Past, present and future therapeutic approaches in nodal peripheral T-cell lymphomas

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Abstract

Peripheral T-cell lymphomas (PTCL) encompass over 30 different entities and although they share post-thymic T- or NK-cell derivation, the disease biology and genomic landscape are very diverse across subtypes. In Western populations, nodal PTCL are the most frequently encountered entities in clinical practice and although important achievements have been made in deciphering the underlying biology and in therapeutic advances, there are still large gaps in disease understanding and clinical scenarios in which controversy over best practice continues. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-based chemotherapy continues to be the 'standard' treatment, with the addition of brentuximab vedotin (BV) in the combination CHP (cyclosphosphamide, doxorubicin, prednisone)-BV representing a new treatment paradigm in $CD30^+$ PTCL although its benefit is less certain in the non-anaplastic large cell lymphoma subtypes. Given the high risk of relapse, consolidative autologous stem cell transplant is considered in nodal PTCL, outside of ALK-positive anaplastic large cell lymphoma; however, in the absence of a randomized controlled trials, practices vary. Beyond CHP-BV, most study activity has focused on adding a novel agent to CHOP (i.e., CHOP + drug X). However, with high complete remission rates observed with some novel therapy combinations, these regimens are being tested in the front-line setting, with a particular rationale in follicular helper T-cell lymphomas which have a clear sensitivity to epigenetic modifying therapies. This is well exemplified in the relapsed/refractory setting in which rational combination therapies are being developed for specific subtypes or guided by underlying biology. Taken together, we have finally moved into an era of a more personalized approach to the management of nodal PTCL.

Introduction

Peripheral T-cell lymphomas (PTCL) represent approximately 10% of all non-Hodgkin lymphomas although geographic variation is notable.[1,2] In 2022, both the World Health Organization (WHO) 5th edition lymphoma classification update (WHO-HAEM5)[1] and the new International Consensus Classification (ICC)[2] were published. These two publications contained classification refinements, including for mature T/NK-cell neoplasms. Most of these refinements are concordant in the two classification systems, although there a few exceptions (see Table 1 in the Introduction to the Review Series on Lymphoma published in this issue of *Haematologica*[3]). The so-called 'nodal' PTCL subtypes, grouped to separate them from predominantly leukemic, extranodal and cutaneous subtypes of PTCL, represent about 60% of all PTCL in Western populations, and include PTCL not otherwise specified (NOS), anaplastic large cell lymphoma (ALCL) and follicular helper T-cell lymphomas. The last group are referred to as nodal T-follicular helper lymphomas in the WHO-HAEM5 and are considered a family of three lymphomas – angioimmunoblastic type (angioimmunoblastic T-cell lymphoma [AITL]), a NOS type and a follicular type – whereas the ICC describes one entity, follicular helper T-cell lymphoma, with three subtypes (angioimmunoblastic type, follicular type and NOS).[3] For the purpose of this review, they are collectively referred to as TFHL with specific subtypes referenced where appropriate. In addition, a new rare nodal PTCL subtype is now recognized, primary nodal Epstein-Barr virus $(EBV)^+$ T/NK-cell lymphoma in the ICC (provisional entity) or EBV^+ nodal T/NK-cell lymphoma in WHO-HAEM5 (distinct entity) (Table 1 in the Introduction to the Review Series[3]) which, in addition to being EBV^+, has an activated cytotoxic phenotype (TIA^+ ± granzyme B/perforin) and a poor outcome that is more similar to that of extranodal NK/T-cell lymphoma.[4]
While progress in PTCL has lagged behind that in B-cell lymphomas, the past decade has been a period of great advancement, both in elucidating disease pathogenesis and in the development of new therapies. Recognizing that drug

Table 1. Largest retrospective series including nodal peripheral T-cell lymphomas treated with primarily anthracycline-based chemotherapy.

First author Study	Period of PTCL diagnosis (age for enrollment)	Nodal PTCL subtypes	N	Received CHOP/CHOP-like therapy, %	5-year PFS %	5-year OS %
Vose[7a] International Peripheral T-cell Lymphoma Project	1990-2002 (≥19 yrs)	PTCL-NOS	340	80	20	32
		AITL	243	82	18	32
		ALK⁻ ALCL	72	95	36	49
		ALK⁺ ALCL	87	88	60	70
Ellin[8] Swedish Registry	2000-2009 (≥18 yrs)	PTCL-NOS	256	84 (All)[b]	21	28
		AITL	104		20	32
		ALK⁻ ALCL	115		38	31
		ALK⁺ ALCL	68		63	79
Brink[9] Netherlands Cancer Registry	1989-2018 (18-65 yrs)	PTCL-NOS	692	NR[c]	NR	32
		AITL	294			44
		ALK⁻ ALCL	89			52
		ALK⁺ ALCL	139			72

[a]Median follow-up reported in subsequent subtype-specific publications. [b]Treatment information was available for 708/757 cases of peripheral T-cell lymphoma: 84% received CHOP/CHOP-like chemotherapy but this estimate includes other non-cutaneous, non-leukemic subtypes. [c]In the whole cohort 1,369/1,427 (96%) patients received chemotherapy but type was not specified with the overall survival estimates. PTCL: peripheral T-cell lymphoma; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; PFS: progression-free survival; OS: overall survival; yrs; years; NOS: not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; ALK: anaplastic lymphoma kinase; ALCL: anaplastic large cell lymphoma; NR: not reported.

sensitivities may be different, clinical trials have evolved to focus specifically on PTCL and more recently, on specific subtypes.

With the exception of ALCL, in which brentuximab vedotin (BV)-CHP (cyclosphosphamide, doxorubicin, prednisone) is considered the new standard treatment, uncertainty remains regarding the optimal front-line therapeutic regimen and the role of consolidative high-dose chemotherapy and autologous stem cell transplant (auto-SCT). This is particularly apparent in TFHL in which sensitivity to epigenetic therapies has led to numerous studies evaluating chemotherapy-free, novel therapy combination treatment approaches, also in treatment-naïve patients. Furthermore, as the genomic landscape is uncovered, evolving studies are targeting specific pathway vulnerabilities (e.g., Janus kinase [JAK]/signal transducer and activator of transcription [STAT], phosphatidyl inositol 3 kinase [PI3K]) as well as integrating biological correlates in an effort to understand biomarkers of response and resistance. As a follow-up to the nodal PTCL pathobiology paper by Bisig, Savage and de Leval in this issue, we review the history of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and transplant for nodal PTCL, highlight new treatment advances in the front-line and relapsed/refractory (R/R) settings as well as the promise of a more 'personalized' therapy approach.

The origin of CHOP and impact of prognostic factors in PTCL

Almost 30 years ago, the landmark Southwest Oncology Group (SWOG) phase III study established the CHOP regimen as the standard combination chemotherapy for all aggressive lymphomas. The study was conducted when diagnoses were based on the Working Formulation, and prior to the integration of routine immunophenotyping, but CHOP treatment was similarly adopted for PTCL.[6] Several large, retrospective series have documented the poor outcome in most patients with PTCL treated with primarily anthracycline-based chemotherapy, including subtype-specific results (Table 1).[7-9] Notably, there is limited information on the new entity, primary nodal EBV⁺ T/NK-cell lymphoma, but it appears to have an outcome that is inferior to that of PTCL-NOS.[4] In these series, given their only recent recognition, primary nodal EBV⁺ T/NK-cell lymphoma and TFHL other than AITL, are combined in the PTCL-NOS subgroup. Of note, the International Prognostic Index (IPI) effectively stratifies patients with PTCL-NOS and ALCL into risk groups[7,10-12] but its usefulness in AITL has been more limited given that most patients fall into a high-risk category.[7,13,14] Overall, patients with ALK⁺ ALCL have a more favorable outcome, although this is in part driven by a younger age at diagnosis and, importantly, those with a high IPI score have a poor outcome, not unlike that of patients with other PTCL subtypes (IPI score ≥3; 5-year progression-free survival [PFS] 23-54%; 5-year overall survival [OS] 23-62%).[10,15] Outcomes are also better in ALK⁻ ALCL,[7-11] a finding that is more evident in larger series and with central pathology review, given the potential for mis-diagnosis as CD30⁺ PTCL-NOS. The outcome of ALK⁻ ALCL may also be impacted by the proportion of cases with *DUSP22* rearrangement and/or *P63* rearrangement, as outlined by Bisig, Savage and de Leval.[5] A recent study suggested that the presence of *TP53* mutations correlates with an inferior PFS in patients treated with

CHOP or CHOP-like chemotherapy and is found in approximately one-third of cases of ALK⁻ ALCL and PTCL-NOS.[16] Overall, longer term follow-up is important in PTCL since, among patients alive and event-free at 24 months, the 5-year risk of subsequent relapse is still 23% for nodal PTCL, compared to only 7% in a prior study of diffuse large B-cell lymphoma.[17,18]

There has been some debate on whether anthracyclines are essential for cure, particularly in PTCL-NOS and AITL,[7,19] leading to studies exploring alternative combination therapy regimens. The UK National Cancer Research Institute (NCRI) Lymphoma Clinical study group compared CHOP to GEM-P (gemcitabine, solumedrol, cisplatin) in a randomized phase II study (CHEMO-T), but results were similar with a 2-year PFS of 37% *versus* 38%, respectively (*P*=0.82) and a 2-year OS of 51% *versus* 64%, respectively (*P*=0.31).[20] Although exploratory, patients with PTCL-NOS (as well as enteropathy-associated T-cell lymphoma) had a significantly better outcome with CHOP (odds ratio [OR]=0.036; *P*=0.012). In contrast, outcomes by treatment arm were similar in AITL (OR=0.69; *P*=0.578). The SWOG PEGS (cisplatin, etoposide, gemcitabine, solumedrol) regimen, built on the premise of using drugs not effluxed by multidrug resistance-1/permeability glycoprotein (MDR-1/P-gp), gave disappointing results with a 2-year PFS of only 12%, which may also reflect the absence of cyclophosphamide in the regimen. Although data are very limited, CHOP appears to be suboptimal in primary nodal EBV⁺ T/NK-cell lymphoma and it may be that regimens used in extranodal NK/T-cell lymphoma are more appropriate in this entity but this requires further study. Taken together, CHOP appears to be most important in ALCL, variably effective in PTCL-NOS especially given disease heterogeneity, and there is less certainty in AITL. Notably, there are limited data on outcomes with CHOP in the other TFHL subtypes.[21]

More intensive regimens, including the integration of etoposide, have also been explored in the front-line treatment of PTCL. This was first evaluated in a retrospective analysis of all patients with a PTCL diagnosis enrolled on prospective German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) studies (now called the German Lymphoma Alliance [GLA]).[18] An improved event-free survival was observed in young (≤60 years), good-risk (normal lactate dehydrogenase level) patients who received etoposide with a front-line CHOP/CHOP-like regimen; however, the benefit was most evident in ALK⁺ ALCL (3-year event-free survival: 91% *vs*. 57%; *P*=0.01) with a trend observed in other nodal PTCL subtypes (3-year event-free survival: 61% *vs*. 48.3%; *P*=0.057). The findings did not translate into an OS benefit, and it was an unadjusted analysis.[22] Other studies have supported improved outcomes with CHOP plus etoposide (CHOEP) over CHOP alone specifically in ALK⁺ ALCL,[9,12] but this is also the group that derives the greatest benefit from upfront BV-CHP as outlined below. Results with CHOEP are more mixed in the other nodal PTCL.[8,9] In the Netherlands Cancer Registry (NCR), there was no OS benefit of CHOEP over CHOP in a multivariate analysis when adjusted for the IPI score and use of auto-SCT.[9] Taken together, CHOEP may still be considered a chemotherapy alternative in select patients but should be avoided in older patients given additional toxicity and lack of firm evidence of benefit.

