Efficacy of Frontline Chemotherapy for Extranodal Natural Killer/T-Cell Lymphoma: A Systematic Review and Network Meta-Analysis

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Abstract

Background: Treatment with non-anthracycline (ANT)-based chemotherapy has increased survival in patients with extranodal natural killer/T-cell lymphoma (ENKTCL). However, the relative efficacy of various drug combinations has been contentious. We aimed to identify the most effective chemotherapy regimens for newly diagnosed ENKTCL.

Methods: A network meta-analysis was performed to evaluate the differences in survival and treatment responses across various regimens. The primary objective was overall survival (OS), while secondary outcomes included progression-free survival (PFS), objective response rate (ORR), and complete response (CR). We utilized a Bayesian framework to perform the network meta-analysis. Rank probabilities were assessed by the surface under the cumulative ranking curve (SUCRA). Node-splitting method was used to assess the inconsistency.

Results: A total of 1,113 patients were enrolled across 10 studies. Chemotherapy regimens were grouped into five modalities, for which six types of direct comparisons were available. We identified the asparaginase (ASP)/gemcitabine (GEM)-based regimens superiority over ANT-based, non-ASP/ANT-based and ASP/methotrexate (MTX)-based regimens on OS. Although no significant differences were observed compared with ASP/not otherwise specified-based, ASP/GEM-based regimens were still the best option chemotherapy for OS. Moreover, the ASP/GEM-based regimens demonstrated advantages in PFS, ORR and CR.

Conclusions: According to our network meta-analysis, it appears that ASP/GEM-based regimens could potentially serve as the most effective frontline chemotherapy option for ENKTCL.

Keywords: NK/T-cell lymphoma; Chemotherapy; Survival outcome; Network meta-analysis

Introduction

Extranodal nasal-type natural killer/T-cell lymphoma (ENK-TCL) is the prevalent and aggressive histological subtype of peripheral T-cell lymphoma in Asia and South America [1-3]. It is known to be associated with Epstein-Barr virus (EBV) infection and frequently located in the upper aerodigestive tract (UADT) with early-stage disease [4-6]. More than 70% of patients present with local disease generally managed with combined modality therapy involving irradiation and chemotherapy, while advanced-stage disease is mainly treated with systemic chemotherapy [6-8]. However, the 2-year overall survival (OS) rate of advanced ENKTCL was only about 30.0% in the era of anthracycline (ANT)-based chemotherapy [9-13].

ENKTCL is usually resistant to ANT-based regimens, as a consequence of overexpression multidrug resistant (MDR) P-glycoprotein and loss of p53 function, which differs from conventional high-grade B-cell lymphomas treated with ANT-based CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CHOP-like regimens [14-16]. A series of phase 2 and large multicenter retrospective studies have shown that non-ANT-based regimens improved survival compared with ANT-based regimens [12, 17-26]. In recent years, the cornerstone of frontline therapy for ENTKCL has been both radiotherapy (RT) and non-ANT-based chemotherapy. Accumulating evidence reveals that asparaginase (ASP)-based regimens significantly increased the survival benefit [12, 18-26]. Due to the upfront RT and ASP-based chemotherapy, the survival outcomes have improved over the last past decade, with 5-year OS rates of 60-90% for early-stage and 30-40% for advanced-stage disease [7, 8, 10, 11, 21-23, 27]. Numerous combinations explored ASP-based chemotherapy regimens, such as best-studied regimen SMILE (L-ASP, methotrexate (MTX), ifosfamide (IFO), etoposide (VP-16), and dexamethasone), and P-GEMOX (pegaspase...
gase, gemcitabine (GEM), and oxaliplatin) regimens. However, the optimal chemotherapy combination remains to be defined.

As a rare cancer, there is limited evidence from randomized clinical trials to inform treatment of advanced disease. Therefore, we systematically searched available literature with the aim to summarize currently available data from the pool of eligible studies to compare different chemotherapy regimens. This will eventually help to find the most optimal treatment for this disease.

