INPLASY

Novel agents versus CHOP regimens as first-line therapy in peripheral T-cell lymphoma (PTCL): a systematic review of randomised controlled trials

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ADMINISTRATIVE INFORMATION

Support - Takeda (China) , Shanghai.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - J.H.L. and L.W. are employees of Takeda. The remaining authors declare no other competing interests.

INPLASY registration number: INPLASY202670038

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 July 2026 and was last updated on 14 July 2026.

INTRODUCTION

Review question / Objective To systematically evaluate the efficacy and safety of novel therapeutic regimens compared to the standard of care (SOC) with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as first-line treatment for patients with newly diagnosed peripheral T-cell lymphoma (PTCL), and to explore subgroup effects by major histological subtypes.

Background Peripheral T-cell lymphomas (PTCLs) are rare but highly aggressive malignancies, with heterogeneous clinicopathologic presentations. PTCLs are derived from mature T-cells or natural killer (NK)/T-cells and represent a group of non-Hodgkin lymphomas (NHLs), which comprise 5-10% of NHLs in Western countries versus 15-20% in Asian countries. PTCL mainly affects adults, with the median age of onset typically around 60 years old. In addition, there is no age limit for the onset of the disease, and the peak is at 60-70 years old. PTCLs mainly invade lymph nodes and are also prone to involve extra-nodal sites such as the skin, gastrointestinal tract, liver, spleen, and bone marrow. PTCLs oncogenesis is a complex process consisting of dysregulation of T-cell receptor (TCR) signaling pathways intrinsic to malignant T cells, and interplay with the tumor microenvironment. According to the recent International Consensus Classification of Mature Lymphoid Neoplasms (ICC) and the 5th edition of World Health Organization Classification of Hematolymphoid Tumors (WHO-HAEM5) 2022, there are over 30 different subtypes. Among them, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), nodal T-follicular helper cell lymphoma (T-FHCL), and anaplastic large cell

lymphoma (ALCL) are common subtypes of PTCLs.

PTCL-NOS is a heterogeneous collection of PTCLs that cannot be classified into any other defined subtype, which is the most common type of PTCL worldwide (36% of all PTCLs), as well as in North America (33%), Europe (37%), South America (40%), and Asia (21-28%). T-FHCL, angioimmunoblastic type, previously known as AITL, is an aggressive PTCL characterized by the proliferation of high endothelial venules and T-follicular helper cells. AITL recently represents 13.5% of PTCLs globally, 21% in Europe and North America, 7% in South America and 18-25% in Asia. ALCL as characterized by large neoplastic cells with pleomorphic nuclei and uniform strong expression of CD30 and is organized into three separate entities-anaplastic lymphoma kinase (ALK)+ ALCL, ALK- ALCL, breast implant associated ALCL (BIA-ALCL) in the WHO-HAEM5. ALK+ ALCL more recently represents 8-9% of PTCLs worldwide, in Asia (5-7%) versus North America (9%), Europe (9%), and South America (4-9%). ALK- ALCL represented about 19% of PTCLs, in North America (8-14%), in Europe (9-14%), in Asia (2.6-4.5%). BIA-ALCL is a relatively new entity with incidence rate of 8.1 per 100 million females per year.

Rationale PTCLs are notoriously challenging to treat and outcomes are typically poor, and the first-line chemotherapy of PTCLs has limited efficacy. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-like regimens such as CHOEP (CHOP + etoposide) and dose adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin), have been the mainstay of front-line therapy of PTCL subtypes being considered the de facto standard of care (SOC). However, CHOP has failed to achieve satisfactory long-term outcomes in PTCLs, with low overall survival rates and high relapse rates. Furthermore, for several rare PTCL subtypes-including extranodal NK/T-cell lymphoma (ENKTL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), and hepatosplenic T-cell lymphoma (HSTCL)-CHOP is not recommended as standard care due to poor efficacy. More recently, CD30 antibody drug conjugate, brentuximab vedotin with CHOP (BV-CHP) was demonstrated superior progression free survival (PFS) and overall survival (OS), and this regimen has become the preferred choice for CD30+ PTCLs, especially ALCL. BV-CHP regimen has been recommended for the treatment of ALCL and CD30+ histologies PTCLs as the preferred regimen by clinical practice guidelines. Currently, several novel agents, including histone deacetylase inhibitors (HDACi, e.g. romidepsin, belinostat, and chidamide), DNA methyltransferase inhibitor (DNMTi, e.g. azacitidine), anti-T-cell monoclonal antibodies (e.g. alemtuzumab and mogamulizumab), immunomodulatory agents (e.g. lenalidomide), oncogenic kinase inhibitors (e.g. inhibitors of the PI3K/Akt/mTOR pathway: duvelisib, copanlisib, and alisertib), immunotherapeutics (e.g. nivolumab and pembrolizumab) and other agents (e.g. proteasome inhibitors, such as bortezomib) have been investigated to improve the therapeutic outcome of PTCLs. Targeted modifications of CHOP regimens, by addition to, substitute within, or replacing CHOP components to explore CHOP-Plus regimens as novel combination therapies may overcome the limitations of current strategies and provide more effective, personalized treatments for PTCLs. However, the lack of the efficacy and safety of novel combination therapeutic regimens has left clinicians with limited alternative options. Up to date, there is no systematically analysis of the efficacy and safety of novel therapeutic regimens compared to the SOC with CHOP regimens as first-line treatment for patients with newly diagnosed PTCL.