Randomized front-line studies in PTCL

The earliest phase III randomized controlled study was conducted by the Groupe Ouest Est d'Etude des Leucemies et Autres Maladies due Sang (GOELAMS) comparing a dose-intensive regimen, VIP-reinforced-ABVD (etoposide, ifosfamide, cisplatin; doxorubicin, bleomycin, vinblastine, decarbazine), to CHOP in newly diagnosed PTCL, including patients with ALCL (ALK status not specified), who represented almost half of enrolled patients (42/86). There was no difference in 2-year event-free survival which was 45% for all patients.[23]

The most significant advancement to date in the treatment of nodal PTCL has been the impact of BV in ALCL. BV is an anti-CD30 antibody-drug conjugate linked to the anti-tubulin agent monomethyl auristatin E and was initially developed and approved for classical Hodgkin lymphoma and systemic ALCL in the R/R setting (see below). A phase I study established the safety and promise of CHP-BV in CD30⁺ PTCL (n=26 [ALCL n=19]: 5-year PFS 52%, 5-year OS 80%), with the omission of vincristine due to overlapping peripheral neuropathy with BV.[24] The subsequent practice-changing, double-blind, double-dummy, randomized phase III ECHELON-2 trial demonstrated improved PFS (3-year: 57.1% *vs*. 44.4%; *P*<0.011) and OS (3 year: 76.8% *vs*. 69.1%; *P*=0.024) with BV-CHP compared to CHOP, in 552 newly diagnosed patients with CD30⁺ PTCL (CD30 ≥10%; ALK⁺ ALCL (IPI score ≥2 only).[25] Results were maintained in the 5-year update (5-year PFS 51.4% *vs*. 43%; *P*=0.0077 and 5-year OS 70.1% *vs*. 61%; *P*=0.042).[25,26] The benefit was most striking in ALCL (5-year PFS 60.6% *vs*. 48.4%; *P*=0.0009 and 5-year OS 75.8% *vs*. 68.7%; *P*=0.053). As a regulatory requirement, the study was powered to evaluate ALCL, and the non-ALCL subtypes were under-represented (AITL n=54, PTCL-NOS n=72). As a result, the statistical comparisons for AITL and PTCL-NOS were unplanned and underpowered but since confidence intervals all crossed 1, the benefit of BV-CHP remains uncertain.[26] This also led to differences in regulatory approval of BV-CHP, with the USA Food and Drug Administration including the intent-to-treat population of CD30⁺ PTCL eligible for the study, Health Canada approving it for ALCL and CD30⁺ PTCL-NOS or AITL only, whereas in Europe and the UK, BV-CHP is only approved for ALCL.

Several additional comments can be made about ECHE-

LON-2. The study was restricted to cases with CD30 expression of ≥10% but regulatory approval did not specify a CD30 cutoff. A separate phase II study in CD30$^+$ (<10%) PTCL is ongoing (NCT04569032) (*Online Supplementary Table S1*). Previous studies in R/R PTCL have not shown a good correlation between CD30 expression and response to BV, which may reflect the insensitivity of immunohistochemical detection or a broader mechanism of action, targeting the microenvironment.[27,28] In addition, information on the presence of *DUSP22* and *P63* rearrangements in ALK$^-$ ALCL is not available, which could have an impact on prognosis. Some have also argued whether CHOP is the appropriate comparator. Although CHOEP is an option in PTCL, in the absence of randomized controlled studies, it has not replaced CHOP as a preferred standard therapy. The strongest retrospective data for the use of CHOEP are those for ALK$^+$ ALCL, but this is also the group with excellent outcomes with CHP-BV in ECHELON-2 with a 5-year PFS of 87% *versus* 67% (P=0.0372), despite restriction to patients with an IPI score ≥2. Outcomes were also more favorable in ALK$^-$ ALCL, although there is still room for improvement (5-year PFS 49% *vs*. 39%; P=0.0054).[26] A separate phase II study explored CHEP-BV (cyclophosphamide, doxorubicin, etoposide, prednisone plus BV) in CD30$^+$ PTCL, including ALCL, with encouraging results (objective response rate [ORR] 91%, complete response [CR 80%]), but the rate of febrile neutropenia was 21% with routine granulocyte colony-stimulating factor support.[29] This regimen may be taken into consideration in very high-risk, younger ALCL patients especially those with an elevated central nervous system risk (e.g., high lactate dehydrogenase, involvement of multiple extranodal sites), given the additional penetration of etoposide across the blood-brain barrier, which does not appear to occur with BV.[29]

Romidepsin and alemtuzumab have also been evaluated in combination with CHOP/CHOP-like therapy in phase III trials. Romidepsin is a selective histone deacetylase (HDAC) inhibitor and demonstrated modest efficacy in a phase II study in R/R PTCL (see below), ultimately leading to a phase III Lymphoma Study Association (LYSA) study evaluating romidepsin plus CHOP (Ro-CHOP) *versus* CHOP in previously untreated PTCL, excluding ALK$^+$ ALCL.[30] The addition of romidepsin did not translate into an improved PFS in the intention-to-treat population (P=0.096) and was associated with increased toxicity.[30] The negative results have unfortunately led to de-listing of romidepsin in the R/R setting in the USA and Canada (see below). Alemtuzumab is an anti-CD52 humanized monoclonal antibody. CD52 antigen is a glycosylphosphatidylinositol-linked glycoprotein that is expressed on lymphocytes and monocytes and is variably expressed in PTCL.[31] Alemtuzumab (A) and CHOP-14 (or CHOEP-14) *versus* CHOP-14 (or CHOEP-14) were evaluated in a collaboration between the Nordic and DSHNHL/GLA groups in parallel, phase III studies in younger (CHOEP-14, 18-65 years; ACT-1 trial)[32] and older (CHOP-14, >65 years; ACT-2 trial)[33] patients with newly diagnosed PTCL, the former incorporating auto-SCT into both treatment arms. In ACT-2, the 3-year event-free survival was 27% *versus* 24% in the A-CHOP and CHOP arms, respectively (P=0.248) and the experimental arm was associated with significant toxicity.[33] Similarly, there was no benefit of A-CHOP observed in the ACT-1 trial (3-year event-free survival: A-CHOP 35% *vs*. 26%).[32]

Role of consolidative autologous transplant in front-line treatment of nodal PTCL: how strong is the evidence?

With the high relapse rate in PTCL, auto-SCT is often considered in first remission. However, in the absence of randomized controlled studies, there is a lack of consensus and, as a result, guidelines, as well as clinical practice, vary. This is highlighted in the randomized studies above in which use of consolidative auto-SCT was at the investigators' discretion in the ECHELON-2 (blinded) trial, not allowed in the Ro-CHOP study and was integrated into both treatment arms in the younger patients in the ACT-1 study.[26,30,34] Overall, it is challenging to compare studies with the inclusion of diverse subtypes, variable responses leading into the transplant and analyses either in an 'intent to transplant' population or from the point of view of auto-SCT with the comparison group for the latter often including non-responders (Table 2).[35-37]

The largest prospective study evaluating consolidative auto-SCT was conducted by the Nordic Lymphoma Group (NLG-T-01),[38] which enrolled 115 patients with newly diagnosed PTCL, excluding ALK$^+$ ALCL, in 24 centers. Patients received CHOEP or CHOP-14 (>60 years) and 70% proceeded to auto-SCT. With a median follow-up of 5 years, the 5-year PFS and OS were 44% and 51%, respectively. With uncertainty around auto-SCT, the GLA and LYSA study groups conducted a phase III study comparing consolidative auto-SCT to allogeneic (allo)-SCT in newly diagnosed, poor-risk PTCL following four courses of CHOEP and one course of DHAP (dexamethasone, high-dose cytarabine, cisplatin); however, this study was stopped early due to futility.[39] Ultimately, with an overall transplant rate of 65%, the 3-year event-free survival was 43% in the allo-SCT group and 38% in the auto-SCT group. Notably, the 3-year cumulative incidence of relapse was 40% in the auto-SCT group and 0% in the allo-SCT group, supporting a graft-*versus*-lymphoma effect; however, non-relapse mortality was significantly higher in the allo-SCT group (3-year 23% *vs*. 0%), offsetting any overall benefit.[39]

Retrospective studies have given conflicting results regarding the benefit of consolidative auto-SCT (Table 2).[8,9,40] The LYSA group performed a propensity score matched analysis of auto-SCT in an intention-to-treat population of nodal PTCL patients (n=269) and did not find a PFS or OS benefit

of auto-SCT in multivariate analysis. In contrast, the NCR noted improved OS in patients with nodal PTCL (excluding ALK$^+$ ALCL) treated in the more recent era when auto-SCT was more routinely applied. Furthermore, in a multivariate analysis of patients diagnosed between 2014-2018 who received CHOP or CHOEP, omission of auto-SCT with primary therapy was associated with a higher risk of death in patients with non-ALK$^+$ ALCL subtypes.[9] As this analysis was

Table 2. Selected large studies evaluating consolidative autologous stem cell transplant in nodal peripheral T-cell lymphomas.

