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**Supplement Article**

# X. Challenges and future directions in peripheral T-cell lymphoma

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## Introduction

Treatment paradigms for peripheral T-cell lymphomas (PTCLs) have been modelled after B-cell lymphomas; however, cyclophosphamide,doxorubicin, vincristine, and prednisone (CHOP)-(like) chemotherapy remains largely ineffective. The clear exception is anaplastic lymphoma kinase positive anaplastic large cell lymphoma (ALCL) (ALK + ALCL), which has high cure rates with CHOP. A subset of ALK-negative (ALK−) ALCL harbouring a *DUSP22* rearrangement has a similarly favourable outcome. Limited studies support that a 'one size fits all' approach is not optimal for all PTCLs, and there is rationale for tailored therapy for some subtypes. Recently, a number of novel agents have been explored in PTCLs, and four have been Food and drug association (FDA)-approved (pralatrexate, brentuximab vedotin, romidepsin and belinostat) for relapsed and refractory disease and are being explored in the front-line setting. Further, there have been several recent advances in the understanding of the biology of PTCLs based on molecular profiling and next-generation sequencing, which may shed light into altered pathways to target therapeutically.

## Update on molecular classification and genetics of nodal peripheral T-cell lymphomas

Despite modern diagnostics, 30–50% of cases are designated as PTCL-not otherwise specified (PTCL-NOS), and more meaningful subclassification has been elusive. The first large-scale study of gene expression profiling assembled 372 cases of PTCLs, and robust molecular classifiers were developed. For PTCL-NOS, two main groups were identified by unsupervised hierarchical clustering: 'GATA3' with high expression of GATA3 and target genes (CCR4, IL18RA, CXCR7 and IK) and 'TBX21' (TBet) with higher expression of TBX21, EOMES and known targets (CXCR3, IL2RB, CCL3 and IFNγ). Cases with a GATA3 profile had an inferior prognosis to TBX21 [1]. Approximately 20% remained unclassified. This is the first study to demonstrate biological and prognostic subgroups in PTCL-NOS. Additionally, a molecular classifier for ALK+ and ALK− ALCL was developed, the latter including three genes [TNSFR8 (CD30), BATF3 and TMOD1] that previously found to be highly specific for this entity. Finally, a prognostic classifier was developed for angioimmunoblastic T-cell lymphoma (AITL) with cases rich in B-cell-associated genes having a favourable outcome versus those with a monocytic, cytotoxic or *P53*-induced signature that had an unfavourable outcome.

Few recurrent genetic abnormalities have been reported in PTCLs with the exception of the *t*(2;5)(p23;q35) (NPM); translocation in ALK+ ALCL. Next-generation sequencing recently identified two recurrent rearrangements in ALK− ALCL: *P63* on 3q28 and *DUSP22-IRF4* locus on 6p25.3. Approximately 1/3 of cases of ALK− ALCL harboured a *DUSP22* rearrangement and had a 5-year OS indistinguishable from ALK+ ALCL (5-year OS of 90% for *DUSP22*+ ALK− ALCL versus 85% for ALK+ ALCL) [2]. Conversely, *TP63*-rearranged cases (8%) had a 5-year OS of only 17%. This study highlights key genetic and clinical heterogeneity within ALK− ALCL that may have therapeutic implications.

Next-generation sequencing and targeted sequencing have identified mutations in RHOA and the epigenetic regulators TET2, IDH2 and DNMT3A to occur frequently in AITL and PTCL-NOS with $T_{FH}$-like features [3–5]. Targeted sequencing of PTCL-NOS has also revealed a high frequency of recurrent mutations in genes involved in epigenetic regulation (25%) and DNA methylation (25%) [6].

## Challenges with CHOP as first-line therapy

The optimal therapy of PTCLs is unknown as there are few RCTs due to disease rarity. CHOP is considered the standard chemotherapy for PTCLs based on treatment paradigms for diffuse large B-cell lymphoma. The International peripheral T-cell lymphoma project reported a 5-year failure free survival rates of ~20% in PTCL-NOS and AITL in patients treated primarily with CHOP-(like) regimens, and outcomes were comparable with non-anthracycline-based regimens.

Outcomes with CHOP or CHOP-like regimens in ALK+ ALCL are generally favourable with the exception of those with multiple International Prognostic Index (IPI) factors [7]. For ALK− ALCL, the prognosis is more variable, which likely reflects not only clinical but also genetic heterogeneity, which makes study comparison difficult. The GELA group evaluated the outcome of ALK+ and ALK− ALCL patients enrolled on previously completed clinical trials, which typically incorporated doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone (ACVBP) [8]. Interestingly, ALK− ALCL patients <40 years old with a normal β2M had an 8-year OS of 100%, suggesting that some young low-risk patients have an excellent outcome with anthracyclines; however, this cohort may also be enriched for the genetically favourable subtype.