METHODS

Strategy of data synthesis Searches will be conducted in PubMed, EMBASE, the Cochrane Library and Web of Science, from inception to now without limitations on the date/time. The search strategy will combine MeSH terms and free-text words. The search will be constructed around the "Population" and "Study Design" components of PICO, keeping the "Intervention" and "Comparator" broad to ensure maximum sensitivity. A detailed search strategy is available in the supplemental.

EMBASE

#1. 'T cell lymphoma'/exp OR (((peripheral OR mature OR "angio-immunoblastic" OR angioimmunoblastic OR cutaneous OR gammadelta OR "gamma-delta" OR "g and d" OR "g d" OR GD OR "hepato-splenic" OR hepatosplenic OR intestinal) NEAR/4 ("T cell lymphoma*" OR "T-cell NHL" OR "T-NHL" OR "T-NHLs" OR "T-cell NHL" OR "T-cell NHLs" OR TCL)) OR ((peripheral OR mature) NEAR/3 "T cell" NEAR/3 lymphoma*) OR "peripheral TCL" OR PTCL OR GDTCL OR AITL OR ALCL OR (anaplastic NEAR/3 cell NEAR/3 lymphoma*) OR ("Ki-1" NEAR/3 lymphoma*) OR NKTCL OR ((NK OR "natural killer") NEAR/3 lymphoma*) OR ATLL OR "T-ALL" OR "coT-ALL" OR ((lymphoblastic OR lymphatic OR "T-cell") NEAR/3 (leukemia OR leukaemia))):ab,ti,kw 158,360

#2. ("newly diagnos*" OR "new diagnos*" OR untreated OR "first line" OR "1ST line" OR "1 line" OR "treatment naive" OR frontline OR "front line"):ab,ti,kw 782,275
#3. CHOP:ab,ti,kw
#4. (cyclophosphamide OR ciclolen OR cyclophosphamid OR endoxan OR ledoxan OR ledoxina OR syklofosfamid):ab,ti,kw
#5. (doxorubicin OR adriamycin OR adrim OR adrimedac OR caelix OR evacet OR farmiblastina OR "mcc 465" OR "nk 911" OR thermodox):ab,ti,kw
#6. (Vincristine OR Oncovin* OR Leurocristine OR Vincrisul OR Vincasar OR Onkocristin OR Vintec):ab,ti,kw
#7. (prednisone OR cortan OR decortisyl OR deltacortene OR deltisona OR fernisone OR lodotra OR panafcort OR sterapred):ab,ti,kw
#8. #1 AND #2 AND (#3 OR (#4 AND #5 AND #6 AND #7)) 1119，会议摘要673
#9. ('controlled clinical trial'/exp OR 'Controlled Clinical Trial (Topic)'/exp OR 'double blind procedure'/de OR 'control group'/de OR 'crossover procedure'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR 'placebo'/de OR 'randomization'/exp OR (random* OR trial OR groups OR placebo* OR crossover OR "cross-over" OR "Factorial design*" OR ((Doubl* OR Singl* OR tripl*) NEAR/2 Blind*)):ab,ti,kw) NOT (('nonhuman'/exp OR 'animal'/exp) NOT 'human'/exp) 6,160,849
#10. #8 and #9 560，会议摘要329.

Eligibility criteria Population(s):
Adults (≥ 18 y) with newly diagnosed, histologically confirmed PTCL (any World Health Organization (WHO) subtype except primary cutaneous T-cell lymphoma).

Prior oncological therapy for PTCL is not permitted. Studies exclusively focused on pediatric patients will be excluded.
Interventions:
Any experimental therapy added to, substituted within, or replacing CHOP components (e.g., BV-CHP, CHOEP, alemtuzumab-CHOP, romidepsin-CHOP, bortezomib-CHOP, lenalidomide-CHOP, etc.).
Comparisons:
Standard CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone)
Outcomes:
1. Primary Outcomes:
Progression-Free Survival (PFS): Defined as the time from randomization to the first documentation of disease progression or death from any cause.
Overall Survival (OS): Defined as the time from randomization to death from any cause. We will use the HR and its 95% CI.