First author Study type[a]	Benefit of auto-SCT	Response prior to auto-SCT CR/PR, %	Outcome of intent to auto-SCT (*vs.* no auto-SCT)		Outcome after auto-SCT (*vs.* no auto-SCT)		Comment auto-SCT
			PFS, %	OS, %	PFS, %	OS, %	
Reimer[108]/ Wilhelm[109] Phase II	Maybe	62/20[e]	3-yr, 36[e] 5-yr, 39	3-yr, 48 5-yr, 44	NR	3-yr, 71 (*vs.* 11)* 5-yr, 57 (*vs.* 23)*	5-yr analysis: 28 additional patients analyzed (on protocol)
D'Amore[38] Phase II NLG-01	Maybe	53/31	5-yr, 44	5-yr, 51	NR	5-yr, 61 (*vs.* 28)*	No auto-SCT group includes those with no response/PD
Abramson[41,b] USA multicenter	Yes (UVA)[f] No (CR)	61/12	NR	NR	3-yr, 58 (*vs.* 30)*	3-yr, 74 (*vs.* 53)	No PFS/OS benefit of auto-SCT in MVA All CR: no PFS/OS benefit of auto-SCT
Ellin[8,c] Swedish Registry	Yes	NR	Auto-SCT MVA*	Auto-SCT MVA*	NR	NR	PFS*/OS* benefit in 'intent to auto-SCT' group <70 yr (not adjusted for response)
Cederleuf[42] Swedish/Danish	No	CR (All by design)	NR	NR	2-yr, 66 (*vs.* 67)	2-yr, 76 (*vs.* 80)	MVA: no OS benefit
Fossard[40] LYSA	No	CR/PR 57	5-yr, 46 (*vs.* 40.5)	59 (*vs.* 60)	NR	NR	No PFS/OS benefit using propensity score matching MVA: no PFS/OS benefit
Park[110] COMPLETE	No	CR (All by design)	NR	NR	*P*=0.23	2-yr, 88 (*vs.* 70)	Improved OS with auto-SCT in IPI score 2-4
Janikova[111] CLSG	No	NR	5-yr, 46 (*vs.* 41)	5-yr, 59.5 (*vs.* 49)	NR	NR	Adjusted by IPI score: no PFS/OS benefit with auto-SCT
Garcia-Sancho[112,d] GELTAMO/FIL	Yes	CR (All by design)	NR	NR	5-yr, 63 (*vs.* 49)*	5-yr, 74 (*vs.* 62)	All CR: PFS*/OS* benefit in MVA
Brink[9] Netherlands Registry	Yes	NR	NR	NR	NR	Landmark 5-yr, 78 (*vs.* 45)* CR: 5-yr, 82 (*vs.* 47)*	MVA: improved OS*
Savage[43] Phase III ECHELON-2 subgroup	BV-CHP Yes	CR (All by design)	NR	NR	3-yr, 80 (*vs.* 55)* 5-yr, 65 (*vs.* 46)*	NR	All CR: PFS* benefit in BV-CHP arm (adjusted for age/region)
	CHOP No				3-yr, 67 (*vs.* 54)[g] 5-yr, 49 (*vs.* 51)[g]	NR	All CR: no PFS benefit in CHOP arm (adjusted for age/region)

[a]All included nodal PTCL and excluded ALK$^+$ anaplastic large cell lymphoma (ALCL) with the exception of Abramson *et al.* (7% ALK$^+$) and Cederleuf *et al.* (19% ALK$^+$). [b]Also included extranodal subtypes: total PTCL, not otherwise specified/angioimmunoblastic T-cell lymphoma/ALK$^-$ ALCL=67% (in addition to 6% ALK unknown). [c]Autologous stem cell transplantation (auto-SCT)-evaluated patients <70 years who received CHOP or CHOEP also included those with enteropathy associated T-cell lymphoma (EATL) and T-cell lymphoma 'unspecified'. [d]Also included patients with EATL, hepatosplenic T-cell lymphoma, NK/T-cell lymphoma, and primary cutaneous γδ lymphoma. [e]Response after induction CHOP in 91/111 (82%) of patients, ultimately 75 (68%) transplanted. [f]Univariate analysis of subset of patients treated with CHOP/CHOP-like *versus* CHOP/CHOP-like + auto-SCT, not adjusted by response or prognostic factors. [g]*P* values not reported for this exploratory analysis, confidence intervals cross 1.0. BV-CHP: brentuximab vedotin - cyclophosphamide, doxorubicin, prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; NLG: Nordic Lymphoma Group; LYSA: Lymphoma Study Group; CLSG: Czech Lymphoma Study Group; GELTAMO: Spanish Lymphoma Group; FIL: Fondazione Italiana Linfomi; auto-SCT: autologous stem cell transplantation; PFS: progression-free survival; OS: overall survival; yr: year; UVA: univariate analysis; MVA: multivariate analysis. Estimates are rounded; NR: not reported; IPI: International Prognostic Index. *Statistically significant.

not adjusted for response, a separate 9-month landmark analysis and a sensitivity analysis were performed exclusively in CR patients, which also demonstrated improved OS in the auto-SCT group.[9] Given the variability in interpretation and definition of a partial response in retrospective studies, some studies have evaluated the role of auto-SCT only in patients in CR at the end of treatment, again with mixed results (Table 2).[41,42] In a similar fashion, a subgroup analysis of patients in CR following BV-CHP enrolled on the ECHELON-2 study was performed and documented an improved PFS with consolidative SCT (auto-SCT n=36; allo-SCT n=2) (5-year PFS: 65.3% *vs*. 46.4%, hazard ratio [HR]=0.36, 95% confidence interval [95% CI]: 0.17-0.77) but a similar benefit of SCT was not observed in the CHOP arm (Table 2).[43]

The recently activated TRANSCRIPT trial will address the role of auto-SCT in patients with nodal PTCL (excluding ALK$^+$ ALCL) in CR following induction therapy (NCT05444712) (*Online Supplementary Table S1*). Despite data limitations, consolidative auto-SCT should still be a strategy to consider with upfront treatment but guidelines differ about whether it should be performed exclusively in patients in CR.[34,44] Further studies are needed, ideally by subtype, to identify lower-risk patients in whom auto-SCT may be omitted and, conversely, determine whether there are molecular markers, such as *P53* or *DNMT3A* mutations, that identify cases in which auto-SCT is futile.

Breast-implant-associated anaplastic large cell lymphoma

After its original description in 1997, breast implant-associated (BIA) was defined as a provisional entity in the revised 4th edition of the WHO classification (WHO-HAEM4R) and was upgraded to a distinct entity by both the ICC and the WHO-HAEM5[1,2] (Table 1 in the Introduction to the Review Series[3]). Although not a 'nodal' PTCL, given its primary extranodal location, it is described here to distinguish it from systemic ALCL as the work-up, management and prognosis differ.

The risk of BIA-ALCL is exclusively associated with textured implants and the time from implant to development of ALCL is 7-11 years. The overall risk varies in series but is likely between 1:1,000 to 1:10,000.[45] Peri-implant effusion is the most common presentation with 85% of patients having stage 1 disease limited to the seroma ± capsule. The effusion, preferably as a large volume, should be sent for cytology with cell block preparation and flow cytometry including CD30 in the panel. A positron electron tomography scan should be done before surgery as post-surgical inflammatory changes can complicate interpretation.[45]

As recently reviewed,[45] the mainstay of treatment is implant removal and *en-bloc* complete capsulectomy, with bilateral removal if textured implants are used. Complete surgical excision in patients with stage 1 disease yields a 5-year disease-specific survival of 95%. For those presenting with stage 2 disease, there are limited data to guide recommendations. Surgery should include removal of the mass and sampling/removal of suspicious lymph nodes.[45] With incomplete resection, radiation may be considered and in rare cases adjuvant BV has been administered although data supporting this approach are lacking. Although patients with BIA-ALCL were not included in ECHELON-2, BV-CHP would be reasonable in those with disease outside of the breast and lymph nodes, or with lymph node involvement.[45]

Treatment options in relapsed/refractory PTCL and the promise of personalized therapy

Unfortunately, despite advances in the front-line setting a large proportion of PTCL patients have lymphoma relapse or have primary refractory disease. The only established curative treatment is SCT, although rare long-term remissions have been observed following systemic therapy alone, which, in some cases, may reflect more indolent disease biology.[46-48]

With the emergence of genomic techniques, there is a greater understanding of underlying disease biology which has also helped to inform therapeutics. This is best shown in TFHL, which are typified by recurrent mutations in epigenetic modifiers,[5] with growing evidence of sensitivity to a broad range of agents of this class (Tables 3-5). In a proportion of ALCL and other rarer PTCL subtypes, there is evidence of JAK/STAT pathway activation, leading to recent trials with JAK inhibitors.[49] Although studies of PTCL-NOS have elucidated the GATA3 and TBX21 molecular subtypes, how this informs treatment decisions remains unknown. Here, we review the overall management of R/R nodal PTCL, highlighting situations in which biology can guide treatment options.

Transplant or no transplant?

Outcomes are historically poor in patients with R/R PTCL, with a median OS from first relapse/progression typically <6 months in those who are not transplanted.[46] Thus, the first therapeutic decision is whether or not a patient is a transplant candidate. SCT is limited to fit, often younger patients with chemosensitive disease, a term that should be redefined as 'systemic therapy-sensitive' with the expanding compendium of modern, novel therapies that also serve as an effective bridge to SCT.[50-53]

The prospective International T-Cell Project collected data on 633 patients with relapsed (n=197) or refractory (n=436) PTCL, including those managed with intent to transplant;

the median OS for all patients was still only about 6 months, and the 3-year OS was 23%. Overall, only 99 patients (16%) underwent SCT (type not specified) as part of salvage therapy and, not surprisingly, this group had a superior 3-year OS of 48% compared to 30% in patients in a partial remission or CR and were not transplanted (for any reason).[54] Data are more limited in patients managed with 'intent to transplant', especially with auto-SCT. Two retrospective, single-institution studies evaluating outcomes from the point of relapse/progression with intention to incorporate SCT suggested a cure rate of 20-35% with auto-SCT, with dismal outcomes in patients with refractory disease.[55,56]

Outside of ALCL, most evidence supports the use of allo-SCT in relapsed and especially refractory PTCL. The Center for International Bone Marrow Transplant Research (CIBMTR)[57] evaluated outcomes in 241 patients with PTCL undergoing SCT between 1996 to 2006 and 2018. Confining the analysis to those beyond first CR, a superior outcome was observed with auto-SCT over allo-SCT (3-year OS 62% *vs*. 33%, respectively; *P*=0.0088) with a lower transplant-related mortality (5% *vs*. 32%; *P*=0.0088), but PFS and relapse/progression rates were similar. This study was largely driven by a high proportion of ALCL patients who may derive the greatest benefit from auto-SCT in the relapse setting (3-year PFS 53%, 3-year OS 65%) compared to PTCL-NOS (3-year PFS 29%, 3-year OS 42%), although specific outcomes by ALK status were not reported. Only six patients with AITL underwent auto-SCT, limiting the evaluation of this group. The proportion of patients with refractory disease was not specified by subtype, a factor that also strongly influences the information on the utility of auto-SCT.