Materials and Methods

Eligibility criteria, literature search, and study selection

The network meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [28, 29]. We systematically searched two databases including PubMed/Medline and EMBASE in March 2022. Studies considered eligible for inclusion were either randomized controlled trials or non-randomized controlled studies, which compared the outcomes of different chemotherapy regimens in the treatment of newly diagnosed ENKTCL patients (adult patients, > 18 years of age) with early-stage and/or advanced-stage.

Based on the previous studies, chemotherapy regimens were classified into five combinations: ANT-based (CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) or CHOP-like), ASP/GEM-based (ASP combined with GEM), ASP/MTX-based (ASP combined with MTX), ASP/not otherwise specified (NOS)-based (ASP-based without GEM or MTX), and non-ASP/ANT regimens (without ASP and ANT, usually with GEM, etoposide (VP-16) or ifosfamide (IFO)). Studies eligible for inclusion met all of the following criteria: 1) included different chemotherapy regimens that can be classified into the five combinations; 2) participants were treated with chemotherapy regimens; 3) reported survival data; and 4) published in English. Studies published online ahead of print were eligible, but meeting abstracts were excluded. When multiple publications reporting on the same study population were identified, the one with the most updated and/or comprehensive adverse event data was selected.

Search strategy

Relevant articles published from 2000 to 2022 were retrieved from MEDLINE and Embase. Keywords as follows were used for searching: “natural killer/T-cell lymphoma, chemotherapy, asparaginase, non-asparaginase drugs”; we searched MEDLINE using medical subject headings (MeSH) and text words. Initial search was performed by two reviewers by screening titles and abstracts of retrieved articles independently. Irrelevant studies were expelled, and full texts of enrolled articles were evaluated for inclusion. Reference lists of acquired articles were also checked manually for relevant studies. The full texts of all articles identified as relevant during the title and abstract screening stage were obtained and reviewed.

Data extraction and quality assessment

The primary efficacy endpoint was OS. The data summarized from the eligible clinical trials included the study, number of patients, Ann Arbor stage, combined modality treatment, chemotherapy, treatment response, and survival outcomes. The extracted results included OS, progression-free survival (PFS) with hazard ratios (HRs) and 95% confidence intervals (CIs). Meanwhile, the numbers and incidences of complete response (CR) and objective response rate (ORR) were also extracted and recorded. The quality of clinical trial was assessed using the modified Newcastle-Ottawa Scale, which involved evaluating patient selection, comparability between the experimental and control groups, and result assessment [30]. Two independent investigators conducted the evaluation, with any discrepancies resolved by a third one.

Statistical analysis

A network meta-analysis was performed to combine studies addressing the same clinical outcome and studied chemotherapy regimens; the results were evaluated by the OR with 95% CI. Heterogeneity was assessed by the I 2 test, with an I 2 > 50% considered as the existence of significant heterogeneity [21]. For groups without significant heterogeneity, fixed-effect model was applied. The network meta-analysis using a Bayesian framework was conducted [31]. The Markov-chain Monte Carlo (MCMC) method was used to obtain the non-informative uniform. Four iteration chains, with 50,000 iterations per chain, were set to fit the model and calculate the posterior distributions of model parameters. Of 95% CI, HRs or ORs did not contain 1, indicating significant differences between interventions. A value of P < 0.05 was considered statistically significant. The surface under the cumulative ranking value (SUCRA) derived from posterior probabilities was used to rank the relative efficacy and safety of interventions with higher SUCRA values indicating better interventions [32]. Clustered ranking plots were used for the determination of optimal intervention choice. A node-splitting method was used to assess local inconsistency for each endpoint with a P < 0.05 indicating significant inconsistency. Sensitivity analysis was conducted to identify any sources of inconsistency. Publication bias within each network was evaluated using a funnel plot and Egger’s test. Statistical analyses were undertaken with GeMTC (version 1.01) and JAGS packages (version 4.3.0) [33] in R 4.1.2 (version 4.1.2) [34].

