amore F, Gaulard P, Trümper L, Corradini P, Kim WS, Specht L, et al. Peripheral T-cell lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl. 5):v108–15.
13. Casulo C, Schöder H, Feeney J, Lim R, Maragulia J, Zelenetz AD, et al. ^{18}F-fluorodeoxyglucose positron emission tomography in the staging and prognosis of T cell lymphoma. Leuk Lymphoma. 2013;54:2163–7.
14. Tomita N, Hattori Y, Fujisawa S, Hashimoto C, Taguchi J, Takasaki H, et al. Post-therapy ^{18}F-fluorodeoxyglucose positron emission tomography for predicting outcome in patients with peripheral T cell lymphoma. Ann Hematol. 2015;94:431–6.
15. Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood. 2004;103:2474–9.
16. Went P, Agostinelli C, Gallamini A, Piccaluga PP, Ascani S, Sabattini E, et al. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol. 2006;24:2472–9.
17. Vose JM. International peripheral T-cell lymphoma (PTCL) clinical and pathologic review project: poor outcome by prognostic indices and lack of efficacy with anthracyclines. Blood. 2005;106:811.
18. Federico M, Rudiger T, Bellei M, Nathwani BN, Luminari S, Coiffier B, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the International Peripheral T-cell lymphoma project. J Clin Oncol. 2012;31:240–6.
19. Weisenburger DD, Savage KJ, Harris NL, Gascoyne RD, Jaffe ES, MacLennan KA, et al. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood. 2011;117:3402–8.
20. Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the

International Peripheral T-Cell Lymphoma Project. Blood. 2008;111:5496–504.
21. Au WY, Weisenburger DD, Intraqumtornchai T, Nakamura S, Kim WS, Sng I, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood. 2009;113:3931–7.
22. Delabie J, Holte H, Vose JM, Ullrich F, Jaffe ES, Savage KJ, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. Blood. 2011;118:148–55.
23. Abramson JS, Feldman T, Kroll-Desrosiers AR, Muffly LS, Winer E, Flowers CR, et al. Peripheral T-cell lymphomas in a large US multicentre cohort: prognostication in the modern era including impact of frontline therapy. Ann Oncol. 2014;25:2211–7.
24. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol. 2004;15:1467–75.
25. Chihara D, Fanale MA. Management of anaplastic large cell lymphoma. Hematol Oncol Clin North Am. 2017;31:209–22.
26. Briski R, Feldman AL, Bailey NG, Lim MS, Ristow K, Habermann TM, et al. The role of front-line anthracycline-containing chemotherapy regimens in peripheral T-cell lymphomas. Blood Cancer J. 2014;4:e214.
27. Simon A, Peoch M, Casassus P, Deconinck E, Colombat P, Desablens B, et al. Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol. 2010;151:159–66.
28. Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116:3418–25.
29. Corradini P, Tarella C, Zallio F, Dodero A, Zanni M, Valagussa P, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia. 2006;20:1533–8.
30. Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol. 2008;19(5):958–63.
31. Reimer P, Rüdiger T, Geissinger E, Weissinger F, Nerl C, Schmitz N, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicentre study. J Clin Oncol. 2009;27:106–13.
32. Wilhelm M, Smetak M, Reimer P, Geissinger E, Ruediger T, Metzner B, et al. First-line therapy of peripheral T-cell lymphoma: extension and long-term follow-up of a study investigating the role of autologous stem cell transplantation. Blood Cancer J. 2016;6:e452.
33. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30:3093–9.
34. Clemens MW, Medeiros J, Butler CE, Hunt KK, Fanale MA, Horwitz S, et al. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. J Clin Oncol. 2016;34:160–8.
35. Miranda RN, Aladily TN, Prince HM, Kanagal-Shamanna R, de Jong D, Fayad LE, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol. 2014;32:114–20.
36. Sieniawski M, Angamuthu N, Boyd K, Chasty R, Davies J, Forsyth P, et al. Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. Blood. 2010;115:3664–70.
37. Jang MS, Baek JW, Kang DY, Kang JS, Suh KS, Kim ST. Subcutaneous panniculitis-like T-cell lymphoma: successful treatment with systemic steroid alone. J Dermatol. 2012;39:96–9.
38. Willemze R, Jansen PM, Cerroni L, Berti E, Santucci M, Assaf C, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood. 2008;111:838–45.