Studies have highlighted favorable outcomes with allo-SCT particularly in R/R AITL, including a recent combined retrospective registry study from the European Society for Blood and Marrow Transplantation (EBMT) and the CIBMTR, which evaluated 1,942 PTCL patients (AITL, PTCL-NOS, ALCL) undergoing allo-SCT between 2008 and 2018 primarily with R/R disease (70%).[52] Overall, the 3-year PFS was 50% and the 3-year OS was 60%, highlighting better outcomes in the more modern treatment era. Furthermore, using PTCL-NOS as the reference group, a reduced risk of lymphoma relapse (*P*<0.001) was observed for AITL, highlighting a unique sensitivity to the graft-*versus*-lymphoma effect, which is consistent with other studies.[58-60] In contrast, an increased risk of relapse was observed for ALCL (HR=1.3, 95% CI: 1.1-1.6; *P*=0.01). Not surprisingly, patients in CR had better outcomes than those with a partial response or resistant disease (3-year PFS 57% *vs*. 47% *vs*. 36%, respectively; *P*<0.0001) with response remaining significant in a multivariate analysis. Although efforts should be made to achieve a deeper response, given that one-third can still be cured, patients should not be denied an allo-SCT if criteria for a partial response are not met. Interestingly, outcomes after haplo-SCT and matched donor transplants were comparable, and use of intensified conditioning did not appear to be advantageous compared with non-myeloablative approaches.[52] Collectively, studies suggest that auto-SCT may be considered in relapsed ALCL if not used with front-line therapy, but allo-SCT should be favored in AITL and patients with PTCL-NOS should most likely receive an allo-SCT. Apart from some cases of ALK$^+$ ALCL, for those with refractory disease, allo-SCT would be preferable.

As outlined by Bisig, Savage and de Leval,[5] the characteristic landscape of TFHL supports a multi-step process derived from underlying clonal hematopoiesis (see Figure 4 in the review published in this issue of *Haematologica*[5]). *TET2* and *DNMT3A* mutations, which typify TFHL, are also common in clonal hematopoiesis. A recent study using bone marrow samples as well as flow-sorted bone marrow and peripheral blood samples supported the finding that clonal hematopoiesis is prevalent in AITL and showed that progenitor cells harboring identical *TET2* and *DNMT3A* mutations can divergently evolve to AITL and myeloid neoplasms.[61] With still limited data, it remains unclear whether the presence of clonal hematopoiesis should affect treatment choices. However, if available, testing for clonal hematopoiesis should ideally be performed as it may inform on the use of auto-SCT in older patients and whether an allo-SCT may be preferred in some settings, as well as follow-up surveillance.

Is there a preferred salvage chemotherapy in transplant-eligible relapsed/refractory PTCL?

As for diffuse large B-cell lymphoma, there is no standard first-line salvage therapy for R/R PTCL patients, and very few studies have detailed outcomes specifically in PTCL. A subgroup analysis of the Canadian Cancer Trials Group phase III LY.12 study comparing GDP (gemcitabine, dexamethasone, cisplatin) and DHAP salvage chemotherapy before auto-SCT in R/R aggressive lymphomas, including PTCL (n=59), demonstrated an ORR of 36% with GDP (compared to 46% in aggressive B-cell lymphomas; *P*=0.12) which was similar to that achieved by DHAP.[62,63] The population was high risk with most patients either having refractory disease (41%) or had relapsed within 1 year (37%), which may have contributed to overall lower response rates, regardless of the study arm. ICE (ifosfamide, carboplatin, etopsoside) chemotherapy is also frequently used,[55] however, there are no comparative studies in PTCL. Given the high frequency of chemorefractory disease, novel agents have been increasingly used as a bridge to transplant as outlined below.

Novel agents in the management of relapsed/refractory PTCL

Over the past decade, there has been a pivot to perform novel therapy studies specifically in R/R PTCL and, more

recently, even in specific subtypes. The majority are single-arm phase II studies and, apart from BV, drug approval may be country specific (Table 2 and Figure 1 from the Introduction to review Series[3]). The scope of agents under investigation is wide but very few are approved (Table 3).[3]

Pralatrexate, a folate analog metabolic inhibitor which competitively inhibits dihydrofolate reductase, was the first novel agent to be studied in PTCL after early studies showed preferential sensitivity in PTCL (including cutaneous T-cell lymphoma) compared to B-cell lymphomas.[64] The PROPEL study[51] evaluated 115 patients with R/R PTCL and the ORR for all patients was 29% (11% CR), the median PFS was 3.5 months, and the median duration of response was 10.1 months (Table 3). The response rate was notably lower in AITL (8%). Subsequent studies explored a different ramped up dosing schedule and use of leucovorin to mitigate mucositis ('Columbia regimen') which improved tolerance and appears to maintain efficacy.[65]

BV was developed for use in Hodgkin lymphoma and ALCL due to the disappointing efficacy of the nascent anti-CD30 antibody in these lymphomas. In the phase II registration study for systemic ALCL, patients were eligible following failure of front-line anthracycline-based therapy. The efficacy was striking with an ORR of 86% and CR rate of 57%. The median PFS and median duration of response were 13.3 months and 12.6 months, respectively[47] (Table 3). In the 5-year follow-up, the PFS was 39% and, overall, 14% of patients remained in CR following single-agent BV in the absence of transplant, suggesting that cure was possible in a minority of patients.[52] This led to global approval of BV in R/R ALCL (Table 3). In a separate study, BV was evaluated in R/R non-ALCL CD30$^+$ PTCL and, although less impressive, efficacy was demonstrated with an ORR of 41% across the entire cohort (n=34) and 54% in AITL, but duration of response was short (all patients 7.6 months). Although not approved, it remains an option in R/R CD30$^+$ PTCL especially as a bridge to SCT if funding is available.[66] More recently, the ALK inhibitor crizotinib was approved by the Food and Drug Administration for patients up to 21 years old with ALK$^+$ ALCL, based on a robust CR rate (81%)[67] (Table 3).

Alisertib is an aurora A kinase inhibitor that produced an ORR of 50% in eight PTCL patients enrolled in a phase I study of hematologic malignancies.[68] This study was followed by the Lumiere study, which was the first randomized phase III study in R/R PTCL, and compared alisertib to investigators' choice of therapy (pralatrexate, romidepsin, gemcitabine) (Table 4). It did not show superiority of alisertib (ORR 33% [alisertib] *vs*. 45% [comparators]; median PFS 3.8 months *vs*. 3.5 months, respectively). This study demonstrated that phase III trials were possible in this setting but also highlighted the challenges with disease heterogeneity.[69]

CCR4 is expressed in 30-40% of cases of PTCL and is associated with the GATA3 subtype of PTCL-NOS. Mogamulizumab is a CCR4 monoclonal antibody and was explored in R/R CCR4$^+$ nodal PTCL in a phase II study in Japan. Among 29 patients, the ORR was 34% with CR in 17%; the median

Table 3. Approved novel agents for the treatment of relapsed/refractory peripheral T-cell lymphomas: global perspective.

Agent	Type of agent	Study phase	Country approval	PTCL subtype(s)	ORR/CR %	Median DoR in months	Median PFS in months	Median OS in months
Pralatrexate[51]	DHFR inhibitor	II	USA/Canada	PTCL/tMF	29/11	10.1	3.5	14.5
Brentuximab vedotin[66]	ADC CD30	II	Global	ALCL	86/57	12.6[a]	13.3	Not reached*
Romidepsin[50,71, b*]	HDAC inhibitor	II	USA/Canada (de-listed)	PTCL AITL	25/15 27/19	17[b] -	4 -	11.3 -
Belinostat[72]	HDAC inhibitor	II	USA	PTCL AITL	26/11 45.5	13.6 -	1.6 -	7.9 -
Chidamide[73]	HDAC inhibitor	II	China	PTCL AITL	28/14 50/40	9.9	2.1	21.4
Forodesine[113]	PNP inhibitor	II	Japan	PTCL	25/10	10.4	1.9	15.6
Mogamulizumab[114,c]	CCR4 antibody	II	Japan	CCR4$^+$ PTCL[c] (2014)	34/17	NR	2.0	14.2
Crizotinib[67]	ALK inhibitor	II	USA 1-21 yr	ALK$^+$ ALCL	88/81	NR	NR	NR

[a]Updated analysis of brentuximab vedotin with a median follow-up of 22.3 months: the median duration of response (DoR) was 28 months. [b]Updated analysis of romidepsin with a median follow-up of 71 months: the median DoR was 25.6 months. [c]Peripheral T-cell lymphoma (PTCL) subtypes: PTCL, not otherwise specified; angioimmunoblastic T-cell lymphoma; ALK$^-$ anaplastic large cell lymphoma. *Approval of the PTCL indication for romidepsin was withdrawn by the Food and Drug Administration in the USA (2021) and Canada (2023) following the negative results of the Ro-CHOP phase III study. ORR: objective response rate; CR: complete response; PFS: progression-free survival; OS: overall survival; DHFR: dihydrofolate reductase; tMF: transformed mycosis fungoides; ADC: antibody-drug conjugate; ALCL: anaplastic large cell lymphoma; AITL: gioimmunoblastic T-cell lymphomas; HDAC: histone deacetylase; PNP: purine nucleoside phosphorylase; NR: not reported.

PFS was 3 months (Table 3) and led to the approval of mogamulizumab in 2014 in Japan in CCR4+ nodal PTCL.[114]

Epigenetic therapies and a personalized treatment approach in T-follicular helper cell lymphomas

Epigenetics reflect changes in gene expression in the absence of DNA sequence changes and include histone modification, DNA methylation, noncoding RNA effects and chromatin reorganization. Abnormal activity of HDAC can affect gene expression with epigenetic silencing of tumor suppressor genes and oncogene activation. Aberrant epigenetic alterations play a role in the pathogenesis of TFHL. Recurrent mutations in epigenetic modifying genes, including *TET2*, *DNMT3A* and *IDH2*^{R17} as well as the disease-specific *RhoA*^{G17V} mutation, characterize TFHL. As a group these lymphomas respond better to epigenetic therapies (Figure 1 in the Introduction to the Review Series[3]), showing much higher response rates than those achieved when considering all PTCL (Tables 3 and 4). Histone modifier gene mutations have been reported in 36% of PTCL-NOS and are associated with inferior PFS but may also define a group with an increased response to the HDAC inhibitor chidamide, suggesting that there may be a larger scope of patients who could benefit from a more personalized approach to therapy.[70]

Romidepsin was the first HDAC inhibitor approved for use in R/R PTCL and was associated with an ORR of 25% (CR

Table 4. Selected novel agent/combination therapy in relapsed/refractory peripheral T-cell lymphomas.