Results

Study selection and characteristics

According to the inclusion criteria, a total of 10 studies published between 2013 and 2022 were identified for the chemotherapy regimens review of ENKTCL [9, 18, 35–42]. The article inclusion and exclusion procedures are demonstrated in
a consort flow diagram of study selection (Fig. 1). All of the included articles were controlled trials, and seven studies were retrospective. The study and clinical characteristics are summarized in Supplementary Material 1 (www.thejh.org). The Newcastle-Ottawa quality assessment scale was applied to evaluate the quality, and the scores ranged from 7 to 9 points (Table 1 [9, 18, 35-42]). The funnel plot shows that there was no significant publication bias in the included studies (Supplementary Material 2, www.thejh.org).

The respective network graph is shown in Figure 2. In total, 1,113 patients were included in the current network meta-analysis and 194 patients (17.4%) received ANT-based regimens while the others (82.6%) received non-ANT-based regimens. Among the non-ANT-based regimens, 515 patients (46.3%) received ASP/GEM-based regimens, 82 patients (7.4%) received ASP/MTX-based regimens, 212 patients (19.0%) received ASP/NOS-based regimens and the others (9.9%) were treated with non-ASP/ANT-based regimens. Most patients (80.4%) had early-stage disease, and more than 42.5% of them were classified into intermediate- and high-risk groups.

### OS and PFS

The primary outcome of this analysis involved conducting a network meta-analysis to assess the effect of five chemotherapy combinations on OS. Ten articles including 1,113 cases were eligible for the analysis of OS. Our results verified that ASP/GEM-based regimens independently predicted superior OS (Fig. 3a). Compared with ASP/GEM-based regimens, the HRs for OS with ASP/MTX-based, non-ASP/ANT-based, and ANT-based regimens were, respectively, 1.68 (95% CI: 1.03 - 2.75), 1.77 (95% CI: 1.06 - 2.95), and 2.32 (95% CI:...
Table 1. Quality Assessment of the Included Studies Based on the Newcastle-Ottawa Scale

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<th>Representativeness of the exposed cohort</th>
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<th>Ascertainment of treatment</th>
<th>Outcome was not present at start</th>
<th>Comparability of cohorts</th>
<th>Assessment of outcome</th>
<th>Follow-up was long enough</th>
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Figure 2. Network diagrams. (a) OS; (b) PFS; (c) ORR; (d) CR. The size of the nodes is proportional to the number of patients, which is given under each treatment category. The width of the lines is proportional to the number of comparisons, which are given on each line. ASP: asparaginase; GEM: gemcitabine; MTX: methotrexate; ANT: anthracycline; NOS: not otherwise specified; OS: overall survival; PFS: progression-free survival; ORR: objective response rate; CR: complete response.
1.45 - 3.72; Fig. 3a). Significant difference in survival was not observed between ASP/NOS-based regimens versus ASP/GEM-based regimens (HR: 1.10; 95% CI: 0.64 - 1.88; Fig. 3a). Chemotherapy groups were compared with each other independently; HRs and corresponding 95% CI were calculated (Fig. 4a).

For PFS analysis, eight articles including 707 cases were reviewed. Although PFS was significantly improved in patients with ASP/GEM-based regimens compared to ASP/MTX-based, non-ASP/ANT-based, and ANT-based regimens were, respectively, 1.69 (95% CI: 1.06 - 2.69), 5.02 (95% CI: 1.42 - 18.07) and 2.10 (95% CI: 1.30 - 3.48; Fig. 3b). Significant difference in survival was not observed between ASP/GEM-based and ASP/NOS-based regimens (HR: 1.01; 95% CI: 0.59 - 1.75; Fig. 3b). The chemotherapy regimens were independently compared, and HRs along with their corresponding 95% CIs were computed (Fig. 4a).