39. Yamaguchi M, Suzuki R, Oguchi M, Asano M, Amaki J, Akiba T, et al. Treatments and outcomes of patients with extranodal natural killer/T-cell lymphoma diagnosed between 2000 and 2013: a cooperative study in Japan. J Clin Oncol. 2017;35:32–9.
40. Yamaguchi M, Kwong YL, Kim WS, Maeda Y, Hashimoto C, Suh C, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-cell tumor study group study. J Clin Oncol. 2011;29:4410–6.
41. Wang L, Wang Z, Chen X, Li YJ, Wang KF, Xia YF, et al. First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer. 2013;119:348–55.
42. Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol. 2013;31:1970–6.
43. Chihara D, Fanale MA, Miranda RN, Noorani M, Westin JR, Nastoupil LJ, et al. The survival outcome of patients with relapsed/refractory peripheral T-cell lymphoma-not otherwise specified and angioimmunoblastic T-cell lymphoma. Br J Haematol. 2017;176:750–8.

44. Chihara D, Fanale M, Noorani M, Westin JR, Nastoupil L, Hagemeister F, et al. The survival outcome of the patients with relapsed/refractory anaplastic large-cell lymphoma. Blood. 2015;126:2738.
45. Mikesch JH, Kuhlmann M, Demant A, Krug U, Thoennissen GB, Schmidt E, et al. DexaBEAM versus ICE salvage regimen prior to autologous transplantation for relapsed or refractory aggressive peripheral T cell lymphoma: a retrospective evaluation of parallel patient cohorts of one center. Ann Hematol. 2013;92:1041–8.
46. Moskowitz CH, Bertino JR, Glassman JR, Hedrick EE, Hunte S, Coady-Lyons N, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. J Clin Oncol. 1999;17:3776–85.
47. Zelenetz AD, Hamlin P, Kewalramani T, Yahalom J, Nimer S, Moskowitz CH. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol. 2003;14(Suppl. 1):i5–i10.
48. Velasquez WS, Cabanillas F, Salvador P, McLaughlin P, Fridrik M, Tucker S, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood. 1988;71:117–22.
49. Velasquez WS, McLaughlin P, Tucker S, Hagemeister FB, Swan F, Rodriguez MA, et al. ESHAP—an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol. 1994;12:1169–76.
50. Kim SJ, Kim K, Kim BS, Suh C, Huh J, Ko YH, et al. Alemtuzumab and DHAP (A-DHAP) is effective for relapsed peripheral T-cell lymphoma, unspecified: interim results of a phase II prospective study. Ann Oncol. 2009;20:390–2.
51. Kogure Y, Yoshimi A, Ueda K, Nannya Y, Ichikawa M, Nakamura F, et al. Modified ESHAP regimen for relapsed/refractory T cell lymphoma: a retrospective analysis. Ann Hematol. 2015;94:989–94.
52. Emmanouilides C, Colovos C, Pinter-Brown L, Hernandez L, Schiller G, Territo M, et al. Pilot study of fixed-infusion rate gemcitabine with cisplatin and dexamethasone in patients with relapsed or refractory lymphoma. Clin Lymphoma. 2004;5:45–9.
53. Park BB, Kim WS, Suh C, Shin DY, Kim JA, Kim HG, et al. Salvage chemotherapy of gemcitabine, dexamethasone, and cisplatin (GDP) for patients with relapsed or refractory peripheral T-cell lymphomas: a consortium for improving survival of lymphoma (CISL) trial. Ann Hematol. 2015;94:1845–51.
54. Qi F, Dong M, He X, Li Y, Wang W, Liu P, et al. Gemcitabine, dexamethasone, and cisplatin (GDP) as salvage chemotherapy for patients with relapsed or refractory peripheral T cell lymphoma-not otherwise specified. Ann Hematol. 2017;96:245–51.
55. Yao YY, Tang Y, Zhu Q, Zhuang Y, Cheng YM, Wang L, et al. Gemcitabine, oxaliplatin and dexamethasone as salvage treatment for elderly patients with refractory and relapsed peripheral T-cell lymphoma. Leuk Lymphoma. 2013;54:1194–200.
56. Sallah S, Wan JY, Nguyen NP. Treatment of refractory T-cell malignancies using gemcitabine. Br J Haematol. 2001;113:185–7.
57. Zinzani PL, Magagnoli M, Bendandi M, Orcioni GF, Gherlinzoni F, Albertini P, et al. Therapy with gemcitabine in pretreated peripheral T-cell lymphoma patients. Ann Oncol. 1998;9:1351–3.
