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Original Article

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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

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Introduction

Extranodal nasal-type natural killer/T-cell lymphoma (ENKTCL) 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 (pegaspar-

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

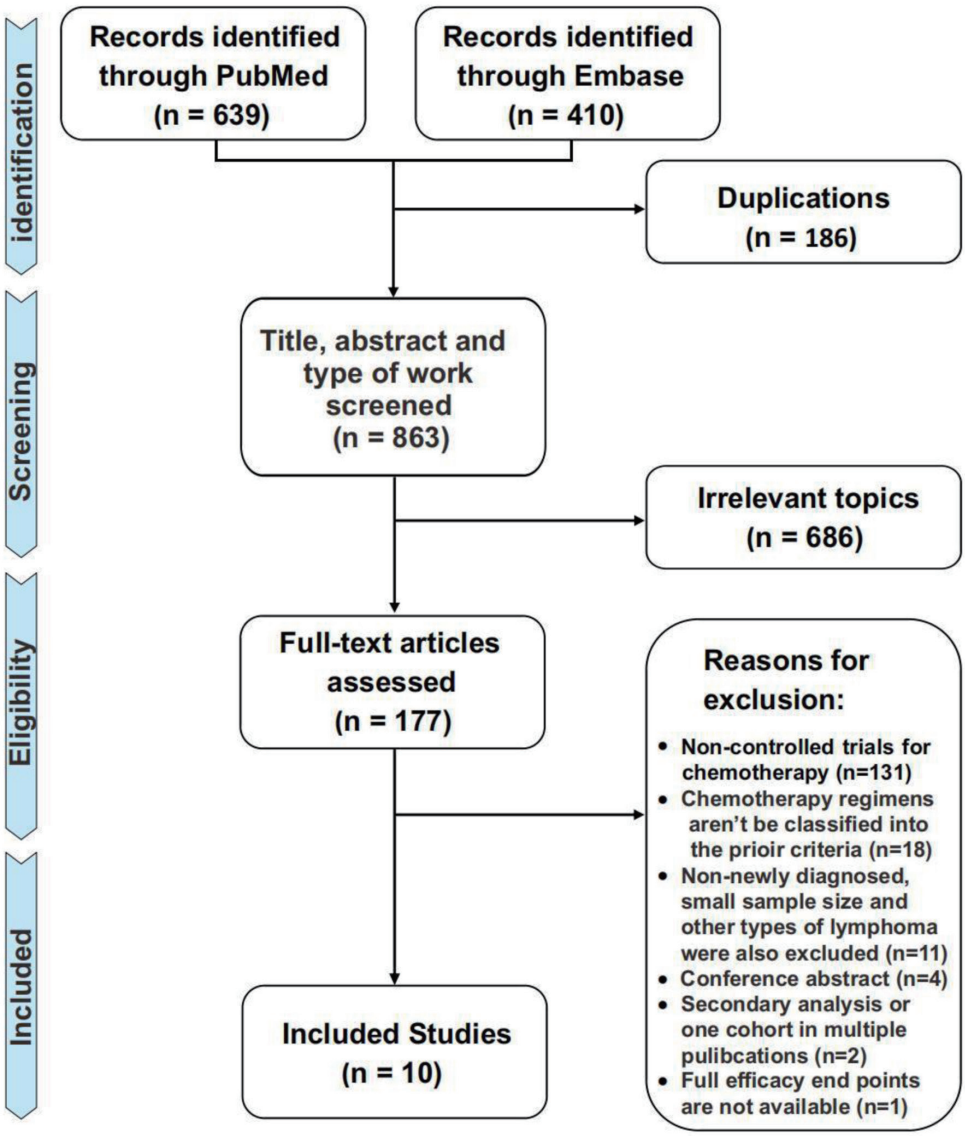

Figure 1. Flow chart of literature search and selection process.

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

Study	Representativeness of the exposed cohort	Selection of the control cohort	Ascertainment of treatment	Outcome was not present at start	Comparability of cohorts	Assessment of outcome	Follow-up was long enough	Adequacy of follow-up	Overall quality
Wang 2015 [42]	1	1	1	1	1	1	1	0	7
Bu 2016 [41]	1	1	1	1	1	1	1	0	7
Qi 2016 [40]	1	1	1	1	0	1	1	1	7
Zhou 2016 [39]	1	1	1	1	2	1	0	1	8
Huang 2017 [38]	1	1	1	1	1	1	1	0	7
Wei 2020 [37]	1	1	1	1	1	1	0	1	7
Li 2021 [9]	1	1	1	1	0	1	1	1	7
Zheng 2021 [36]	1	1	1	1	1	1	1	0	7
Wang 2022 [18]	1	1	1	1	2	1	1	1	9
Zhang 2022 [35]	1	1	1	1	1	1	1	1	8

