# L-asparaginase-Based Chemotherapy Regimens for Advanced, Relapsed or Refractory Extranodal NK/T-cell Lymphoma:A Systematic Review and Meta-Analysis

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**Abstract:** Extranodal NK/T-cell Lymphoma (ENKL) are uncommon hematological malignancies with an aggressive clinical course and poor prognosis. Conventional anthracycline containing regimens demonstrate an unsatisfactory outcome. The frequent expression of the multidrug resistance (MDR) gene (P-glycoprotein) in NK lymphoma cells contributes to the refractoriness and dismal prognosis. We performed this meta-analysis to evaluate the efficacy and safety of L-asparaginase-based chemotherapy regimens in the treatment of advanced, relapsed or refractory ENKL. Electronic databases, including the PubMed database, Cochrane Library, EMBA, SE, were searched for clinical trials involving L-asparaginase-based regimens for ENKL. Fixed-effects analysis demonstrated the summary CR (complete remission) rates was 52% (95% CI=42% to 61%), summary OR (overall remission) rates was 78% (95% CI = 70% to 86%). With respect to main adverse events, the incidence rates of leukopenia, liver dysfunction and anaphylactic reactions were 60. 0%, 50. 8%, 11. 4%, respectively. In conclusion, L-asparaginase-based chemotherapy regimens present remarkable efficacy in the treatment for advanced, relapsed or refractory ENKL, while the incidence of adverse events is high.

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**Key Words:** extranodal NK/T-cell lymphoma;L-Asparaginase;systematic review; Meta-Analysis

## 1 Introduction

Extranodal NK/T-cell Lymphomas(ENKL) are uncommon lymphoid neoplasms, accounting for 38. 0% of peripheral T-cell lymphomas, predominantly involve the nasal cavity, nasopharynx and the upper aerodigestive tract[1,2]. Populations from Asia and South America are more frequently affected, representing a unique geographic distribution[3]. In clinical practice, NK-cell lymphomas comprise three subtypes:nasal, non-nasal and aggressive lymphoma/leukemia, sharing different clinical behaviors and treatment responses[4]. Histologically, they are charactered by polymorphic neoplastic lymphoid infiltrates with angioinvasion and angiodestruction[2]. Severe necrosis is frequently present which may require repeated biopsy for diagnosis. The typical immunophenotypes of tumor cells are surface CD3-, cytoplasmic CD3ε+, NK cell marker CD56+, EBER+[5]. Consistent EBV positive in the neoplastic cells suggests its important role in the pathogenesis[6]. EBV-DNA load in peripheral blood has been found of great use in predicting tumor response, prognosis, toxicity[7].

For localized ENKL, radiotherapy combined with chemotherapy have shown better outcome, while the relapse rate is high[8]. Owning to the rarity of this disease and few large randomized controlled trials were conducted, the optimum treatment strategies have not been established. Conventional anthracycline containing regimens demonstrate an unsatisfactory outcome with a CR rate 20% or less, overall survival less than 1 year [5,6,9]. The frequent expression of the multidrug resistance(MDR) gene(P-glycoprotein) in NK lymphoma cells contributes to the refractoriness and dismal prognosis[10,11,12]. L-asparaginase, a crucial drug in the treatment of childhood acute lymphoblastic leukaemia (ALL), has been proved efficient in inducing apoptosis of natural killer-cell tumours in vitro[13]. Recent clinical studies also indicate that L-Asparaginase-based chemotherapy regimens which contain MDR-independent agents significantly improve the response rate for advanced, relapsed or refractory NK-cell malignancies[14,15,16,17].

In this systematic review and meta-analysis, we collected relative trials and examined the summary CR and OR rates associated with L-Asparaginase-based regimens. We aimed to investigate the efficacy and safety of L-asparaginase-based chemotherapy regimens in the treatment of advanced, relapsed or refractory ENKL.

## 2 Materials and Methods

### 2.1 Systematic Literature Search

A comprehensive search strategy was employed to retrieve all relevant literatures, and search terms included “L-Asparaginase”, “NK-cell lymphoma”. According to this strategy, we searched a variety of

electronic databases, including the PubMed database, Cochrane Library, EMBASE. We also manually searched the following conference proceedings for relevant abstracts:the American Society of Hematology, the American Society of Clinical Oncology(ASCO), and the European Society of Medical Oncology(ESMO).

**2.2 Inclusion and Exclusion Criteria**

Criterias of eligible studies were (1) patients with advanced, relapsed or refractory NK-cell malignancies (2) treatment strategy was L-Asparaginase-based regimen(3)full text reporting in English (4)endpoints such as, CR, OR and toxicity, were reported. (5) either prospective or retrospective. We excluded ongoing studies, interim analyses, and studies with 5 or fewer patients.

**2.3 Study Selection and Data Extraction**

Two reviewers independently inspected the titles and the abstracts of all studies in the search, and applied the inclusion criteria. A study was considered acceptable if it evaluated the effectiveness of L-Asparaginase based regimen for treating advanced, relapsed or refractory ENKL. Where relevant articles were identified, the full article was obtained and screened independently by the above two reviewers and inclusion criteria applied. In cases of disagreement between the two reviewers, the full article was inspected independently by a third reviewer. The same reviewers who screened the studies independently performed data extraction and quality assessment of all included articles.