2. Secondary Outcomes:
Overall Response Rate (ORR): The proportion of patients achieving a complete response (CR) or partial response (PR);
Complete Response (CR) Rate: The proportion of patients achieving a CR;
Safety and Tolerability: Incidence of total adverse events (AEs), treatment-related adverse events (TRAE).
Incidence of Grade ≥ 3 AEs. We will focus on key AEs such as febrile neutropenia, peripheral neuropathy, sepsis, anemia, and thrombocytopenia.

Subgroup:
Systemic Anaplastic Large-Cell Lymphoma (sALCL)
Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS)
Angioimmunoblastic T-Cell Lymphoma (AITL)
Study design: Only randomized controlled trials (RCTs) will be included.
Other: Original full articles written in English or Chinese.

Source of evidence screening and selection
The study selection process will be conducted by two reviewers independently in a two-stage process, using a systematic review management software (e.g., Rayyan: AI-Powered Systematic Review Management Platform). Phase 1 – Two reviewers will independently screen the titles and abstracts of all records retrieved from the searches against the pre-defined PICO eligibility criteria. Phase 2 – all potentially relevant citations will be requested and examined in detail using the full-text version. In cases where data of the same population are reported more than once, the latest publication will be retained. If disagreements arise, a third reviewer can help resolve the disagreement. Reasons for exclusion will be recorded verbatim and presented in a PRISMA diagram.

Data management Two reviewers will extract data from each study independently using a standardized data extraction form. Any disagreements will be resolved by discussion, with the assistance from a third reviewer if necessary. Where more information relating to a potentially includable study is lacking, we will contact study authors and request further information. We plan to extract all relevant characteristics of all included studies and remove duplicated data.
Data extraction form:

Publication and study characteristics
• First author and year
• Publication title • Trial or study name
• Country and region
Patient characteristics
• Sample size
• Age (mean/median)
• Sex (n, %)
• Distribution of PTCL subtypes • Race (n, %)
• ECOG/WHO performance status
• International Prognostic Index (IPI) scores
• CD30 expression levels
Treatment
• Drug
• Dosage • Cycle
• Follow-up
Efficacy and safety
• OS
• PFS
• ORR
• CR • Any AEs
• TRAE.

Reporting results / Analysis of the evidence We first create a heatmap to show the tendency of different therapies compared to SOC regimens in terms of different outcomes, for an overview. In the heat-map, rows and columns represent different drug combinations and outcome measures, respectively. The color intensity indicates the performance strength of each combination for a specific outcome—darker colors denote a better or more pronounced effect. Here is an example of a heatmap in tabular form, illustrating the performance of different drug combinations across various outcome measures. In the figure, dark green indicates that the intervention group is significantly better than the control group; light green indicates that the intervention group has a better point estimate than the control group, but the difference is not statistically significant; red indicates that the intervention group is significantly worse than the control group; light red indicates that the intervention group has a worse point estimate than the control group, but the difference is not statistically significant. This visualization allows researchers to rapidly identify which regimens are advantageous or disadvantageous versus the SOC, across various efficacy or safety endpoints.
If studies are deemed sufficiently homogeneous (clinically and statistically), we will perform a meta-analysis. Given the expected clinical heterogeneity in PTCL populations and treatments, a random-effects model will be the primary method for pooling effect estimates using R. For dichotomous variables, the effect size is assessed using risk ratio (RR) and 95% confidence interval (CI). For time to events variables, such as PFS and OS, hazard ratios (HR) and 95% CI values are extracted for different comparisons. HR estimates the risk rate ratio between two comparison groups over the entire study period, indicating the treatment effect on the occurrence of the event.
Subgroup analyses:

PTCL Histology；Age；CD30 Expression.

Presentation of the results We intend to publish the results of this systematic review in a leading, peer-reviewed international journal in the field of hematology or oncology. The reporting of the review will strictly adhere to the PRISMA 2020 statement.

Proposed Publication Outline:

Introduction:
Overview of PTCL, limitations of current SOC, rationale for the systematic review.
Methods: Detailed description of the protocol, including eligibility criteria (PICO), search strategy, study selection, data extraction, risk of bias assessment, and statistical analysis methods.
Results:
Study selection (PRISMA flow diagram).
Characteristics of included studies (table).
Risk of bias assessment (summary graph and plot).
Synthesis of findings for primary and secondary outcomes, including forest plots for meta-analyses.
Results of subgroup.
Discussion:
Summary of main findings.
Interpretation of results in the context of clinical practice.
Strengths and limitations of the review (e.g., heterogeneity of PTCL, risk of bias in primary studies, po.

Language restriction none.

Country(ies) involved China.

Keywords Lymphoma, T-Cell,peripheral.

Contributions of each author
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