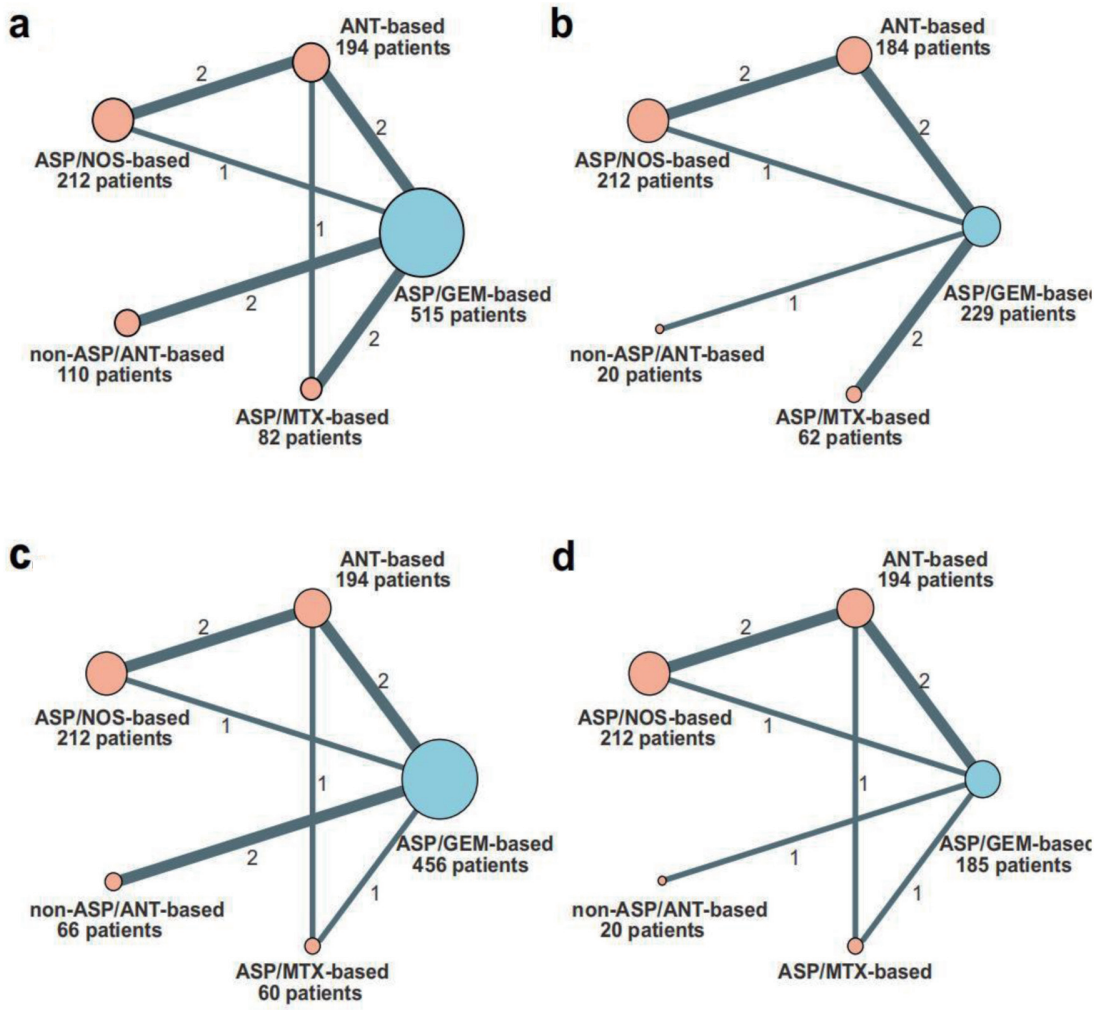

Figure 2. Network diagrams. (a) OS; (b) PFS; (c) ORR; (d) CR. The size of the nodes is proportional to the number of patients, which is given under each treatment category. The width of the lines is proportional to the number of comparisons, which are given on each line. ASP: asparaginase; GEM: gemcitabine; MTX: methotrexate; ANT: anthracycline; NOS: not otherwise specified; OS: overall survival; PFS: progression-free survival; ORR: objective response rate; CR: complete response.