58. Zinzani PL, Venturini F, Stefoni V, Fina M, Pellegrini C, Derenzini E, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol. 2010;21:860–3.
59. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol. 2011;29:1182–9.
60. Piekarz RL, Robey RW, Zhan Z, Kayastha G, Sayah A, Abdeldaim AH, et al. T-cell lymphoma as a model for the use of histone deacetylase inhibitors in cancer therapy: impact of depsipeptide on molecular markers, therapeutic targets, and mechanisms of resistance. Blood. 2004;103:4636–43.
61. Piekarz RL, Frye R, Prince HM, Kirschbaum MH, Zain J, Allen SL, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood. 2011;117:5827–34.
62. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol. 2012;30:631–6.
63. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. J Hematol Oncol. 2014;7:11.
64. Chihara D, Oki Y, Fayad L, Wesson E, Ruben C, Horowitz SB, et al. Phase I study of romidepsin in combination with ICE (ifosfamide, carboplatin and etoposide) in patients with relapsed or refractory peripheral T-cell lymphoma. Blood. 2014b; 124:1748.
65. O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, et al. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: results of the Pivotal Phase II BELIEF (CLN-19) Study. J Clin Oncol. 2015a;33:2492–9.
66. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol. 2012;30:2190–6.
67. Pro B, Advani RH, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, et al. Five-year survival data from a pivotal phase 2 study of brentuximab vedotin in patients

with relapsed or refractory systemic anaplastic large cell lymphoma. Blood. 2016;128:4144.
68. Bartlett NL, Chen R, Fanale MA, Brice P, Gopal A, Smith SE, et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. J Hematol Oncol. 2014;7:24.
69. Gibb A, Jones C, Bloor A, Kulkarni S, Illidge T, Linton K, et al. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK center. Haematologica. 2013;98:611–4.
70. Oki Y, Feldman T, Chihara D, Fanale MA, Connors JM, Wong S, et al. Prognostic factors in patients with relapsed or refractory systemic anaplastic large T-cell lymphoma (ALCL) receiving brentuximab vedotin and outcome after treatment failure. Hematol Oncol. 2017;35(Suppl S2):252.
71. Fanale MA, Horwitz SM, Forero-Torres A, Bartlett NL, Advani RH, Pro B, et al. Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. J Clin Oncol. 2014;32:3137–43.
72. Fanale MA, Horwitz SM, Forero-Torres A, Bartlett NL, Advani RH, Pro B, et al. Four-year survival and durability results of brentuximab vedotin in combination with CHP in the frontline treatment of patients with CD30-expressing peripheral T-cell lymphomas. Blood. 2016;128:2993.
73. O'Connor OA, Pro B, Illidge T, Trumper LH, Larsen EK, Kennedy DA. Phase 3 trial of brentuximab vedotin and CHP versus CHOP in the frontline treatment of patients (pts) with CD30+ mature T-cell lymphomas (MTCL). J Clin Oncol. 2014;32(Suppl 15):TPS8612.
74. Horwitz SM, Advani RH, Bartlett NL, Jacobsen ED, Sharman JP, O'Connor OA, et al. Objective responses in relapsed T-cell lymphomas with single agent brentuximab vedotin. Blood. 2014;123:3095–100.
75. Damaj G, Gressin R, Bouabdallah K, Cartron G, Choufi B, Gyan E, et al. Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLEY trial. J Clin Oncol. 2013;31:104–10.
76. Morschhauser F, Fitoussi O, Haioun C, Thieblemont C, Quach H, Delarue R, et al. A phase 2, multicentre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide (Revlimid) in subjects with relapsed or refractory peripheral T-cell non-Hodgkin lymphoma: the EXPECT trial. Eur J Cancer. 2013;49:2869–76.
77. Toumishey E, Prasad A, Dueck G, Chua N, Finch D, Johnston J, et al. Final report of a phase 2 clinical trial of lenalidomide monotherapy for patients with T-cell lymphoma. Cancer. 2015;121:716–23.
78. Zinzani PL, Pellegrini C, Broccoli A, Stefoni V, Gandolfi L, Quirini F, et al. Lenalidomide monotherapy for relapsed/refractory peripheral T-cell lymphoma not otherwise specified. Leuk Lymphoma. 2011;52:1585–8.
79. Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, Yoshida S, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol. 2012;30:837–42.
80. Ogura M, Ishida T, Hatake K, Taniwaki M, Ando K, Tobinai K, et al. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. J Clin Oncol. 2014;32:1157–63.
