Editorial Commentary

Beyond CHOP: optimising frontline therapy in peripheral T-cell lymphoma

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Comment on: 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 2022;40:242-51.

Submitted May 15, 2022. Accepted for publication Jun 08, 2022.

doi: 10.21037/apm-22-598

View this article at: https://dx.doi.org/10.21037/apm-22-598

The peripheral T-cell lymphomas (PTCLs) are well known for their rarity, diverse disease characteristics and aggressive clinical course. Accounting for less than 15% of all non-Hodgkin lymphomas, this group of mature lymphoproliferative disorders comprises 27 subtypes broadly divided into nodal, extranodal, cutaneous and leukaemic forms (1). Apart from a few indolent, predominantly cutaneous diseases, the majority of PTCL subtypes carry a poor prognosis. Nodal forms are more prevalent in the Western world, with PTCL, not otherwise specified (PTCL-NOS; ~30%), angioimmunoblastic T-cell lymphoma (AITL; 15–30%), and systemic anaplastic large cell lymphoma (ALCL; ~15%) comprising the most common subtypes (2). ALCL is further subdivided into anaplastic lymphoma kinase positive (ALK-positive) and ALK-negative ALCL. In the UK, five-year overall survival (OS) for nodal PTCL ranges from approximately 25% to 46% with the exception of ALK-positive ALCL, which has been shown to have a more favourable outcome, exceeding 75% (hmrn.org). Most patients present with advanced-stage disease, with almost two-thirds having an intermediate to high-risk International Prognostic Index (IPI) score. Risk factors for poor outcome include advanced age, stage III-IV disease, >1 extranodal site, performance status ≥2 and an elevated LDH. Clinical presentation can vary widely between subtypes depending on the primary disease site. This, coupled with heterogeneous morphology and the lack of a specific characteristic immunophenotype, make PTCLs a diagnostic challenge. Advances in gene expression profiling (GEP) and next-generation sequencing (NGS) have broadened our understanding of PTCL in recent years, building on a cell of origin model and identifying specific mutations and biomarkers to aid with diagnosis and improve definition and prognostication (3,4).

PTCLs originate from mature post-thymic T lymphocytes. The pathogenesis, although complex, is fundamentally based on the dysregulation of key signalling pathways required for normal T-cell development and differentiation and in specific cases, the role of virus-mediated transformation. The cell of origin model which identified a T follicular helper (TFH) phenotype requiring the expression of at least two antigens including PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5 has improved definitions in the latest WHO classification of this group of disorders (1). Knowledge of underlying molecular and genetic patterns is helping to refine this further. Analysis by NGS has led to the discovery of mutations in several epigenetic modifiers such as TET2, IDH2 and DNMT3A, and RHOA and TCR signalling genes including PLCG1, CD28 and PI3K. In the case of PTCL-NOS, GEP studies have identified two prognostic subgroups characterised by overexpression of transcription factors TBX-21 and GATA-3, the latter associated with a poorer clinical outcome. Within ALK-negative ALCL, similar prognostic subsets have been noted by the presence of recurrent chromosomal rearrangements involving the favourable DUSP22 gene and unfavourable *TP63* gene (5).

A deeper understanding of PTCL pathobiology has also informed newer targeted therapies resulting in the approval of several novel agents by the United States (US) Food

and Drug Administration (FDA) for single-agent use in PTCL in the relapsed/refractory (r/r) setting in recent years (pralatrexate 2009, romidepsin 2011, brentuximab 2011, belinostat 2014); leading to their subsequent evaluation in the front-line setting.

Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) has been the longstanding reference regimen for patients with previously untreated PTCL. With the exception of the rare ALK-positive ALCL subtype, responses to CHOP in nodal PTCLs are rarely durable (6) and therefore younger patients responding to induction chemotherapy frequently proceed to autologous stem cell transplantation (ASCT), although this approach is only suitable for a minority of PTCL patients (~28%) (7). The role of ASCT consolidation remains controversial however (8,9), and requires further investigation within a randomised controlled trial setting. Upfront allograft consolidation has also been evaluated in a recent randomised phase 3 study which compared consolidative ASCT versus allograft in first remission in patients aged 18–60 years, however no benefit for allograft in this setting could be demonstrated as the strong graft versus lymphoma effect was counteracted by increased transplant-related mortality (10).