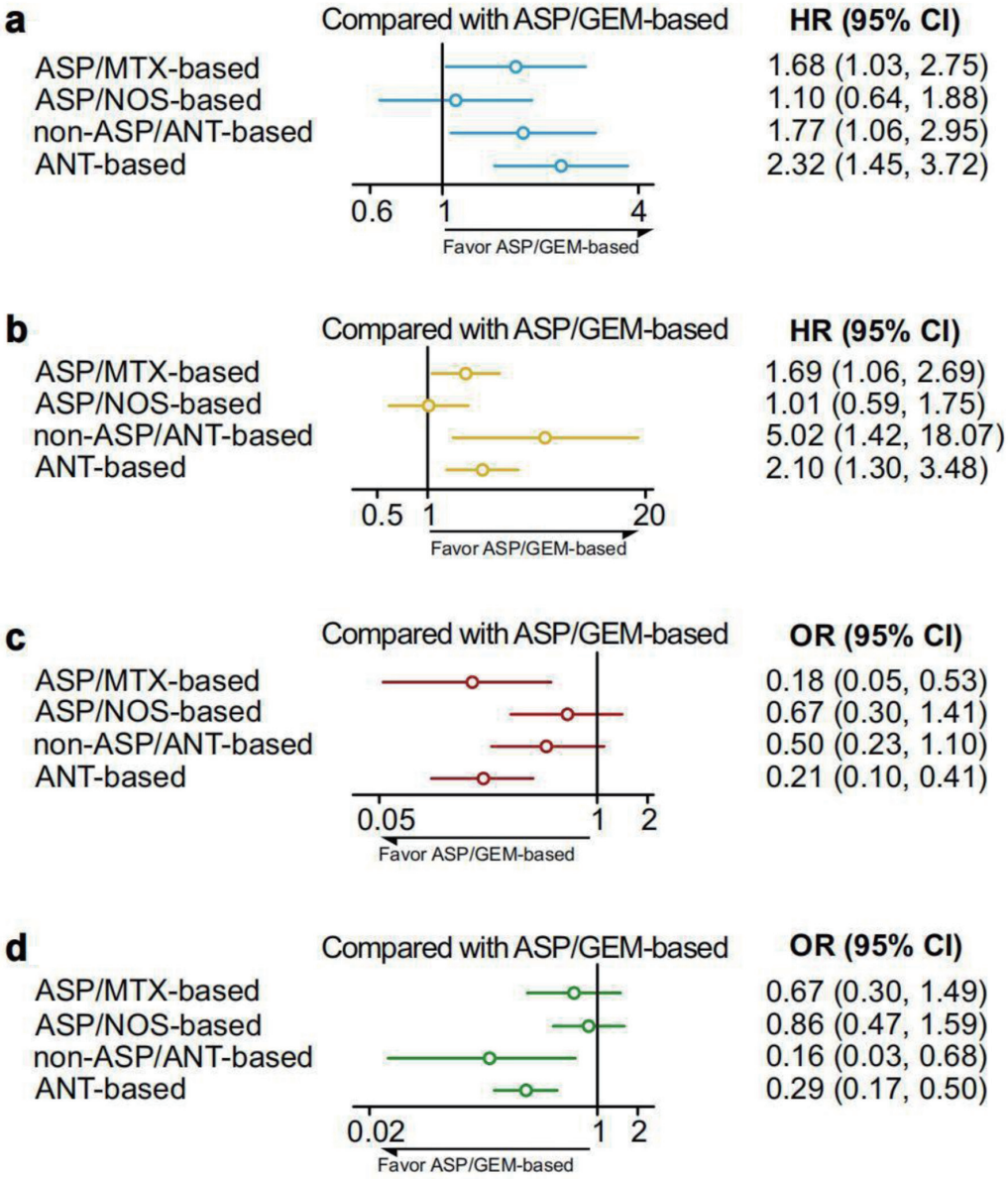

Figure 3. The forest plot shows the effect of five chemotherapy combinations. (a) OS; (b) PFS; (c) ORR; (d) CR. ASP: asparaginase; GEM: gemcitabine; MTX: methotrexate; ANT: anthracycline; NOS: not otherwise specified; OS: overall survival; PFS: progression-free survival; ORR: objective response rate; 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