Alternative regimens have not definitively proven superior to CHOP. The GOELAMS group evaluated VIP (etoposide, ifosfamide and cisplatin)/ABVD (adriamycin, bleomycin, vinblastine and dacarbazine for six cycles compared with CHOP in an RCT [9]. The 2-year event-free survival (EFS) was similar at 45% and 41% ($P = 0.7$) for the VIP/ABVD and CHOP arms, respectively.

The addition of etoposide, typically in the form of CHOEP, was explored in a German High Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) retrospective analysis [10]. For selected young good-risk patients (<60 years old, normal lactate dehydrogenase (LDH)), incorporating etoposide improved the 3-year EFS (70.5% vs 51%, $P = 0.003$) particularly in ALK+ ALCL (3-year EFS of 91% vs 57%) with a trend observed for other nodal PTCLs 60.7% vs 48.3% ($P = 0.057$). The OS was similar for all comparisons. The Swedish registry study similarly reported that CHOEP was associated with an improvement in progression-free survival (PFS) ($P = 0.008$) in multivariate analysis with a trend towards an improved OS ($P = 0.052$) in PTCL patients <60 years old, excluding ALK+ ALCL [11]. Conversely, a US retrospective study did not find a benefit in adding etoposide ($P = 0.80$), but patient numbers were small [12].

It is unclear whether dose intensification beyond CHOP improves outcomes in PTCLs, yet this forms the basis of the rationale for consolidative autologous stem cell transplant (auto-SCT). The DSHNHL group compared CHOP and etoposide (CHOEP) with dose-escalated (high CHOEP) or a mega-dose (MegaCHOEP) variant, which incorporated stem cell rescue. Neither high CHOEP [13] nor MegaCHOEP [14] improved OS. The MD Anderson Cancer Centre reviewed 135 patients with PTCLs receiving CHOP or an intensive regimen [15]. There was no difference in the 3-year OS (62% CHOP versus 56% intensive). A recent review of 341 cases of PTCLs did not find a difference comparing CHOP to more dose-intensive regimens [12].

## Combinations with CHOP with novel agents and novel combinations in the first line setting

Several studies have evaluated the addition of a novel agent to CHOP-(like) chemotherapy. The most widely explored agent is alemtuzumab, a monoclonal antibody that binds to CD52, which is expressed on B, T and NK cells. Phase 2 studies have evaluated CHOP-(like) chemotherapy with alemtuzumab and did not clearly demonstrate superiority yet were associated with severe infections including cytomegalovirus (CMV) reactivation and epstein barr virus (EBV)-related lymphomas. Ongoing RCTs of alemtuzumab with or without CHOP14 in young patients with planned consolidative auto-SCT (ACT1 NCT00646854) and in older patients without auto-SCT (ACT2 NCT00725231) will clarify the role of alemtuzumab.

The Eastern Co-opertive Oncology Group (ECOG) group evaluated CHOP with bevacizumab in newly diagnosed PTCL, but the trial was closed early due to excess cardiac toxicity [16]. Efficacy was also poor with a 1-year PFS rate of 44% (median PFS 7.7 months). The Southwestern Oncology Group (SWOG) group evaluated a novel regimen, PEGS, combining cisplatin, etoposide, gemcitabine and methylprednisolone, and the results were disappointing with a 2-year PFS of only 14% [17]. There is an ongoing UK study comparing CHOP to gemcitabine, cisplatin and methylprednisolone (NCT01719835) in the up-front setting.

### Consolidative auto-stem cell transplant in first remission

Patients with PTCLs (excluding ALK+ ALCL) often receive a consolidative auto-SCT in first remission; however, it remains challenging to know which patients to select for this intensified approach. The Nordic group completed the largest prospective phase 2 trial (NLG-T-01) in 160 patients with PTCLs who were planned to receive CHOEP-14 (or CHOP14 for patients >60 years old) followed by high-dose chemotherapy and auto-SCT [18]. With a median follow-up of 5 years, the 5-year PFS was 44% and 5-year OS was 51% for all patients. Outcomes were superior in ALK− ALCL compared with the other PTCL subtypes (5-year PFS and OS of 61%, $P = 0.04$ and 70% $P = 0.03$). The 5-year OS and PFS for PTCL NOS were 47% and 38%, which are comparable with estimates with



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CHOP alone in the clinical trial setting. Patients who received an auto-SCT had a 5-year OS of 61%, suggesting that some patients benefit from dose intensity. Data on response status prior to transplant would be helpful as the US retrospective study failed to demonstrate a benefit of consolidative auto-SCT controlling for complete response (CR) to initial therapy [12].