Attempts have been made to improve on CHOP as a front-line regimen in PTCL, either with novel chemotherapy drug combinations or through the incorporation of novel agents with the CHOP backbone. Surpassing CHOP has proven historically challenging however, with gains in efficacy frequently being offset by increased toxicity (11,12).

The addition of etoposide to CHOP (CHOEP) was associated with improved event-free survival (EFS) in post hoc analyses of the German high grade lymphoma study group, however the effect was limited to the subgroup of younger PTCL patients (aged ≤60 years) with low LDH, and there was no demonstrable OS benefit (13). Consequently, the CHOEP regimen is frequently administered as induction therapy for this younger patient subgroup, although the benefit remains to be proven in a randomised trial setting.

Undoubtedly the most significant development in the first-line treatment of PTCL to date has been the incorporation of the antibody drug conjugate brentuximab vedotin (BV) targeting the CD 30 surface antigen into upfront therapy. CD 30 is expressed in almost all systemic ALCL, ~60% of PTCL-NOS and ~50% of AITL (14). In the landmark ECHELON-2 phase 3 study, patients with previously untreated PTCL with >10% CD30+ expression were randomised between BV in combination with cyclophosphamide, doxorubicin and prednisolone (A+CHP) and standard CHOP. A+CHP treated patients demonstrated a significant reduction in disease progression and improved OS versus standard CHOP (15). This targeted drug is now approved upfront for those with CD30+ PTCL in the US and Japan, whilst in the UK, approval by the European Medicines Agency (EMA) is currently restricted to CD30+ systemic ALCL only (~15% of all PTCLs), given the small numbers of non-ALCL subtypes enrolled in the trial, with consequent lack of power to confirm a clear benefit for non-ALCL subgroups.

CHOP in combination with novel agents continues to be the focus of most new approaches in the management of previously untreated PTCL with potential candidates taken from novel agents currently approved in the r/r setting. Romidepsin, the selective class I histone deacetylase (HDAC) inhibitor, is such an example presented in the phase 3 Ro-CHOP study published by Bachy and colleagues from the LYSA group in the *Journal of Clinical Oncology* in November 2021 (16). Single-agent romidepsin was found to be efficacious in r/r PTCL following a pivotal study which demonstrated an overall response rate (ORR) of 25% and CR in 15% (17). The Ro-CHOP phase 3 multi-centre international study recruited an impressive 448 patients with early- to advanced-stage PTCL, covering several nodal, extranodal and cutaneous PTCL subtypes excluding the more favourable ALK-positive ALCL subgroup. The authors report the largest front-line randomised controlled trial in PTCL to date which is commendable given the rarity of this lymphoma. Patients were randomised to either standard CHOP or romidepsin in combination with CHOP (Ro-CHOP) and assessed for response, toxicity and survival, with PFS defined as the primary end point. Despite a longer duration of response by the addition of romidepsin, there was no significant difference in OS and PFS between treatment arms, and the primary endpoint was not met. Moreover, patients in the Ro-CHOP arm experienced higher toxicity rates, particularly haematological toxicity and increased infection risk, a common theme in previous trials attempting to build on the CHOP regimen. While the combination of Ro-CHOP did not emerge as a new standard of care for PTCL in this trial, there was a suggestion of improved PFS for Ro-CHOP-treated patients with the TFH phenotype in the subgroup analysis, which would be anticipated given the pathobiology of this PTCL subtype.

In line with the Ro-CHOP study findings, several recent studies evaluating upfront novel combination regimens with

CHO(E)P have had disappointing results. The recently reported PTCL 13 trial also did not demonstrate any improvement in outcomes with the addition of romidepsin to CHOEP (18). Furthermore, the immunomodulatory agent lenalidomide which demonstrated activity as a single agent in r/r PTCL (particularly of the AITL subtype) was trialled in combination with CHOP in elderly patients with AITL, as well as with CHOEP in newly diagnosed PTCL, with unsatisfactory outcomes (19,20). In the latter phase 2 study, modest response rates were once again blighted by haematological toxicities leading to therapy discontinuation. Pralatrexate, the FDA-approved antifolate agent in r/r PTCL has also been evaluated with anthracycline-free chemotherapy regimen (COEP) as first-line therapy, but was not found to be superior when compared to historical CHOP data (21).