Agents Study	Target	Phase	PTCL subtype (N)	ORR/CR %	Median DoR in months	Median PFS in months
Alisertib[69] *vs.* Investigators' choice[a] Lumiere	Aurora kinase	III	PTCL (271 total)[c]	33/18 45/27	7.4 5.6	3.8 3.5
Lenalidomide[82]	Immunomodulatory Anti-angiogenic	II	PTCL (54) AITL (26)	22/11 31/15	3.6 3.5	2.5 4.6
Duvelisib[89]	PI3K γδ	II	PTCL (78) AITL (21)	50/32 67/48	7.8 NR	3.6 NR
Cerdulatinib[91]	Dual JAK/SYK	II	PTCL (65) TFHL (29)	35 52	NR 12.9	NR 4.6
Ruxolitinib[49]	JAK1/2	II	PTCL (53) Cohort 1 *JAK/STAT*+ Cohort 2 pSTAT3+ Cohort 3 unselected	25 33 29 12	8.4 7.5 14.7 Not reached	2.8 NR NR NR
Golidocitinib JAKPOT8[92]	JAK1	I/II	PTCL (51) AITL (20)	43/22 60	Not reached	NR
Tipifarnib[90]	Farnesyltransferase	II	CXCL12 3'UTR (12) AITL (11)[d]	42/25 45/27	NR NR	NR
Azacitidine[76] *vs.* Investigators' choice[b] ORACLE	DNMT1	III	TFHL (86 total)	33/12 43/23	NR NR	5.6* 2.8
Valemetostat[78]	EZH2	I	PTCL (45) AITL	56/24 70.6	NR NR	NR NR
Combination therapies						
Romidepsin + azacitidine[95]	HDAC + DNMT1	II TN/RR	PTCL (25) TFHL (15)	61/43 80/60	20.3 NR	8.0 8.9
Romidepsin + duvelisib[53]	HDAC + PI3K γδ	I	PTCL (55) TFHL (19)	58/42 68/58	8.1 NR	6.9 NR
Romidepsin + pralatrexate[115]	HDAC + DHFR	I	PTCL (14)	71/29	NR	NR

[a]Comparator 'investigators' choice': gemcitabine (N=30), romidepsin (N=23), pralatrexate (N=80). [b]Comparator 'investigators' choice': gemcitabine (N=24), romidepsin (N=4), bendamustine (N=16). *P=0.042, however, the pre-specified P value was P=0.025. [c]Angioimmunoblastic T-cell lymphoma (N=61; 23% of all patients); objective response rate to alisertib 28% *vs.* 46% for comparators. [d]Angioimmunoblastic T-cell lymphoma 11/23 evaluable. Estimates are rounded. PTCL: peripheral T-cell lymphoma; ORR: objective response rate; CR: complete response; DoR: duration of response; PFS: progression-free survival; AITL: angioimmunoblastic T-cell lymphoma; PI3K: phosphoinositide 3 kinase; NR: not reported; JAK: Janus kinase; SYK: spleen tyrosine kinase; UTR: untranslated region; DNMT: DNA methyltransferase; TFHL: T-follicular helper cell lymphoma; EZH2: enhancer of zeste homolog; HDAC: histone deactylase; TN: treatment-naïve; R/R: relapsed/refractory; DHFR: dihydrofolate reductase.

15%) (Table 3).[50] Although responses were infrequent and overall median PFS was only 3 months, some responses were notably durable with a median duration of 28 months with longer follow-up.[50,71] Furthermore, 4/27 (15%) of patients enrolled with AITL still remained in CR over 3 years after entering the study.[48] Unfortunately, in 2021, the PTCL indication for romidepsin was withdrawn from the USA market and more recently Canada has followed, due to the negative results of a phase III study evaluating Ro-CHOP in the first-line setting. Belinostat, a hydroxamic acid-derived pan-HDAC inhibitor, and chidamide, the only oral class I/II HDAC inhibitor, are approved in the USA and China, respectively, and have similar efficacy to romidepsin and also a higher ORR in AITL (ORR 46% with belinostat; 50% with chidamide) (Table 3).[72,73] A retrospective multicenter study that compared the efficacy of HDAC inhibitors in TFHL *versus* PTCL-NOS confirmed a higher response rate in the former (ORR and CR 56.5% and 28.9%, respectively, in TFHL *vs*. 9.4% and 19.6%, respectively, in PTCL-NOS; *P*=0.0035)[74] and in those PTCL cases with 'typical' AITL mutations as described above.

Beyond HDAC inhibitors, other epigenetic therapies produce high response rates in TFHL (Table 4; Figure 1 in the Introduction to the Review Series[3]). Oral 5-azacitidine (CC-486) is a hypomethylating agent that inhibits DNA methyltransferase and was first evaluated in a retrospective study of 12 patients with R/R AITL, five of whom had a concurrent myeloid neoplasm; the ORR was 75%, the CR rate was 50% and the median PFS was 15 months.[75] This led to the recently reported ORACLE phase III study (NCT03593018) comparing oral azacitidine (n=42) to investigators' choice of therapy (n=44) (romidepsin n=4, gemcitabine n=24, bendamustine n=16) in TFHL.[61] The median PFS favored 5-azacitidine (5.6 months *vs*. 2.8 months; *P*=0.042) but did not reach the pre-specified significance level of *P*<0.025, suggesting that the study may have been underpowered. Interestingly, despite the favorable PFS, lower ORR and CR rate were observed with 5-azacitidine (ORR and CR 33% and 12%, respectively, with 5-azacitidine *vs*. 43% and 23%, respectively, with investigators' choice of therapy) supporting that a greater proportion of patients may have had stable disease as best response, which is also reflected in a more favorable OS (median OS 18.4 months *vs*. 10.3 months) (HR=0.56, 95% CI: 0.323-0.961).[76] A separate, ongoing, phase III study in Japan is comparing oral azacitidine to investigators' choice of therapy (romidepsin or gemcitabine) in R/R AITL, but the results have not yet been reported (NCT03703375) (*Online Supplementary Table S1*).

Valemetostat is a potent, selective dual inhibitor of enhancer of zeste homologs (EZH2 and EZH1) and stimulates the expression of pro-apoptotic and tumor suppressor genes (Table 4; Figure 1 in the Introduction to the Review Series[3]).[77] A phase I dose-escalation trial reported an ORR of 55.6% (24% CR) and 70.6% in AITL (Table 4).[78] The phase II VALENTINE-PTCL01 trial (NCT04703192) has completed accrual, but results have not yet been reported.

There is also emerging evidence to support the integration of epigenetic therapies into the front-line therapy of TFHL. An unplanned subgroup analysis of patients with TFHL enrolled on the LYSA Ro-CHOP study demonstrated a PFS benefit of Ro-CHOP *versus* CHOP (*P*=0.046)[30] (Table 5). Belinostat-CHOP was evaluated in a phase I study of 23 patients, with AITL as the predominant subtype (n=10, 43%); the ORR was 86% and the CR rate was 57%.[81] In a phase I study of vorinostat-CHOP, all evaluable patients (n=12) achieved a CR, providing additional support for this approach.[79] Several additional, ongoing studies are integrating chidamide in the front-line setting (*Online Supplementary Table S1*).

Similarly, a phase II study evaluated CHOP with oral 5-azacitidine (CC-486) in 20 newly diagnosed patients with PTCL, of whom 81% had TFHL.[80] The azacitidine was given as 'priming' to enhance chemosensitization and deepen the response. The ORR and CR rate was 75%, rising to 88% for both in TFHL. Overall, half of all patients underwent consolidative auto-SCT and, with a median follow-up of 21 months, the 2-year PFS was 65.8% for all patients and 69.2% in patients with TFHL.[80] The presence of *TET2* mutations was associated with a more favorable PFS (*P*=0.014), whereas a trend towards an inferior PFS was observed in cases with a *DNMT3A* mutation. Building on this regimen, the Alliance group launched a randomized phase II study comparing CHOP (or CHOEP for patients <60 years old) with either the same backbone with oral azacitidine or duvelisib in a 1:1:1 design (*Online Supplementary Table S1*).

Not surprisingly, adding a novel therapy to the CHOP backbone is associated with additional toxicity. Febrile neutropenia occurred in 21% and 10% of patients treated with Ro-CHOP and CHOP, respectively (Table 5).[81]

Beyond epigenetic therapies: promise in T-follicular helper lymphomas and beyond

Lenalidomide is an immunomodulatory drug with a complex mechanism of action including direct effects on the tumor cell mediated by inhibition of the protein CEREBLON as well as anti-angiogenic and immunogenic effects through its impact on the tumor microenvironment (Figure 1 in the Introduction to the Review Series[3]). Previous studies have shown modest single-agent activity in R/R PTCL (ORR 22-30%, CR 0-11%) and a median PFS of approximately 3 months across studies[82-85] including patients with AITL (ORR 31%, CR 15%).[82] A phase II study of CHOP and lenalidomide in patients 60-80 years old with

Table 5. Studies evaluating CHOP + epigenetic therapies *versus* epigenetic therapy combinations in treatment naïve PTCL: focus on T-follicular helper lymphomas.

Experimental regimen	PTCL subtype (N)	Median FU in months	ORR/CR %	2-year PFS %	2-year OS %	Grade 3/4 ↓ neutrophils, %	Grade 3/4 ↓ platelets, %
Romidepsin-CHOP[30] Phase III	PTCL (421)[#] TFHL (101)	27.5	63/41 (Ro-CHOP) 60/37 (CHOP)	43 36 ~50[a]	64 63	49 (FN 21) 33 (FN 10) + GCSF All	50 10
Azacitidine-CHOP[80] Phase II	PTCL (20)[#] TFHL (17)	21	75/75 88/88	66 69	68 76	71 (FN 14) + GCSF All	10
Belinostat-CHOP[81] Phase I	PTCL/tMF (23) AITL (10)	NR	86/57-71[b] 89	NR	NR	30 (FN 17) + GCSF as per ASCO guidelines	NR
Vorinostat-CHOP[79,c] Phase I	PTCL (14) AITL (5)	27	93/93[c]	79	81	57 (FN 13) + GCSF schedule B	14
Romidepsin + 5-azacitidine[95] Phase II	PTCL (11 TN)	13.5 (All)	70/50 (TN)	NR	NR	40 (FN 12) (All) GCSF as per investigator discretion	48
Romidepsin + lenalidomide[97] Phase II	PTCL (29)[#] AITL (11)	8	75/30 85/38.5	54 (1-year)	76 (1-year)	45 (FN NR) (All) GCSF guidelines NR	34

[a]Subgroup analysis of T-follicular helper lymphoma: point estimates are estimated from Kaplan-Meier curves. [b]Complete response 57% in cohort 3; 71% at maximum tolerated dose (1,000 mg/m^2 belinostat x 5 days). [c]Vorinostat days 5-14 schedule A 200 mg *bid*, schedule B 300 mg *tid*; two patients considered not evaluable because of early treatment discontinuation. [#]Excludes ALK$^+$ anaplastic large cell lymphoma. Estimates are rounded. FU: follow-up; ORR: objective response rate; CR: complete response; PFD: progression-free survival; OS: overall survival; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; Ro: romidepsin; TFH: T-follicular helper; FN: febrile neutropenia; GCSF: granulocyte colony-stimulating factor; AITL: angioimmunoblastic T-cell lymphoma; NR: not reported; ASCO: American Society of Clinical Oncology; TN: treatment-naïve; PTCL: peripheral T-cell lymphomas; tMF: transformed mycosis fungoides.