### One size does not fit all: peripheral T-cell lymphoma subtype-tailored therapy

Although CHOP is considered first-line therapy for most entities, for some subtypes, alternate regimens appear to be more efficacious. For localized extranodal NK/TCL, cisplatin-based therapies with concurrent radiotherapy (RT) appear to be superior to CHOP + RT in non-randomized comparisons. A phase 2 Korean study evaluated concurrent cisplatin and RT (40Gy) followed by etoposide, ifosfamide, cisplatin and dexamethasone (VIPD) in localized NK/TCL and demonstrated a 2-year OS and PFS of 85% and 86%, respectively, and was more favourable than a historical comparison of CHOP + RT (5-year PFS of 60%) [19]. A similar approach combined dexamethasone, etoposide, ifosfamide, carboplatin (DEVIC) for three cycles with RT with encouraging results (2-year OS of 78%, 2-year PFS of 67%) [20]. For advanced stage disease, which historically has cure rates of <20%, the asparaginase-based regimen methotrexate, etoposide, ifosfamide, dexamethasone, L-asparasginase (SMILE) demonstrated an overall response rate (ORR) of 79% (CR of 45%) in newly diagnosed stage 4 patients or relapsed/refractory disease with a 1-year OS of 55% [21] and should be considered in fit patients. Hepatosplenic TCL is a rare PTCL that can occur in the setting of chronic immune suppression with only anecdotal survivors with CHOP alone. The best outcomes are observed with primary allo-SCT with over 40% of patients remaining alive and in remission [22].

For the nodal subtypes, there is more limited data for tailored therapy, but this may evolve particularly as we learn more about underlying disease biology as well as subtype-specific response to novel therapies.

## The role of transplantation in relapsed and refractory peripheral T-cell lymphoma

A detailed review describing outcomes following SCT for relapsed and refractory PTCL was recently described [23]. Although there have been no RCTs in PTCLs, collectively, retrospective studies support that auto-SCT in relapsed PTCL remains a potentially curative option if chemosensitivity is demonstrated. The Centre for International Blood and Bone Marrow Transplant Research evaluated 241 patients receiving either an auto-SCT or allogeneic SCT (allo-SCT) [24]. Excluding patients receiving auto-SCT in CR1, the 3-year PFS and OS were 42% and 53%, respectively.

There are more limited data evaluating allo-SCT in relapsed/refractory PTCL. Allo-SCT remains a viable option, particularly in refractory patients with responses observed after donor lymphocyte infusion, supporting the existence of a graft-versus-lymphoma effect. A recent literature review reported long-term disease-free rates of 35–50% and non-relapse mortality ranging from 12% to 36% including both myeloablative and non-myeloablative conditioning [25]. Although the Centre for International Blood and Bone Marrow Transplant Research study did not demonstrate a clear superiority of allo-SCT over auto-SCT, comparisons are difficult as more high-risk patients are often chosen for allo-SCT.

## Novel therapies

The most significant progress in recent years has been the evaluation of novel agents in relapsed/refractory PTCLs including the FDA approval of four agents (pralatrexate, brentuximab vedotin, romidepsin, belinostat) (Table 1).

**Table 1.** Summary of phase 2 trials in relapsed/refractory PTCLs

| Drug | Class | Type | *N* | ORR (%) | CR (%) | Median DoR (months) | Median PFS (months) | Median OS (months) |
|---|---|---|---|---|---|---|---|---|
| Pralatrexate[39] | Chemotherapy | PTCLs | 115 | 29 | 11 | 10.5 | 3.5 | 14.5 |
| Gemcitabine[34] | Chemotherapy | PTCL | 20[a] | 55 | 30 | — | — | — |
| Bendamustine[40] | Chemotherapy | PTCL | 60 | 50 | 28 | 3.5 | 3.6 | 6.2 |
| Romidepsin[30] | Epigenetic | PTCLs | 131 | 25 | 15 | 17 | 4 | 11.3 |
| Belinostat[33] | Epigenetic | PTCLs | 129 | 26 | 10 | 8.3 | 1.6 | 7.9 |
| Brentuximab[21] | Antibody drug conjugate | ALCL | 58 | 86 | 57 | 12.6 | 13.3 | NR |
| Lenalidomide[36] | Immunomodulator | PTCL | 29[a] | 24 | - | 5 | 4 | 12 |
| Alisertib[35] | Kinase inhibitor | PTCL | 37 | 24 | - | — | — | — |
| Crizotinib[37] | ALK inhibitor | ALK+ | 9 | 100 | 100 | — | — | — |

PTCL, peripheral T-cell lymphoma; DoR, duration of response; NR, not reached.
[a]Only data regarding PTCL-NOS, AITL and ALCL are reported here.