**Treatment response**

The analysis of ORR was conducted on nine studies including 988 cases. Using ASP/GEM-based regimens as the reference, ASP/MTX-based (OR: 0.18; 95% CI: 0.05 - 0.53) and ANT-based (OR: 0.21; 95% CI: 0.10 - 0.41) regimens were significantly associated with lower ORR. Neither ASP/NOS-based...
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(OR: 0.67; 95% CI: 0.30 - 1.41) nor non-ASP/ANT-based (OR: 0.50; 95% CI: 0.23 - 1.10; Fig. 3c) regimens showed significant differences. The comparative analysis of five chemotherapy combinations is presented in the league chart located in the lower-left corner of Figure 4b.

For CR analysis, eight articles including 671 cases were considered. As illustrated by forest plot, ASP/GEM-based regimens helped more patients achieve a CR than non-ASP/ANT-based (OR: 0.16; 95% CI: 0.03 - 0.68) and ANT-based regimens (OR: 0.29; 95% CI: 0.17 - 0.50; Fig. 3d). However, there were no significant differences in CR when comparing ASP/GEM-based with ASP/MTX-based (OR: 0.67; 95% CI: 0.30 - 1.49) or ASP/NOS-based (OR: 0.86; 95% CI: 0.47 - 1.59; Fig. 3d) regimens. All regimens are compared with each other in the league table in the upper-right corner of Figure 4b.

Figure 4. League chart. (a) Combined HR (95% CI) of OS (lower triangle) and PFS (upper triangle). (b) Combined OR (95% CI) of ORR (lower triangle) and CR (upper triangle). The data in each cell are HR or OR (95% CI) comparing row definition processing and column definition processing. HR < 1 or OR > 1 indicates better results. PFS: progression-free survival; OS: overall survival; HR: hazard ratio; OR: odds ratio; ORR: objective response rate; CR: complete response.
In the following analyses, we utilized the SUCRA value to compare the estimated rank probabilities of various groups. The outcomes were visually presented in the ranking diagram (Fig. 5). As indicated by the data, ASP/GEM-based regimen ranked the highest in both survival and treatment response, which suggested the advantage of ASP/GEM-based regimens over ASP-drug conjugate MTX, or other drugs. ASP/NOS-based regimens ranked the second for OS, PFS, ORR and CR. Moreover, the results indicated that the ANT-based regimen exhibited the lowest OS among the five groups, while the non-ASP/ANT-based regimen demonstrated the lowest rank of PFS and CR. It is rendered them the least satisfactory chemotherapy combinations, particularly ANT-based, which is always ranked fourth or fifth.

Comparisons between direct and indirect evidences

The assessment of the inconsistency of our findings was conducted through the utilization of the node-splitting method, along with Bayesian P value. In most cases, the CIs derived from direct and indirect evidence were largely congruent, albeit with minor discrepancies. However, notable disparities were detected in certain comparisons, thereby constraining the applicability of our results. Specifically, the comparison of ASP/MTX-based and ASP/GEM-based regimens in terms of their efficacy in achieving CR (P = 0.033), as well as the comparison of ASP/MTX-based and ANT-based regimens in this regard (P = 0.035), yielded similar outcomes (Supplementary Material 3, www.thejh.org). Nevertheless, it was observed that there was no significant distinction between direct and indirect evidence (Supplementary Materials 3-6, www.thejh.org).

Discussion

The optimal chemotherapy regimens for ENTKCL have not been defined. Considering that it is a rare disease, current clinical trial approaches are challenging. To our best knowledge, this is the first systematic review and meta-analysis that has been performed with survival as the primary endpoint to evaluate the optimal chemotherapy combination. We performed a systematic review and network meta-analysis to evaluate the efficacy of various chemotherapy regimens. We identified the ASP/GEM-based regimens superiority over ANT-based, non-ASP/ANT-based and ASP/MTX-based regimens on OS. Although no significant differences were observed compared with ASP/NOS-based, ASP/GEM-based regimens were still the best option chemotherapy for OS. Moreover, the ASP/GEM-based regimen demonstrated superior survival rates and treatment response compared to ANT and even ASP-drug conjugate MTX, indicating the potential advantages of ASP/GEM-based regimens.
GEM-based regimens. These findings have important implications for both clinical trial design and therapeutic practice.