AITL demonstrated a CR rate of 41%, which was below the pre-specified target of 55%, although the 2-year PFS and OS rates of 42% and 59% were better than expected based on results from historical series.[86]

Duvelisib is a dual inhibitor of PI3K-δ and PI3K-γ and showed encouraging activity in a phase I study in which the ORR was 50%.[87] The findings of the phase II PRIMO registration trial of duvelisib in R/R PTCL were reported at the 2021 American Society of Hematology (ASH) meeting. The ORR was 50% (32% CR); results were not detailed by histological subtype (Table 4).[88,89] The GATA3 molecular subtype of PTCL-NOS is enriched for PI3K-induced signatures providing a potential rationale for duvelisib (Table 4; Figure 1 in the Introduction to the Review Series[3]). PI3K inhibitors can cause immune-mediated toxicities reminiscent of those caused by checkpoint inhibitors, and these toxicities have led to discontinuation of drug development in many settings in B-cell lymphomas/leukemias. In the PRIMO study, duvelisib was associated with grade 3/4 transaminitis in 27% of patients and pneumonitis in two patients, both of whom died.[89] However, immune toxicities may be favorably modified by certain concurrent therapies (see below).

Tipifarnib is an oral inhibitor of farnesyltransferase which reduces CXCL12, a chemokine that is highly expressed in AITL and some PTCL-NOS. In a phase II study of tipifarnib for the treatment of PTCL the ORR was 39.7% but was 56.3% in AITL (CR 28.5%) and wildtype *CXCL12* genotype in PTCL-NOS was predictive of response (ORR 40%).[90]

With activation of the JAK/STAT pathway being a feature in many PTCL, including ALK$^+$ ALCL and a subset of ALK$^-$ ALCL, a JAK inhibitor (ruxolitinib) and a dual JAK/SYK inhibitor (cerdulatinib) have also been explored (Table 4; Figure 1 in the Introduction to the Review Series[3]).[49,91] Cerdulatinib produced an ORR of 35% across R/R PTCL, increasing to 52% for those with a TFH phenotype.[91] Ruxolitinib was associated with an ORR of 33% in cases with activating mutations in *JAK/STAT* (cohort 1) and 29% in those pSTAT3-positive by immunohistochemistry (cohort 2).[49] A preliminary report of a phase I/II study of golidocitinib (JAKPOT8), a selective JAK1 inhibitor, in R/R PTCL described an ORR of 43% (65% in AITL), a CR of 22% and a median duration of response that had not been reached at that time (Table 4).[92]

EBV is present in most AITL (70-80%) in the surrounding B-cell immunoblasts, as well as in a proportion of PTCL-NOS, although some of the latter cases would be re-classified today as primary nodal EBV$^+$ T-cell/NK-cell lymphoma by the WHO-HAEM5 if also positive for cytotoxic markers. Regardless, nanatinostat, which induces EBV kinase genes, and valganciclovir which is subsequently activated (i.e., 'kick and kill'), are being evaluated in a phase II basket study (NAVAL-1) (Figure 1 in the Introduction to the Review Series[3]) including a cohort with

nodal (non-ALCL) PTCL (*Online Supplementary Table S1*) following an initial report of an ORR of 40% (CR 19%). In the six patients with PTCL-NOS/AITL from the phase I study, the ORR was 67% (CR 50%).[93]

Are combination novel therapies ready for prime time in treatment-naïve patients?

In an effort to deepen CR, activity in R/R PTCL trials has centered around combination therapies chosen to capitalize on complementary, additive or synergistic activities. In some cases, these chemotherapy-free combination therapies are also being evaluated in treatment-naïve cohorts, challenging the paradigm of upfront CHOP-based approaches (Table 5). A phase I study of romidepsin and 5-azacitidine noted sensitivity in T-cell lymphomas with an ORR of 73% in five patients in an expansion cohort, four of whom had a CR (AITL n=3).[94] A phase II study followed in PTCL including both treatment-naïve and R/R PTCL cohorts, with the analysis including the five patients from the earlier study.[95] Considering the evaluable patients, the ORR was 61% (CR 43%) and was 70% (CR 50%) in treatment-naïve patients (n=10) *versus* 54% (CR 38%) in R/R PTCL patients. With a median follow-up of 13.5 months, the median PFS for all patients was 8 months.[95] For the TFHL subgroup, the ORR was 80% and the CR was 67%, with a median PFS of 8.9 months *versus* 2.3 months in other PTCL subtypes. Considering all patients, grade 3/4 thrombocytopenia occurred in 48%, grade 3/4 neutropenia in 40%, and febrile neutropenia in 12% (Table 5). Targeted mutation information was available for 15 patients: numerically higher ORR and CR rate were demonstrated in those with *TET2* mutations (69% and 53%, respectively) compared to those with a wildtype genotype (40% and 20%, respectively); however, the differences did not reach statistical significance. A retrospective series evaluating azacitidine (oral or subcutaneous) and romidepsin demonstrated similar favorable efficacy in 26 patients with R/R PTCL, 23 of whom had TFHL, of which one was a composite with diffuse large B-cell lymphoma. The ORR was 76.9% (CR 53%) in the TFHL subgroup.[96] The combination of azacitidine and romidepsin is being compared to investigators' choice of therapy (belinostat, pralatrexate, gemcitabine) in an ongoing phase III trial (*Online Supplementary Table S1*). Romidepsin and lenalidomide were evaluated in a phase I study in treatment-naïve PTCL patients ≥60 years or those <60 years and not considered chemotherapy candidates by the treating physician. Of 20 evaluable patients, 13 (65%) had AITL. Overall the ORR was 75% (CR 30%), rising to 85% (CR 38.5%) in the patients with AITL[97] (Table 5). Although not evaluated in a treatment-naïve population, a phase I study of duvelisib with romidepsin in R/R patients demonstrated encouraging efficacy (ORR 58%/42%; TFHL 68%/58%) but interestingly, also less hepatic toxicity than lead-in treatment with duvelisib alone (40% *vs*. 8%), suggesting that romidepsin may offset the immunotoxicity of duvelisib.

Long-term follow-up is needed to determine the curative potential of these chemotherapy-free approaches and it is important to note that the toxicities are not negligible (Table 5). There are ongoing studies evaluating both combination therapies as well as CHOP + novel therapy approaches in treatment-naïve nodal PTCL.

What is the promise of immunotherapy in PTCL?

The efficacy of therapy targeting the programmed death pathway, either through programmed cell death protein 1 (PD1) or its ligand (PDL1), has been well described in extranodal NK/T-cell lymphomas[85] and with upregulation of PDL1 in primary nodal EBV$^+$ T/NK-cell lymphoma, it may also be a potential therapeutic approach in this rare entity.[4] There are limited data for the remaining nodal PTCL, but in all PTCL, there is a potential concern about hyperprogression given that PD1 on T cells may function as a tumor suppressor.[98] In a phase I study of 12 patients with R/R PTCL, half of whom had AITL, the ORR was only 33% and median PFS <3 months with hyperprogression reported to occur in four patients.[99] A combination study of romidepsin and pembrolizumab showed more encouraging efficacy (ORR 47.3%, CR 37%), but hyperprogression was reported in two patients, so further studies are needed.[100]

Cellular therapy is still in the development phase in PTCL and a full review is beyond the scope of this article, but some of the ongoing studies are highlighted in *Online Supplementary Table S1*. The majority of studies in PTCL have focused on CD30 as a target and some have reported CR in ALCL but the numbers of patients and the follow-up time are limited and thus the curative potential is still unknown.[101,102] Third-generation products utilizing the CD28 (CD28z) co-stimulatory domain may persist long term and appear to have a more potent anti-tumor effect.[102]

Apart from CD30, chimeric antigen receptor (CAR) T-cell targets in PTCL have been challenging due to three main barriers: (i) T-cell aplasia; (ii) fratricide; and (iii) the potential for contamination of CAR T-cell products with malignant cells.[103] Strategies to circumvent fratricide include capitalizing on the selection of either TRBC1 or TRBC2 for the β-chain constant region to spare normal T cells[104] as detailed in the phase I/II AUTO4 trial (NCT03590574) evaluating TRBC1$^+$ PTCL as well as use of NK-cell CAR products which do not express T-cell antigens.[105] Early results from AUTO4 demonstrated that five of nine patients with PTCL achieved a CR, but lack of CAR T-cell expansion may limit the durability of responses.[106] Use of 'off the shelf' products, such

as allogeneic CD70 CRISPR-Cas9-engineered T cells from healthy donors which incorporate editing of T-cell receptor α and β2-microglobulin genes (NCT04502446 COBALT-LYM) avoids normal T-cell killing and does not rely on personalized manufacturing. AFM13, an innate bispecific CD16/CD30 antibody, is also under investigation in CD30$^+$ PTCL (REDIRECT NCT04101331), including ALCL, demonstrating ORR of 40% in a phase Ib/II study (NCT03192202).[107]

Conclusions

Advances in the understanding of the biology and molecular underpinnings of PTCL have refined both classifications and therapeutic approaches. BV-CHP has changed the treatment landscape in ALCL and may be considered in selected cases of CD30$^+$ PTCL-NOS/AITL but it is recognized that the data are not definitive in the latter subtypes. Auto-SCT still remains a possible choice in upfront treatment, but definitive recommendations are difficult to make in the absence of randomized data. Recent studies highlight the sensitivity of TFHL to epigenetic therapies and, in the future, genomic information may also inform therapy. Future studies should focus on the evaluation of new treatments in specific PTCL subtypes or molecularly defined subgroups, to further refine personalized therapeutic options across a broader range of PTCL.

Disclosures

HSN has no conflicts of interest to disclose. KJS has received honoraria from and provided consulting for BMS, Merck, Seagen, and Janssen; has sat on a steering committee for Beigene; has received research funding from BMS; has received institutional research funding from Roche; and sat on a Data Safety and Monitoring Committee for DSMC.

Contributions

KJS and HSN co-wrote the paper.