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### Antibody-based therapy

Brentuximab vedotin (BV) is an antibody drug conjugate composed of an anti-CD30 antibody conjugated to the anti-microtubule agent, monomethyl auristatin E. A phase 2 study in relapsed/refractory ALCL demonstrated an ORR of 86% (CR of 57%), median duration of response (DoR) and median PFS of 12.6 and 3.3 months, respectively [26]. Based on these data, BV was FDA approved in 2012 for relapsed/refractory ALCL following one line of therapy. With longer follow-up, the median DoR for CR patients was 26.3 months, and 16/34 (47%) remained in remission at the time of the analysis [27]. Interestingly, the results are much less striking in CD30 + PTCL-NOS with an ORR of only 33% (CR of 14%) and a median PFS of only 1.6 months [28].

Brentuximab vedotin with CHP (CHOP with omission of vincristine due to overlapping neurotoxicity with brentuximab vedotin) or preceding CHOP in the front-line setting resulted in an ORR of 85% (CR of 62%) for sequential therapy and 100% (CR of 88%) with combination treatment in CD30+ PTCLs [29]. These data form the basis of the ongoing ECHELON-2 phase 3 RCT comparing standard CHOP to CHP and BV in newly diagnosed CD30+ PTCLs, including ALCL (NCT01777152).

## Epigenetic-based therapy

There is a growing body of literature providing rationale for epigenetic therapies in PTCLs, including proven activity of histone deacetylase inhibitors. It is unclear whether recently reported mutations in epigenetic genes correlate with efficacy of these agents. The histone deacetylase inhibitors (HDACI) romidepsin was evaluated in a phase 2 study of 130 patients with relapsed/refractory PTCLs [30]. The ORR was 25% for all PTCLs, CR 15% and median DoR 17 months. This led to FDA approval in 2011. Interestingly, in a follow-up study of 19 CR patients, 10 remained in remission for over a year with a median PFS of 29 months [31]. The most common grade ≥3 side-effects were thrombocytopenia, neutropenia and infection. A phase 1b/2 study combined romidepsin with CHOP (Ro-CHOP) and reported an ORR of 68% (CR 51%) and estimated 18-month PFS of 57%. The most common toxicity was neutropenia (38%) [32]. An RCT is underway comparing Ro-CHOP to CHOP (NCT01796002). Romidepsin is under investigation in combination with GDP (gemcitabine, dexamethasone, cisplatin) in a phase 1 study through the National Cancer Institute of Canada (NCIC) in relapsed/refractory PTCLs (NCT01846390). Belinostat is another HDACI recently FDA approved (2014) based on a phase 2 study in 129 patients with relapsed/refractory PTCLs, which demonstrated an ORR of 26% and median DoR of 8.3 months [33].

## Other chemotherapeutics and novel therapies

The anti-folate pralatrexate was the first FDA approved drug approved for the treatment of relapsed/refractory PTCLs based on a phase 2 demonstrated an ORR of 29% (CR 11%) and a median PFS of 3.5 months [39]. Gemcitabine is active in pre-treated PTCL-NOS patients with an ORR of 55% and CR of 30% [34]. Despite a moderate ORR with bendamustine (50%) and CR rate of 28%, the median DoR was only 3.5 months and OS was 6.2 months. The SWOG group evaluated the aurora A kinase inhibitor alisertib in a phase 2 study in relapsed/refractory PTCLs and reported an ORR of 24% and median PFS of 3 months [35]. A separate phase 3 study is ongoing comparing alisertib to investigator's choice (NCT01482962). In a phase II trial, lenalidomide at 25 mg on days 1–21 every 28 days demonstrated an ORR of 26% and CR of 8% ($n = 40$). Median DoR was 13 months with a median OS of 12 months [36].

Crizotinib is an oral ALK inhibitor that demonstrated significant activity in pre-treated ALK+ ALCL patients. ORR was 90% (10/11) with a 2-year OS of 72% and PFS of 63% [37]. Finally, preliminary reports of the efficacy of the PI3K inhibitor duvelisib (IPI-145) in relapsed PTCLs are promising with an ORR of 47% [38].

## Future directions

Insights into the molecular basis of PTCLs will hopefully aid future risk stratification, predict treatment response and provide the basis for novel drug design. Given modest efficacy of most agents, improving outcome will likely rely on drug combinations with complementary mechanisms of action. Further, we need to better identify patients who will respond to therapies with correlative studies performed in parallel. Novel randomized phase study designs that 'pick the winner' will facilitate enrichment of populations that will benefit from the myriad of therapy options.

## Conflict of interest

K.J.S. has received honoraria from Seattle Genetics, Celgene, and Bristol Meyers Squibb.

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