The primary objective of this study was to enhance our comprehension of the impact of various drug combinations on survival rates in ENKTCL. Given the widespread acknowledgement of MDR mechanisms and genomic heterogeneity, it seems likely that patients with ENTKCL could not benefit from ANT-based chemotherapy [14, 16, 43, 44]. ASP, an anti-tumor drug independent of MDR, was used for ENKTCL treatment since 2000s. It hydrolyzes serum asparagine that ENKTCL cells cannot synthesize, thereby inducing the tumor cells apoptosis [45, 46]. Non-ANT-based regimens, especially ASP-based regimens, have shown survival benefit, regardless of stage and radiation [12, 21-24, 26, 47-49]. Several of the best-studied regimens including platinum-based (DeVIC, GDP), ASP/MTX-based (SMILE, AspaMetDex) regimens and the ASP/GEM-based regimens (GELOX, P-GEMOX) were developed based on rationally selected agents. Nevertheless, in the absence of large randomized controlled trials, it is difficult to achieve consensus on the standard chemotherapy regimen. In this present network meta-analysis that incorporated 10 controlled trials for newly diagnosed ENKTCL, ASP/GEM-based regimens ranked first in OS, PFS, CR and ORR. Pharmacologically, GEM is a new generation of pyrimidine anti-tumor drugs, also independent of MDR [50, 51]. Moreover, the combination of ASP/GEM-based regimens and RT exhibits durable anti-tumor responses and potential synergistic anti-programmed cell death protein-1 (PD-1) immunotherapy efficacy in ENKTCL.

The reported 5-year OS was ranging from 60% to 82% for non-ASP/ANT regimens in the patients with early stage, and similarly it was between 65.3% and 82.4% for the ASP-based regimens [11, 20, 25, 26, 37, 49, 52-55]. Whether the outcome with ASP-based regimens is superior to non-ASP/ANT regimens is still inconclusive. In the network meta-analysis, ASP-based regimens resulted in significant benefit in OS and PFS than non-ASP/ANT-based regimens. Furthermore, it was observed that ASP/GEM dramatically prolonged OS compared to ASP/MTX-based in our current analysis.

Improvements in long-term survival have been reported in the frontline treatment for ENTKCL, both in early-stage and advanced stage, mainly as a result of upfront RT and ASP-based regimens [27]. Although, ASP has been recommended as a fundamental drug, no consensus on the group of combinations. Here, we further demonstrated that ASP/GEM-based chemotherapy significantly improved survival outcomes. Survival outcomes in the large multicenter studies were similar to that of prospective phase 1/2 trials (3-year OS, 66-87.5%; 5-year OS, 60-82.1%) and retrospective studies (about 75%) in the early-stage ENKTCL [10, 11, 20, 23, 26, 37, 48, 49, 53, 54, 56-58]. Furthermore, the survival benefits of ASP/GEM-based regimens were prominent/substantial in advanced stage patients [9, 18, 37]. Consistent with the randomized controlled trial study [18], even compared with SMILE, one of the best-studied regimens, ASP/GEM-based regimens still resulted in superior outcomes. Patients with advanced-stage disease had extremely good prognoses after DDGP (ASP/GEM-based regimen) chemotherapy, with a median OS of not reach and a 5-year OS of 74.3%, compared to 75.2 months and a 5-year OS of 51.7% in SMILE (ASP/NOS-based regimen) group.