References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720-1748.
2. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229-1253.
3. Savage KJ, de Leval L. Introduction to the peripheral T-cell lymphoma review series: advances in molecular characterization, classification refinement and treatment optimization. Haematologica. 2023;108(12):3204-3210.
4. Wai CMM, Chen S, Phyu T, et al. Immune pathway upregulation and lower genomic instability distinguish EBV-positive nodal T/NK-cell lymphoma from ENKTL and PTCL-NOS. Haematologica. 2022;107(8):1864-1879.
5. Bisig B, Savage KJ, de Leval L. Pathobiology of nodal peripheral T-cell lymphomas: current understanding and future directions. Haematologica 2023;108(12):3227-3243.
6. Fisher RI, Gaynor ER, Dahlberg S, et al. A phase III comparison of CHOP vs. m-BACOD vs. ProMACE-CytaBOM vs. MACOP-B in patients with intermediate- or high-grade non-Hodgkin's lymphoma: results of SWOG-8516 (Intergroup 0067), the National High-Priority Lymphoma Study. Ann Oncol. 1994;5(Suppl. 2):91-95.
7. 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(25):4124-4130.
8. 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(10):1570-1577.
9. Brink M, Meeuwes FO, van der Poel MWM, et al. Impact of etoposide and ASCT on survival among patients <65 years with stage II-IV PTCL; a population-based cohort study. Blood. 2022;140(9):1009-1019.
10. Savage KJ, Harris NL, Vose 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(12):5496-5504.
11. Shustov A, Cabrera ME, Civallero M, et al. ALK-negative anaplastic large cell lymphoma: features and outcomes of 235 patients from the International T-Cell Project. Blood Adv. 2021;5(3):640-648.
12. Sibon D, Nguyen DP, Schmitz N, et al. ALK-positive anaplastic large-cell lymphoma in adults: an individual patient data pooled analysis of 263 patients. Haematologica. 2019;104(12):e562-e565.
13. Federico M, Bellei M, Marcheselli L, et al. Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS). A new prognostic model developed by the International T cell Project Network. Br J Haematol. 2018;181(6):760-769.
14. Advani R, Skrypets T, Civallero M, et al. Outcomes and prognostic factors in angioimmunoblastic T-cell lymphoma: final report from the International T-Cell Project. Blood. 2021;138(3):213-220.
15. Sibon D, Fournier M, Brière J, et al. Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the Groupe d'Étude des Lymphomes de l'Adulte trials. J Clin Oncol. 2012;30(32):3939-3946.
16. Johnson WT, Ganesan N, Epstein-Peterson ZD, et al. TP53 mutations identify high-risk events for peripheral T-cell lymphoma treated with CHOP-based chemotherapy. Blood Adv. 2023;7(17):5172-5186.
17. Maurer MJ, Ghesquières H, Jais JP, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. J Clin Oncol. 2014;32(10):1066-1073.
18. Maurer MJ, Ellin F, Jerkeman M, et al. International assessment of event-free survival at 24 months and subsequent survival in peripheral T-cell lymphoma. J Clin Oncol. 2017;35(36):4019-4026.
19. Briski R, Feldman AL, Bailey NG, et al. The role of front-line anthracycline-containing chemotherapy regimens in peripheral

T-cell lymphomas. Blood Cancer J. 2014;4(5):e214.
20. Gleeson M, Peckitt C, To YM, et al. CHOP versus GEM-P in previously untreated patients with peripheral T-cell lymphoma (CHEMO-T): a phase 2, multicentre, randomised, open-label trial. Lancet Haematol. 2018;5(5):e190-e200.
21. Martín García-Sancho A, Rodríguez-Pinilla SM, Domingo-Domenech E, et al. Peripheral T-cell lymphoma with a T follicular-helper phenotype: a different entity? Results of the Spanish Real-T study. Br J Haematol. 2023;203(2):182-193.
22. Schmitz N, Trümper L, Ziepert M, 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(18):3418-3425.
23. Simon A, Peoch M, Casassus P, 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(2):159-166.
24. Fanale MA, Horwitz SM, Forero-Torres A, 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(28):3137-3143.
25. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229-240.
26. Horwitz S, O'Connor OA, Pro B, et al. The ECHELON-2 trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol. 2022;33(3):288-298.
27. Horwitz SM, Advani RH, Bartlett NL, et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood. 2014;123(20):3095-3100.
28. Gardai SJ, Epp A, Law C-L. Brentuximab vedotin-mediated immunogenic cell death. Cancer Res. 2015;75(15_Suppl):2469.
29. Herrera AF, Zain J, Savage KJ, et al. Brentuximab vedotin plus cyclophosphamide, doxorubicin, etoposide, and prednisone (CHEP-BV) followed by BV consolidation in patients with CD30-expressing peripheral T-cell lymphomas. Blood. 2021;138(Suppl 1):133.
30. Bachy E, Camus V, Thieblemont C, et al. Romidepsin plus CHOP versus CHOP in patients with previously untreated peripheral T-cell lymphoma: results of the Ro-CHOP phase III study (conducted by LYSA). J Clin Oncol. 2021;40242-40251.
31. Rodig SJ, Abramson JS, Pinkus GS, et al. Heterogeneous CD52 expression among hematologic neoplasms: implications for the use of alemtuzumab (CAMPATH-1H). Clin Cancer Res. 2006;12(23):7174-7179.
32. d'Amore F, Leppä S, Silva MG da, et al. Final analysis of the front-line phase III randomized ACT-1 trial in younger patients with systemic peripheral T-cell lymphoma treated with CHOP chemotherapy with or without alemtuzumab and consolidated by autologous hematopoietic stem cell transplant. Blood. 2018;132(Suppl 1):998.
33. Wulf GG, Altmann B, Ziepert M, et al. Alemtuzumab plus CHOP versus CHOP in elderly patients with peripheral T-cell lymphoma: the DSHNHL2006-1B/ACT-2 trial. Leukemia. 2021;35(1):143-155.
34. d'Amore F, Gaulard P, Trümper L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v108–v115.
35. Blystad AK, Enblad G, Kvaløy S, et al. High-dose therapy with autologous stem cell transplantation in patients with peripheral T cell lymphomas. Bone Marrow Transplant. 2001;27(7):711-716.
36. Rodríguez J, Caballero MD, Gutiérrez A, et al. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. Ann Oncol. 2003;14(12):1768-1775.
37. Jantunen E, Wiklund T, Juvonen E, et al. Autologous stem cell transplantation in adult patients with peripheral T-cell lymphoma: a nation-wide survey. Bone Marrow Transplant. 2004;33(4):405-410.
38. D'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin. Oncol. 2012;30(25):3093-3099.
39. Schmitz N, Truemper L, Bouabdallah K, et al. A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL. Blood. 2021;137(19):2646-2656.
40. Fossard G, Broussais F, Coelho I, et al. Role of up-front autologous stem-cell transplantation in peripheral T-cell lymphoma for patients in response after induction: an analysis of patients from LYSA centers. Ann Oncol. 2018;29(3):715-723.
41. Abramson JS, Feldman T, Kroll-Desrosiers AR, et al. Peripheral T-cell lymphomas in a large US multicenter cohort: prognostication in the modern era including impact of frontline therapy. Ann Oncol. 2014;25(11):2211-2217.
42. Cederleuf H, Hjort Jakobsen L, Ellin F, et al. Outcome of peripheral T-cell lymphoma in first complete remission: a Danish-Swedish population-based study. Leuk Lymphoma. 2017;58(12):2815-2823.
43. Savage KJ, Horwitz SM, Advani R, et al. Role of stem cell transplant in CD30+ PTCL following frontline brentuximab vedotin plus CHP or CHOP in ECHELON-2. Blood Adv. 2022;6(19):5550-5555.
44. Horwitz SM, Ansell S, Ai WZ, et al. T-cell lymphomas, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2022;20(3):285-308.
45. Mehta-Shah N, Ghione P. An updated approach and understanding of breast implant-associated anaplastic large cell lymphoma. J Natl Compr Canc Netw. 2022;20(3):309-315.
46. Mak V, Hamm J, Chhanabhai M, 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(16):1970-1976.
47. Pro B, Advani R, Brice P, 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(18):2190-2196.
48. Pro B, Horwitz SM, Prince HM, et al. Romidepsin induces durable responses in patients with relapsed or refractory angioimmunoblastic T-cell lymphoma. Hematol Oncol. 2017;35(4):914-917.
49. Moskowitz AJ, Ghione P, Jacobsen E, et al. A phase 2 biomarker-driven study of ruxolitinib demonstrates effectiveness of JAK/STAT targeting in T-cell lymphomas. Blood. 2021;138(26):2828-2837.
50. Coiffier B, Pro B, Prince HM, 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(6):631-636.
51. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol. 2011;29(9):1182-1189.
52. Pro B, Advani R, Brice P, et al. Five-year results of brentuximab

vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood. 2017;130(25):2709-2717.
53. Horwitz SM, Moskowitz AJ, Mehta-Shah N, et al. The combination of duvelisib and romidepsin (DR) is highly active against relapsed/refractory peripheral T-cell lymphoma with low rates of transaminitis: final results. Hematol Oncol. 2021;39(S2):100-101.
54. Bellei M, Foss FM, Shustov AR, et al. The outcome of peripheral T-cell lymphoma patients failing first-line therapy: a report from the prospective, International T-Cell Project. Haematologica. 2018;103(7):1191-1197.
55. Horwitz S, Moskowitz C, Kewalramani T, et al. Second-line therapy with ICE followed by high dose therapy and autologous stem cell transplantation for relapsed/refractory peripheral T-cell lymphomas: minimal benefit when analyzed by intent to treat. Blood. 2005;106(11):2679.
56. Ngu HS, Parkin S, Scott DW, et al. Outcome of relapsed and refractory peripheral T-cell lymphoma (PTCL) with intention for curative therapy incorporating high dose chemotherapy and hematopoietic stem cell transplant (HDC/SCT). Blood. 2021;138(Suppl 1):624.
57. Smith SM, Burns LJ, Inwards DJ, et al. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. J Clin Oncol. 2013;31(25):3100-3109.
58. Le Gouill S, Milpied N, Buzyn A, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Société Francaise de Greffe de Moëlle et de Thérapie Cellulaire. J Clin Oncol. 2008;26(14):2264-2271.
59. Epperla N, Ahn KW, Litovich C, et al. Allogeneic hematopoietic cell transplantation provides effective salvage despite refractory disease or failed prior autologous transplant in angioimmunoblastic T-cell lymphoma: a CIBMTR analysis. J Hematol Oncol. 2019;12(1):6.
60. Hamadani M, Ngoya M, Sureda A, et al. Outcome of allogeneic transplantation for mature T-cell lymphomas: impact of donor source and disease characteristics. Blood Adv. 2022;6(3):920-930.
61. Lewis NE, Petrova-Drus K, Huet S, et al. Clonal hematopoiesis in angioimmunoblastic T-cell lymphoma with divergent evolution to myeloid neoplasms. Blood Adv. 2020;4(10):2261-2271.
62. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-3496.
63. Skamene T, Crump M, Savage KJ, et al. Salvage chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: a subset analysis of the Canadian Cancer Trials Group LY.12 randomized phase 3 study. Leuk Lymphoma. 2017;58(10):2319-2327.
64. O'Connor OA, Hamlin PA, Portlock C, et al. Pralatrexate, a novel class of antifol with high affinity for the reduced folate carrier-type 1, produces marked complete and durable remissions in a diversity of chemotherapy refractory cases of T-cell lymphoma. Br J Haematol. 2007;139(3):425-428.
65. O'Connor OA, Amengual J, Colbourn D, Deng C, Sawas A. Pralatrexate: a comprehensive update on pharmacology, clinical activity and strategies to optimize use. Leuk Lymphoma. 2017;58(11):2548-2557.
66. Horwitz SM, Advani RH, Bartlett NL, et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood. 2014;123(20):3095-3100.
67. Merino M, Kasamon Y, Li H, et al. FDA approval summary: crizotinib for pediatric and young adult patients with relapsed or refractory systemic anaplastic large cell lymphoma. Pediatr Blood Cancer. 2022;69(8):e29602.
68. Friedberg JW, Mahadevan D, Cebula E, 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(1):44-50.
69. O'Connor OA, Ozcan M, Jacobsen ED, et al. Randomized phase III study of alisertib or investigator's choice (selected single agent) in patients with relapsed or refractory peripheral T-cell lymphoma. J Clin Oncol. 2019;37(8):613-623.
70. Ji MM, Huang YH, Huang JY, et al. Histone modifier gene mutations in peripheral T-cell lymphoma not otherwise specified. Haematologica. 2018;103(4):679-687.
71. Coiffier B, Pro B, Prince HM, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. J Hematol Oncol. 2014;7(1):11.
72. O'Connor OA, Horwitz S, Masszi T, 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. 2015;33(23):2492-2499.
73. Shi YK, Dong M, Hong X, et al. Results from a multicenter, open-label, pivotal phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma. Ann Oncol. 2015;26(8):1766-1771.
74. Ghione P, Faruque P, Mehta-Shah N, et al. T follicular helper phenotype predicts response to histone deacetylase inhibitors in relapsed/refractory peripheral T-cell lymphoma. Blood Adv. 2020;4(19):4640-4647.
75. Lemonnier F, Dupuis J, Sujobert P, et al. Treatment with 5-azacytidine induces a sustained response in patients with angioimmunoblastic T-cell lymphoma. Blood. 2018;132(21):2305-2309.
76. Dupuis J, Tsukasaki K, Bachy E, et al. Oral azacytidine in patients with relapsed/refractory angioimmunoblastic T-cell lymphoma: final analysis of the ORACLE phase III study. Blood. 2022;140(Suppl 1):2310-2312.
77. Honma D, Kanno O, Watanabe J, et al. Novel orally bioavailable EZH1/2 dual inhibitors with greater antitumor efficacy than an EZH2 selective inhibitor. Cancer Sci. 2017;108(10):2069-2078.
78. Ishitsuka K, Izutsu K, Maruyama D, et al. First-in-human study of the EZH1 and EZH2 dual inhibitor (DS-3201b) in patients with relapsed or refractory non-Hodgkin lymphomas. Hematol Oncol. 2021;39(s2):38-40.
79. Oki Y, Younes A, Copeland A, et al. Phase I study of vorinostat in combination with standard CHOP in patients with newly diagnosed peripheral T-cell lymphoma. Br J Haematol. 2013;162(1):138-141.
80. Ruan J, Moskowitz AJ, Mehta-Shah N, et al. Multicenter phase 2 study of oral azacitidine (CC-486) plus CHOP as initial treatment for peripheral T-cell lymphoma. Blood. 2023;141(18):2194-2205.
81. Johnston PB, Cashen AF, Nikolinakos PG, et al. Belinostat in combination with standard cyclophosphamide, doxorubicin, vincristine and prednisone as first-line treatment for patients with newly diagnosed peripheral T-cell lymphoma. Exp Hematol Oncol. 2021;10(1):1-11.
82. Morschhauser F, Fitoussi O, Haioun C, 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(13):2869-2876.
83. Fabbri A, Cencini E, Pietrini A, et al. Impressive activity of

lenalidomide monotherapy in refractory angioimmunoblastic T-cell lymphoma: report of a case with long-term follow-up. Hematol Oncol. 2013;31(4):213-217.
84. Dueck G, Chua N, Prasad A, et al. Interim report of a phase 2 clinical trial of lenalidomide for T-cell non-Hodgkin lymphoma. Cancer. 2010;116(19):4541-4548.
85. Toumishey E, Prasad A, Dueck G, et al. Final report of a phase 2 clinical trial of lenalidomide monotherapy for patients with T-cell lymphoma. Cancer. 2015;121(5):716-723.
86. Lemonnier F, Safar V, Beldi-Ferchiou A, et al. Integrative analysis of a phase 2 trial combining lenalidomide with CHOP in angioimmunoblastic T-cell lymphoma. Blood Adv. 2021;5(2):539-548.
87. Horwitz SM, Koch R, Porcu P, et al. Activity of the PI3K-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. Blood. 2018;131(8):888-898.
88. Pro B, Brammer JE, Casulo C, et al. Duvelisib in patients with relapsed/refractory peripheral T-cell lymphoma from the phase 2 PRIMO trial: dose optimization efficacy update and expansion phase initial results. Blood. 2020;136(Suppl 1):38-39.
89. Brammer JE, Zinzani PL, Zain J, et al. Duvelisib in patients with relapsed/refractory peripheral T-cell lymphoma from the phase 2 PRIMO trial: results of an interim analysis. Blood. 2021;138(Suppl 1):2456.
90. Witzig TE, Sokol L, Foss FM, et al. Proof of concept for tipifarnib in relapsed or refractory angioimmunoblastic T-cell lymphoma (AITL) and CXCL12+ peripheral T-cell lymphoma (PTCL): preliminary results from an open-label, phase 2 study. Blood. 2019;134(Suppl_1):468.
91. Horwitz SM, Feldman TA, Ye JC, et al. Phase 2a study of the dual SYK/JAK inhibitor cerdulatinib (ALXN2075) as monotherapy in patients with relapsed/refractory peripheral T-cell lymphoma. Blood. 2021;138(Suppl 1):622.
92. Kim WS, Yoon DH, Song Y, et al. A phase I/II study of golidocitinib, a selective JAK1 inhibitor, in refractory or relapsed peripheral T-cell lymphoma. J Clin Oncol. 2022;40(16_suppl):7563.
93. Haverkos BM, Alpdogan O, Baiocchi R, et al. Nanatinostat (Nstat) and valganciclovir (VGCV) in relapsed/refractory (R/R) Epstein-Barr virus-positive (EBV +) lymphomas: final results from the phase 1b/2 VT3996-201 study. Blood. 2021;138(Suppl 1):623.
94. O'Connor OA, Falchi L, Lue JK, et al. Oral 5-azacytidine and romidepsin exhibit marked activity in patients with PTCL: a multicenter phase 1 study. Blood. 2019;134(17):1395-1405.
95. Falchi L, Ma H, Klein S, et al. Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: a multicenter phase 2 study. Blood. 2021;137(16):2161-2170.
96. Kalac M, Jain S, Tam CS, et al. Real-world experience of combined treatment with azacitidine and romidepsin in patients with peripheral T-cell lymphoma. Blood Adv. 2023;7(14):3760-3763.
97. Ruan J, Zain JM, Palmer B, et al. Multicenter phase II study of romidepsin plus lenalidomide for patients with previously untreated peripheral T-cell lymphoma (PTCL). J Clin Oncol. 2021;39(15_suppl):7514.
98. Rauch DA, Conlon KC, Janakiram M, et al. Rapid progression of adult T-cell leukemia/lymphoma as tumor-infiltrating Tregs after PD-1 blockade. Blood. 2019;134(17):1406-1414.
99. Nora Bennani N, Kim HJ, Pederson LD, et al. Nivolumab in patients with relapsed or refractory peripheral T-cell lymphoma: modest activity and cases of hyperprogression. J Immunother Cancer. 2022;10(6):e004984.
100. Agbedia OO, Prakash R, Xu J, et al. Updated results of an investigator-initiated phase II study of pembrolizumab and romidepsin for patients with relapsed or refractory T-cell lymphoma (TCL) with survival analysis. Blood. 2022;140(Suppl 1):2313-2315.
101. Ramos CA, Ballard B, Zhang H, et al. Clinical and immunological responses after CD30-specific chimeric antigen receptor-redirected lymphocytes. J Clin Invest. 2017;127(9):3462-3471.
102. Zhang S, Gu C, Huang L, et al. The third-generation anti-CD30 CAR T-cells specifically homing to the tumor and mediating powerful antitumor activity. Sci Rep. 2022;12(1):10488.
103. Fleischer LC, Spencer HT, Raikar SS. Targeting T cell malignancies using CAR-based immunotherapy: challenges and potential solutions. J Hematol Oncol. 2019;12(1):141.
104. Maciocia PM, Wawrzyniecka PA, Philip B, et al. Targeting the T cell receptor β-chain constant region for immunotherapy of T cell malignancies. Nat Med. 2017;23(12):1416-1423.
105. Daher M, Melo Garcia L, Li Y, Rezvani K. CAR-NK cells: the next wave of cellular therapy for cancer. Clin Transl Immunol. 2021;10(4):e1274.
106. Cwynarski K, Iacoboni G, Tholouli E, et al. First in human study of AUTO4, a TRBC1-targeting CAR T-cell therapy in relapsed/refractory TRBC1-positive peripheral T-cell lymphoma. Blood. 2022;140(Suppl 1):10316-10317.
107. Sawas A, Elgedawe H, Vlad G, et al. Clinical and biological evaluation of the novel CD30/CD16A tetravalent bispecific antibody (AFM13) in relapsed or refractory CD30-positive lymphoma with cutaneous presentation: a biomarker phase Ib/IIa study (NCT03192202). Blood. 2018;132(Suppl 1):2908.
108. Reimer P, Rüdiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clinl Oncol. 2009;27(1):106-113.
109. Wilhelm M, Smetak M, Reimer P, 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(7):e452.
110. Park SI, Horwitz SM, Foss FM, et al. The role of autologous stem cell transplantation in patients with nodal peripheral T-cell lymphomas in first complete remission: report from COMPLETE, a prospective, multicenter cohort study. Cancer. 2019;125(9):1507-1517.
111. Janikova A, Chloupkova R, Campr V, et al. First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients. Ann Hematol. 2019;98(8):1961-1972.
112. García-Sancho AM, Bellei M, López-Parra M, et al. Autologous stem-cell transplantation as consolidation of first-line chemotherapy in patients with peripheral T-cell lymphoma: a multicenter GELTAMO/FIL study. Haematologica. 2022;107(11):2675-2684.
113. Maruyama D, Tsukasaki K, Uchida T, et al. Multicenter phase 1/2 study of forodesine in patients with relapsed peripheral T cell lymphoma. Ann Hematol. 2019;98(1):131-142.
114. Ogura M, Ishida T, Inagaki H, 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(11):1157-1163.
115. Amengual JE, Lichtenstein R, Lue J, et al. A phase 1 study of romidepsin and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma. Blood. 2018;131(4):397-407.