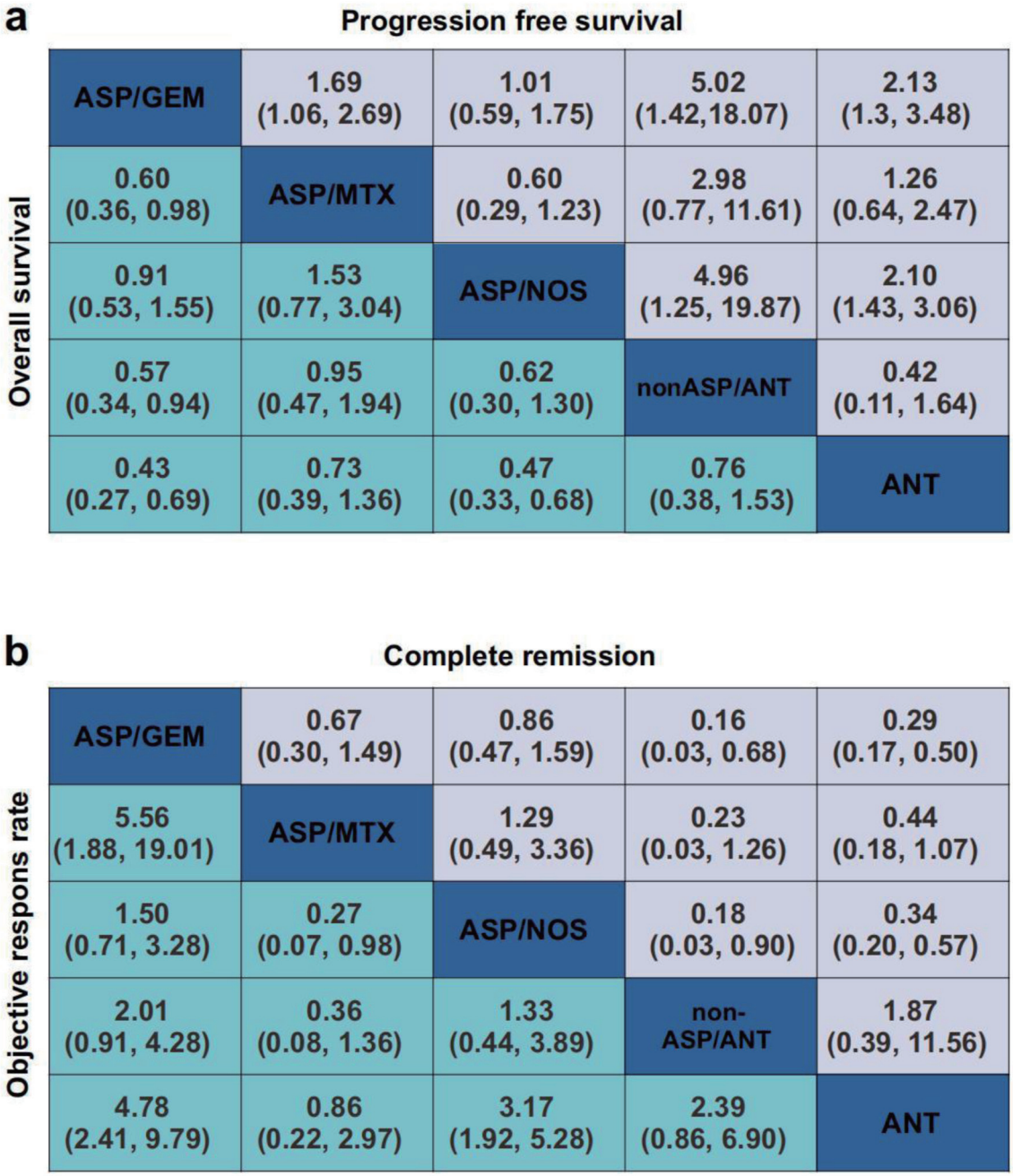

Figure 4. League chart. (a) Combined HR (95% CI) of OS (lower triangle) and PFS (upper triangle). (b) Combined OR (95% CI) of ORR (lower triangle) and CR (upper triangle). The data in each cell are HR or OR (95% CI) comparing row definition processing and column definition processing. HR < 1 or OR > 1 indicates better results. PFS: progression-free survival; OS: overall survival; HR: hazard ratio; OR: odds ratio; ORR: objective response rate; CR: complete response.

(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.