As network meta-analysis did not account for treatment-related adverse effects due to the inconsistency in retrospective trials’ toxicity profiles, treatment-related adverse effects were not considered during network meta-analysis. Toxicity has the potential to impact the clinical decision-making. Research indicates that ASP/MTX-based regimens have been associated with grade-3/4 toxicities (about 80%) and treatment-related mortality (as high as 17.5%) in relapse/refractory or advanced-stage ENKTCL [23, 24]. In addition, Wang and colleagues reported that treatment-related mortality rate was 2.5% in the ASP/GEM-based (DDGP) group and 17.5% in the ASP/MTX (SMILE) group [18]. The high treatment-related mortality in the SMILE group highlights the difficulty of delivering this regimen even in the clinical trial setting [18, 22-24]. In contrast, ASP/GEM-based regimens are technically feasible with acceptable acute toxicity in modern chemotherapy era. Therefore, it is crucial to optimize drug combinations to ensure that patients receive treatments that maximize efficacy while minimizing toxicity and treatment-related mortality.

This work has several strengths. First, some trials used as input to this network meta-analysis are retrospective study due to the rarity of NKTL. Second, the Bayesian network meta-analysis approach is a validated method, widely reported in previous studies [31]. Moreover, the ranking results are likely to be robust in additional analyses which included use of different survival outcomes and treatment response. This network meta-analysis has limitations. First, most of the included studies are observational retrospective with small sample size, and the study results are high heterogeneous. Second, the included studies are within the last 10 years, and some trials accrual spanned decades. It was impossible to ensure comparability between studies. Due to the low number of studies, certain important clinical features, including Ann Arbor stage and EBV status, were not segregated further for subgroup analysis. As a result, clear conclusions could not be drawn from the subgroup analysis. Further stratified analyses based on larger sample size are recommended. Third, as previously mentioned, the consistency between direct and indirect evidence was not entirely flawless. The results might be affected by inconsistent results in the calculation. In addition, the ranking should be assessed carefully, because it tends to overestimate the effect of chemotherapy regimens with fewer studies. Given the role of a network meta-analysis is not to provide recommendations but rather to summarize the research in a way that facilitates interpretation. In network meta-analyses, the results are used to support rather than to make decisions.

In conclusion, the network meta-analysis indicates that ASP/GEM-based regimens were the best option chemotherapy for OS in the current treatment of ENKTCL. However, it is important to exercise caution in interpreting this conclusion due to the retrospective nature of the studies included. Nonetheless, our findings provide a basis for the development of prospective randomized clinical trials. In the absence of further randomized studies, the results may provide some evidence when selecting a rational chemotherapy regimen.
Supplementary Material

Suppl 1. Clinical Characteristics of Studies Included in the Network Meta-Analysis
Suppl 2. The funnel plot exhibited that there was no significantly publication bias about the associations of OS included studies.
Suppl 3. The node-splitting analysis of direct and indirect evidence in relation to CR.
Suppl 4. The node-splitting analysis of direct and indirect evidence in relation to OS.
Suppl 5. The node-splitting analysis of direct and indirect evidence in relation to PFS.
Suppl 6. The node-splitting analysis of direct and indirect evidence in relation to ORR.

Acknowledgments

The present work was supported by grants from the National Natural Science Foundation of China (81970185); the National Key Research and Development of China (2020AAA0109504).

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

YXL and FL designed the research; FL, JNW and XL collected and analyzed data; FL, JNW and XW did statistical analysis; FL and YXL wrote the paper; all authors provided patients data and approved the paper.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

ANT: anthracycline; ASP: asparaginase; CI: confidence interval; CR: complete response; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; ENKTCL: extranodal natural killer/T-cell lymphoma; GEM: gemcitabine; HR: hazard ratio; IFO: ifosfamide; MDR: multidrug resistance; MTX: methotrexate; NK: natural killer; NOS: not otherwise specified; OS: overall survival; PD-1: programmed cell death protein-1; ORR: objective response rate; PFS: progression-free survival; RT: radiotherapy; UADT: upper aerodigestive tract; SUCRA: the surface under the cumulative ranking curve; VP-16: etoposide

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