Despite historical challenges, the future therapeutic landscape in PTCL looks promising, with several novel combinations currently undergoing further evaluation both in the treatment-naïve and r/r settings, many with encouraging results. Particularly noteworthy emerging therapeutic approaches in PTCL at present are the PI3K kinase-δγ inhibitor duveslisib, and novel epigenetic modifier combinations.

Duvelisib, a P13K tyrosine-kinase inhibitor that acts on signalling pathways essential to B and T-cell lymphoproliferation, is currently used in the treatment of r/r B-cell lymphomas. It has demonstrated efficacy as a single agent in PTCL from the PRIMO trial with an ORR of 50% and CR in 32% in the r/r setting (22). Duvelisib has also been evaluated in combination with romidepsin in r/r PTCL with encouraging results (NCT02783625).

The DNA hypomethylating agent azacitidine is a logical new therapeutic agent in PTCL given the emerging molecular landscape. A recent multicentre phase 2 study evaluated the combination of azacitidine with romidepsin in r/r PTCL with ORRs of 61% and CR 48%, although the effect was even more marked in patients with a TFH subtype (23). Furthermore, a phase 2 study investigating azacitidine-CHOP as initial treatment in PTCL with a predominantly TFH phenotype, demonstrated excellent end of treatment CR rates and PFS at 1 year; unlike other CHOP combinations, haematological toxicities in this study were as expected and manageable (24). Evaluation of duvelisib as a potential induction therapy in combination with anthracycline-based regimen for CD30- PTCL is also underway in a phase 2 study, alongside Azacitidine-CHO(E)P (NCT04803201). Belinostat, an FDA-approved HDAC inhibitor for use in r/r PTCL, is another novel agent to be drawn from the relapsed setting and combined with CHOP for upfront use. Results from a phase 1 study are encouraging, appearing to show better CR rates and fewer toxicities in comparison to Ro-CHOP; further studies to validate these findings are awaited (25).

Other promising therapeutic approaches undergoing evaluation in the front-line PTCL setting include and the combination of the proteasome inhibitor bortezomib, an inhibitor of nuclear factor kappa B pathway with cyclophosphamide, epirubicin, etoposide and prednisone (BCHEP) which is currently being evaluated in a phase 2 front-line study (NCT04061772); while CD 30-directed CAR-T cell therapy (NCT 04083495) and the EZH2 inhibitor valemetostat (NCT04703192) are also being investigated in the r/r setting, alongside several other novel agents.

While Ro-CHOP was not superior to CHOP in the first-line treatment of PTCL, the role of romidepsin most certainly warrants further exploration in PTCL, particularly in patients with the TFH phenotype. Novel combinations of romidepsin with more targeted agents as outlined above rather than chemotherapy may mitigate against the significant toxicity observed with the Ro-CHOP combination. Initial data suggest that the combination of other epigenetic modifiers (azacitidine, belinostat) with CHOP appears to be more efficacious and better tolerated in comparison to Ro-CHOP and further evaluation of these combinations +/– duvelisib in front-line clinical studies is awaited. Another area warranting further exploration in PTCL is the role of maintenance therapy with a targeted agent following front-line induction, with the potential for deepening responses and prolonging remissions. The Ro-CHOP study investigators have also clearly demonstrated that conducting a successful large multi-centre trial in a rare disease entity is feasible, and ongoing international collaboration remains critical to moving the treatment paradigm forward in PTCL. Unmasking the genetic and molecular landscape of this diverse and complex disease has led to greater diagnostic accuracy and prognostication. More importantly, it is paving the way for new targeted agents and expanding the options for potential drug combinations, both old and new, hopefully moving towards an era of more individualised therapy in biomarker-driven populations and in turn, better overall outcomes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Palliative Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-598/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Amin F, Gleeson M. Beyond CHOP: optimising frontline therapy in peripheral T-cell lymphoma. Ann Palliat Med 2022;11(7):2548-2552. doi: 10.21037/apm-22-598