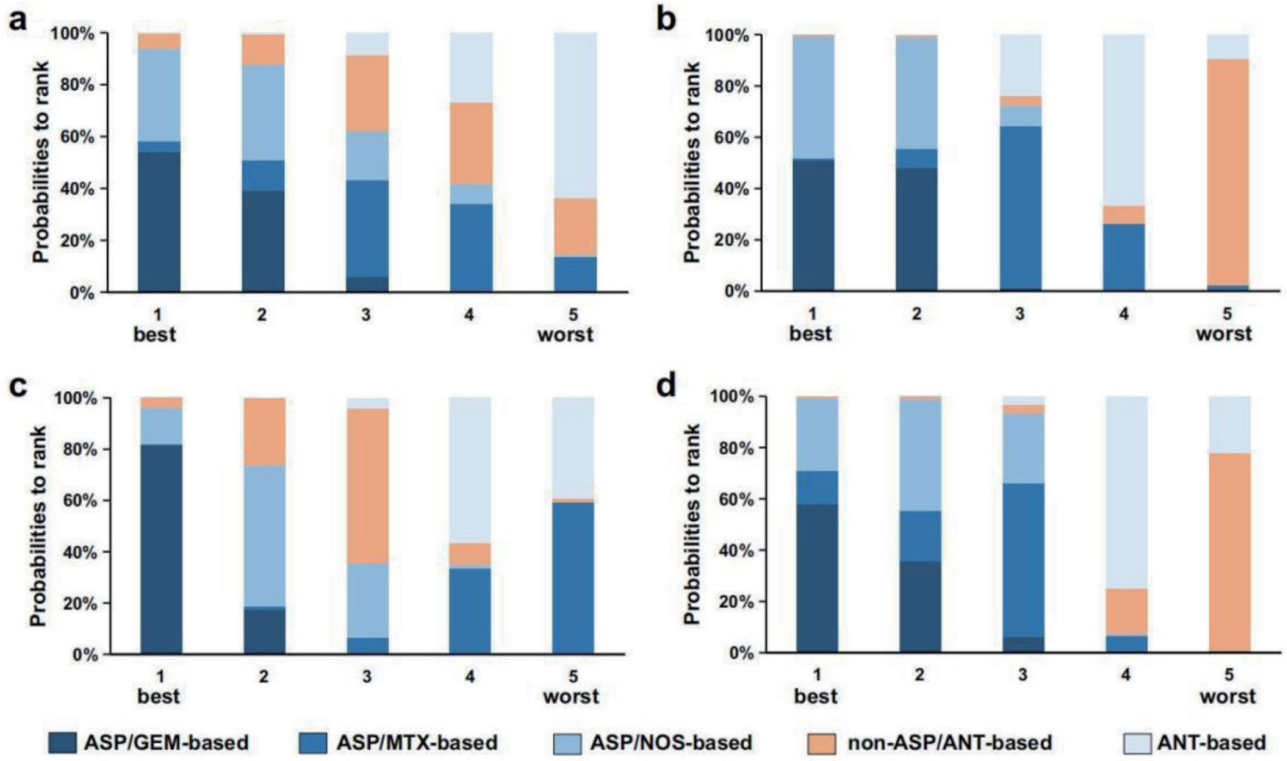

Figure 5. Ranking diagram of five chemotherapy combinations. (a) OS; (b) PFS; (c) ORR; (d) CR. ASP: asparaginase; GEM: gemcitabine; MTX: methotrexate; ANT: anthracycline; NOS: not otherwise specified; OS: overall survival; PFS: progression-free survival; ORR: objective response rate; CR: complete response.

Relative ranking of five combinations

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. 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 regimens) 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 NKTCL. 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.

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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

References

1. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, Bhagat G, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748. doi pubmed pmc
2. Liu QF, Wang WH, Wang SL, Liu YP, Huang WT, Lu N, Zhou LQ, et al. Immunophenotypic and clinical differences between the nasal and extranasal subtypes of upper aerodigestive tract natural killer/T-cell lymphoma. Int J Radiat Oncol Biol Phys. 2014;88(4):806-813. doi pubmed
3. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-4130. doi pubmed
4. Lei KI, Chan LY, Chan WY, Johnson PJ, Lo YM. Diagnostic and prognostic implications of circulating cell-free Epstein-Barr virus DNA in natural killer/T-cell lymphoma. Clin Cancer Res. 2002;8(1):29-34. pubmed
5. Wang ZY, Liu QF, Wang H, Jin J, Wang WH, Wang SL, Song YW, et al. Clinical implications of plasma Epstein-Barr virus DNA in early-stage extranodal nasal-type NK/T-cell lymphoma patients receiving primary radiotherapy. Blood. 2012;120(10):2003-2010. doi pubmed
6. Kim SJ, Yoon DH, Jaccard A, Chng WJ, Lim ST, Hong H, Park Y, et al. A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. Lancet Oncol. 2016;17(3):389-400. doi pubmed
7. Yang Y, Zhu Y, Cao JZ, Zhang YJ, Xu LM, Yuan ZY, Wu JX, et al. Risk-adapted therapy for early-stage extranodal nasal-type NK/T-cell lymphoma: analysis from a multicenter study. Blood. 2015;126(12):1424-1432. doi pubmed
8. Li YX, Yao B, Jin J, Wang WH, Liu YP, Song YW, Wang SL, et al. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol. 2006;24(1):181-189. doi pubmed
9. Li J, Li J, Zhong M, Zhou H, Yu B. The clinical features and survival outcome of 107 newly diagnosed advanced stage extranodal NK/T-cell lymphoma cases: a triple-center study. Cancer Manag Res. 2021;13:1541-1549. doi pubmed pmc
10. Fox CP, Civallero M, Ko YH, Manni M, Skrypets T, Pileri