81. Friedberg JW, Mahadevan D, Cebula E, Persky D, Lossos I, Agarwal AB, et al. Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas. J Clin Oncol. 2014;32:44–50.
82. Barr PM, Li H, Spier C, Mahadevan D, LeBlanc M, Ul Haq M, et al. Phase II intergroup trial of alisertib in relapsed and refractory peripheral T-cell lymphoma and transformed mycosis fungoides: SWOG 1108. J Clin Oncol. 2015;33:2399–404.
83. O'Connor OA, Ozcan M, Jacobsen E, Vidal JMR, Trotman J, Demeter J. First multicenter, randomized phase 3 study in patients (pts) with relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL): alisertib (MLN8237) versus investigator's choice (Lumiere trial; NCT01482962). Blood. 2015b;126:341.
84. Fanale MA, Wang Z, Ma W, Oki Y, Hagemeister FB, Fayad LE, et al. Gene expression profiling for molecular features of response in a phase I trial of alisertib plus romidepsin for relapsed/refractory aggressive B- and T-cell lymphomas. Blood. 2015; 126:2705.
85. Amengual JE, Lichtenstein R, Rojas C, Sawas A, Deng C, Lichtenstien E, et al. The pralatrexate—romidepsin doublet: a well tolerated and highly effective combination for patients with relapsed or refractory peripheral T-cell lymphoma. Blood. 2016;128:1824.
86. Mehta-Shah N, Lunning MA, Boruchov AM, Ruan J, Nair S, Lynch P, et al. A phase I/II trial of the combination of romidepsin and lenalidomide in patients with relapsed/refractory lymphoma and myeloma: activity in T-cell lymphoma. J Clin Oncol. 2015;33(Suppl 15):8521.
87. Beitinjaneh A, Saliba RM, Medeiros LJ, Turturro F, Rondon G, Korbling M, et al. Comparison of survival in patients with T cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. Biol Blood Marrow Transplant. 2015;21:855–9.
88. Chen AI, McMillan A, Negrin RS, Horning SJ, Laport GG. Long-term results of autologous hematopoietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. Biol Blood Marrow Transplant. 2008;14:741–7.
89. Jantunen E, Wiklund T, Juvonen E, Putkonen M, Lehtinen T, Kuittinen O, et al. Autologous stem cell transplantation in adult patients with peripheral T-cell lymphoma: a nation-wide survey. Bone Marrow Transplant. 2004;33:405–10.

90. Smith SD, Bolwell BJ, Rybicki LA, Brown S, Dean R, Kalaycio M, et al. Autologous hematopoietic stem cell transplantation in peripheral T-cell lymphoma using a uniform high-dose regimen. Bone Marrow Transplant. 2007;40:239–43.
91. Kim MK, Kim S, Lee SS, Sym SJ, Lee DH, Jang S, et al. High-dose chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: complete response at transplant predicts survival. Ann Hematol. 2007;86:435–42.
92. Corradini P, Dodero A, Zallio F, Caracciolo D, Casini M, Bregni M, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol. 2004;22:2172–6.
93. Dodero A, Spina F, Narni F, Patriarca F, Cavattoni I, Benedetti F, et al. Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas: long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. Leukemia. 2012;26:520–6.
94. Kim SW, Yoon SS, Suzuki R, Matsuno Y, Yi HG, Yoshida T, et al. Comparison of outcomes between autologous and allogeneic hematopoietic stem cell transplantation for peripheral T-cell lymphomas with central review of pathology. Leukemia. 2013;27:1394–7.
95. Jacobsen ED, Kim HT, Ho VT, Cutler CS, Koreth J, Fisher DC, et al. A large single-center experience with allogeneic stem-cell transplantation for peripheral T-cell non-Hodgkin lymphoma and advanced mycosis fungoides/Sezary syndrome. Ann Oncol. 2011;22:1608–13.
96. Le Gouill S, Milpied N, Buzyn A, De Latour RP, Vernant JP, Mohty M, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol. 2008;26:2264–71.
97. Shustov AR, Gooley TA, Sandmaier BM, Shizuru J, Sorror ML, Sahebi F, et al. Allogeneic haematopoietic cell transplantation after nonmyeloablative conditioning in patients with T-cell and natural killer-cell lymphomas. Br J Haematol. 2010;150:170–8.
98. Aoki K, Suzuki R, Chihara D, Suzuki T, Kim S-W, Fukuda T, et al. Reduced-intensity conditioning of allogeneic transplantation for nodal peripheral T-cell lymphomas. Blood. 2014;124:2585.