S, Kim SJ, et al. Survival outcomes of patients with extranodal natural-killer T-cell lymphoma: a prospective cohort study from the international T-cell Project. Lancet Haematol. 2020;7(4):e284-e294. doi pubmed
11. Yamaguchi M, Suzuki R, Oguchi M, Asano N, Amaki J, Akiba T, Maeda T, et al. Treatments and Outcomes of Patients With Extranodal Natural Killer/T-Cell Lymphoma Diagnosed Between 2000 and 2013: A Cooperative Study in Japan. J Clin Oncol. 2017;35(1):32-39. doi pubmed
12. Wang YQ, Yang Y, Zhuo HY, Zou LQ, Jiang Y, Jiang M. Trial of LVDP regimen (L-asparaginase, etoposide, dexamethasone, and cisplatin, followed by radiotherapy) as first-line treatment for newly diagnosed, stage III/IV extranodal natural killer/T cell lymphoma. Med Oncol. 2015;32(2):435. doi pubmed
13. Kim M, Kim TM, Kim KH, Keam B, Lee SH, Kim DW, Lee JS, et al. Ifosfamide, methotrexate, etoposide, and prednisolone (IMEP) plus L-asparaginase as a first-line therapy improves outcomes in stage III/IV NK/T cell-lymphoma, nasal type (NTCL). Ann Hematol. 2015;94(3):437-444. doi pubmed
14. Dong G, Liu X, Wang L, Yin W, Bouska A, Gong Q, Shetty K, et al. Genomic profiling identifies distinct genetic subtypes in extra-nodal natural killer/T-cell lymphoma. Leukemia. 2022;36(8):2064-2075. doi pubmed
15. Tian XP, Ma SY, Young KH, Ong CK, Liu YH, Li ZH, Zhai QL, et al. A composite single-nucleotide polymorphism prediction signature for extranodal natural killer/T-cell lymphoma. Blood. 2021;138(6):452-463. doi pubmed
16. Yamaguchi M, Kita K, Miwa H, Nishii K, Oka K, Ohno T, Shirakawa S, et al. Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. Cancer. 1995;76(11):2351-2356. doi pubmed
17. Chai Y, Chen B, Qi F, Fang H, Qi SN, Guo RY, Li N, et al. First-line chemoradiation with or without chidamide (Tucidinostat) in patients with intermediate- and high-risk early-stage extranodal nasal-type natural killer/T-cell lymphoma: a randomized phase 2 study in China. Int J Radiat Oncol Biol Phys. 2022;113(4):833-844. doi pubmed
18. Wang X, Zhang L, Liu X, Li X, Li L, Fu X, Sun Z, et al. Efficacy and Safety of a Pegasparaginase-Based Chemotherapy Regimen vs an L-asparaginase-Based Chemotherapy Regimen for Newly Diagnosed Advanced Extranodal Natural Killer/T-Cell Lymphoma: A Randomized Clinical Trial. JAMA Oncol. 2022;8(7):1035-1041. doi pubmed pmc
19. Liu T, Zhu F, Xiao Y, Li Q, Liu X, Yang K, Wu G, et al. Pegaspargase, gemcitabine, dexamethasone, and cisplatin (P-GDP) combined chemotherapy is effective for newly diagnosed extranodal NK/T-cell lymphoma: a retrospective study. Cancer Manag Res. 2018;10:5061-5069. doi pubmed pmc
20. Li JW, Li YJ, Zhong MZ, Liu XL, Li J, Li KL, Liu XY, et al. Efficacy and tolerance of GELOXD/P-GEMOXD in newly diagnosed nasal-type extranodal NK/T-cell lymphoma: A multicenter retrospective study. Eur J Haematol. 2018;100(3):247-256. doi pubmed
21. Wang L, Wang ZH, Chen XQ, Li YJ, Wang KF, Xia YF, Xia ZJ. First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer. 2013;119(2):348-355. doi pubmed
22. Kwong YL, Kim WS, Lim ST, Kim SJ, Tang T, Tse E, Leung AY, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. Blood. 2012;120(15):2973-2980. doi pubmed
23. Yamaguchi M, Kwong YL, Kim WS, Maeda Y, Hashimoto C, Suh C, Izutsu K, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. J Clin Oncol. 2011;29(33):4410-4416. doi pubmed
24. Jaccard A, Gachard N, Marin B, Rogez S, Audrain M, Suarez F, Tilly H, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood. 2011;117(6):1834-1839. doi pubmed
25. Yamaguchi M, Tobinai K, Oguchi M, Ishizuka N, Kobayashi Y, Isobe Y, Ishizawa K, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211. J Clin Oncol. 2009;27(33):5594-5600. doi pubmed
26. Kim SJ, Kim K, Kim BS, Kim CY, Suh C, Huh J, Lee SW, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma study. J Clin Oncol. 2009;27(35):6027-6032. doi pubmed
27. Qi SN, Yang Y, Zhang YJ, Huang HQ, Wang Y, He X, Zhang LL, et al. Risk-based, response-adapted therapy for early-stage extranodal nasal-type NK/T-cell lymphoma in the modern chemotherapy era: A China Lymphoma Collaborative Group study. Am J Hematol. 2020;95(9):1047-1056. doi pubmed
28. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. doi pubmed pmc
29. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-784. doi pubmed
30. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
31. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med. 2002;21(16):2313-2324. doi pubmed
32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and

numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64(2):163-171. doi pubmed
33. https://sourceforge.net/projects/mcmc-jags/.
34. www.rproject.org/.
35. Zhang L, Shangguan C, Li X, Li L, Wang X, Fu X, Sun Z, et al. DDGP followed by radiotherapy vs VIPD followed by radiotherapy in newly diagnosed early NK/T-cell lymphoma. Leuk Res. 2022;118:106881. doi pubmed
36. Zheng X, He X, Yang Y, Liu X, Zhang LL, Qu BL, Zhong QZ, et al. Association of improved overall survival with decreased distant metastasis following asparaginase-based chemotherapy and radiotherapy for intermediate- and high-risk early-stage extranodal nasal-type NK/T-cell lymphoma: a CLCG study. ESMO Open. 2021;6(4):100206. doi pubmed pmc
37. Wei L, Yang L, Ye J, Cong J, Li X, Yao N, Yang J, et al. Outcomes of patients treated with SVILE vs. P-GemOx for extranodal natural killer/T-cell lymphoma, nasal type: a prospective, randomized controlled study. Cancer Biol Med. 2020;17(3):795-804. doi pubmed pmc
38. Huang L, Yuan B, Wu H, Chu H, Liu Y, Wu S, Li H, et al. Comparative study of L-asparaginase-based LOP regimen over CHOP regimen before radiotherapy for stage IIE extranodal nasal type NK/T cell lymphoma: a study of 2 centers. Clin Lymphoma Myeloma Leuk. 2017;17(3):152-158. doi pubmed
39. Zhou F, Xue HW, Zhao YW, Liu XR, Dong Q, Yu HS. A prospective study of chemoradiotherapy for early stage extranodal natural killer (NK)/T-cell lymphoma. Int J Clin Exp Med. 2016;9(7):14397-14403.
40. Qi S, Yahalom J, Hsu M, Chelius M, Lunning M, Moskowitz A, Horwitz S. Encouraging experience in the treatment of nasal type extra-nodal NK/T-cell lymphoma in a non-Asian population. Leuk Lymphoma. 2016;57(11):2575-2583. doi pubmed pmc
41. Bu S, Yuan F, Wei X, Yin Q, Li Y, Mi R, Yang H, et al. L-asparaginase-based regimen as a first-line treatment for newly diagnosed nasal type extranodal natural killer cell/T-cell lymphoma. Exp Ther Med. 2016;11(6):2437-2445. doi pubmed pmc
42. Wang H, Wuxiao ZJ, Zhu J, Wang Z, Wang KF, Li S, Chen X, et al. Comparison of gemcitabine, oxaliplatin and L-asparaginase and etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone as first-line chemotherapy in patients with stage IE to IIE extranodal natural killer/T-cell lymphoma: a multicenter retrospective study. Leuk Lymphoma. 2015;56(4):971-977. doi pubmed
43. Takahara M, Kishibe K, Bandoh N, Nonaka S, Harabuchi Y. P53, N- and K-Ras, and beta-catenin gene mutations and prognostic factors in nasal NK/T-cell lymphoma from Hokkaido, Japan. Hum Pathol. 2004;35(1):86-95. doi pubmed
44. Drenou B, Lamy T, Amiot L, Fardel O, Caulet-Maugendre S, Sasportes M, Diebold J, et al. CD3- CD56+ non-Hodgkin's lymphomas with an aggressive behavior related to multidrug resistance. Blood. 1997;89(8):2966-2974. pubmed
45. van den Berg H. Asparaginase revisited. Leuk Lymphoma. 2011;52(2):168-178. doi pubmed
46. Ando M, Sugimoto K, Kitoh T, Sasaki M, Mukai K, Ando J, Egashira M, et al. Selective apoptosis of natural killer-cell tumours by l-asparaginase. Br J Haematol. 2005;130(6):860-868. doi pubmed
47. Tsai HJ, Lin SF, Chen CC, Chen TY, Su WC, Hwang WL, Lin JC, et al. Long-term results of a phase II trial with frontline concurrent chemoradiotherapy followed by consolidation chemotherapy for localized nasal natural killer/T-cell lymphoma. Eur J Haematol. 2015;94(2):130-137. doi pubmed
48. Kim TM, Kim DW, Kang YK, Chung J, Song HS, Kim HJ, Kim BS, et al. A phase II study of ifosfamide, methotrexate, etoposide, and prednisolone for previously untreated stage I/II extranodal natural killer/T-cell lymphoma, nasal type: a multicenter trial of the Korean Cancer Study Group. Oncologist. 2014;19(11):1129-1130. doi pubmed pmc
49. Kim SJ, Yang DH, Kim JS, Kwak JY, Eom HS, Hong DS, Won JH, et al. Concurrent chemoradiotherapy followed by L-asparaginase-containing chemotherapy, VIDL, for localized nasal extranodal NK/T cell lymphoma: CISL08-01 phase II study. Ann Hematol. 2014;93(11):1895-1901. doi pubmed
50. Reislander T, Groelly FJ, Tarsounas M. DNA damage and cancer immunotherapy: a sting in the tale. Mol Cell. 2020;80(1):21-28. doi pubmed
51. Mini E, Nobili S, Caciagli B, Landini I, Mazzei T. Cellular pharmacology of gemcitabine. Ann Oncol. 2006;17(Suppl 5):v7-12. doi pubmed
52. Zhang Y, Ma S, Cai J, Yang Y, Jing H, Shuang Y, Peng Z, et al. Sequential P-GEMOX and radiotherapy for early-stage extranodal natural killer/T-cell lymphoma: A multicenter study. Am J Hematol. 2021;96(11):1481-1490. doi pubmed pmc
53. Tian S, Li R, Wang T, Wang S, Tao R, Hu X, Ding H. Gemcitabine, dexamethasone, and cisplatin (GDP) chemotherapy with sandwiched radiotherapy in the treatment of newly diagnosed stage IE/IIE extranodal natural killer/T-cell lymphoma, nasal type. Cancer Med. 2019;8(7):3349-3358. doi pubmed pmc
54. Qi F, Wang WH, He XH, Chen B, Gui L, Fang H, Liu P, et al. Phase 2 study of first-line intensity modulated radiation therapy followed by gemcitabine, dexamethasone, and cisplatin for high-risk, early stage extranodal nasal-type NK/T-cell lymphoma: the GREEN study. Int J Radiat Oncol Biol Phys. 2018;102(1):61-70. doi pubmed
55. Bi XW, Xia Y, Zhang WW, Sun P, Liu PP, Wang Y, Huang JJ, et al. Radiotherapy and PGEMOX/GELOX regimen improved prognosis in elderly patients with early-stage extranodal NK/T-cell lymphoma. Ann Hematol. 2015;94(9):1525-1533. doi pubmed
56. Kwong YL, Kim SJ, Tse E, Oh SY, Kwak JY, Eom HS, Do YR, et al. Sequential chemotherapy/radiotherapy was comparable with concurrent chemoradiotherapy for stage I/II NK/T-cell lymphoma. Ann Oncol. 2018;29(1):256-263. doi pubmed
57. Xu PP, Xiong J, Cheng S, Zhao X, Wang CF, Cai G,

Zhong HJ, et al. A phase II study of methotrexate, etoposide, dexamethasone and pegaspargase sandwiched with radiotherapy in the treatment of newly diagnosed, stage IE to IIE extranodal natural-killer/T-cell lymphoma, Nasal-Type. EBioMedicine. 2017;25:41-49. doi pubmed pmc

58. Yamaguchi M, Tobinai K, Oguchi M, Ishizuka N, Kobayashi Y, Isobe Y, Ishizawa K, et al. Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211. J Clin Oncol. 2012;30(32):4044-4046. doi pubmed