**2.4 Data Analysis and Statistical Methods**

Studies included in the meta-analyse were evaluated for heterogeneity and evaluated for suitability for pooling. The $\chi 2$-based Cochran's Q test, and the $I^2$ statistic were employed to examine the consistency of results among studies. P value less than 0. 10 and $I^2$ statistic >50% were considered representative of significantly statistical heterogeneity. Fixed effect model was assumed to pool CR, OR. In the presence of statistical heterogeneity, random effects model was employed. Analyses were performed using the computer program R-2. 15. 1 for Windows[18]. Freeman-Tukey Double arcsine transformation method was used to calculate the overall CR rate and the OR rate for patients treated with L-Asparaginase-containing regimens. A forest plot was generated to display results. Statistical tests for heterogeneity were one-sided; statistical tests for effect estimates and publication bias were two-sided.

**3 Results**

The search yielded 62 potentially relevant trials describing treatment related to L-Asparaginase and NK-cell malignancies. After reviewing the abstacts and full texts, we found only 7 articles met the inclusion criterias. What we should emphasize is one trial was updates of two previously published studies and was included only once in the current analysis. Finally, five eligible trials involing 122 patients were included in this meta-analysis (Table 1, 2).

**Table 1. Characteristics of Included Studies**

| Study, year | N patients | Design | Chemotherapy | Median Age | Male/Female |
|---|---|---|---|---|---|
| Yong et al, 2009 [15] | 45 | Retrospective | LVD | 43 | 34/11 |
| Yamaguchi et al, 2008 [23] | 6 | Prospective | SMILE | 48 | 5/1 |
| Jaccard et al, 2009 [16] | 15 | Retrospective | L-Asparaginase-based | 45 | 10/5 |
| Jaccard et al, 2011 [22] | 18 | Prospective | LMD | 60 | 15/4 |
| Yamaguchi et al, 2011 [17] | 38 | Prospective | SMILE | 47 | 21/17 |

**SMILE**: Methotrexate 2 g/m2 IV (6 hours) day1, Leucovorin 15 mg x4 IV or PO day2 to 4, Ifosfamide 1,500 mg/m2 IV day2 to 4, Mesna 300 mg/m2 x3 IV day2 to 4, Dexamethasone 40 mg/d IV or PO day2 to 4, Etoposide 100 mg/m2 IV day2 to 4, L-asparaginase 6,000 U/m2 IV day8, 10, 12, 14, 16, 18, 20, every 28 days.

**LVD**: L-asparaginase 6,000 IU/m2 IV days 1 to 7, vincristine 1. 4 mg/m2 IV day 1, dexamethasone 10 mg IV days 1 to 7, every 28 days. **LMD**: L-asparaginase 6000 IU/m2 IV days 2, 4, 6, and 8, methotrexate 3 g/m2 IV day 1, and dexamethasone 40 mg PO day 1 to 4, every 21 days.

**Table 2. Summary of response rates**

| Study, year | N patients | CR(n; %) | PR(n; %) | 0R(n; %) |
|---|---|---|---|---|
| Yong et al, 2009 [15] | 45 | 25; 55% | 12;27% | 37;82% |
| Yamaguchi et al, 2008 [23] | 6 | 3; 50 % | 1 ;17% | 4;67% |
| Jaccard et al, 2009 [16] | 15 | 7;47 % | 2;13% | 9;60% |
| Jaccard et al, 2011 [22] | 18 | 11;61 % | 3;17% | 14;78% |
| Yamaguchi et al, 2011 [17] | 38 | 17; 45% | 13;34% | 30;79% |

**3. 1 Complete Response:**The rates of complete response ranged from 45 % to 61%. No statistically

significant heterogeneity was demonstrated among the trials(P=0. 7877, $I^2$=0), and summary estimate for CR was 52% (95% CI =42% to 61%, fixed-effects model). (Figure 1)

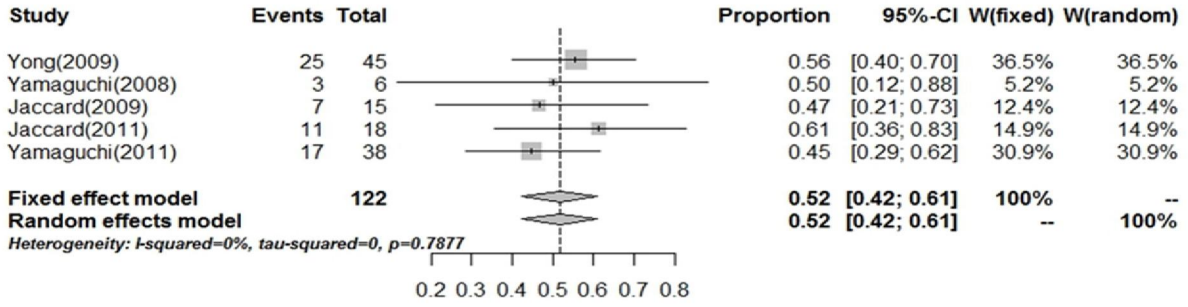


**Figure1. Meta-analysis of complete response rate of patients undergoing L-asparaginase-based chemotherapy regimens. Forest plot of the complete response rate along with summary estimates and its 95% CI.**

**3. 2 Overall Response:**The rates of overall response anged from 60 % to 82%. No statistically significant heterogeneity was demonstrated among the trials (p=0. 503, $I^2$=0), and summary estimate for OR was 78% (95% CI = 70% to 86%, fixed-effects model). (Figure 2)

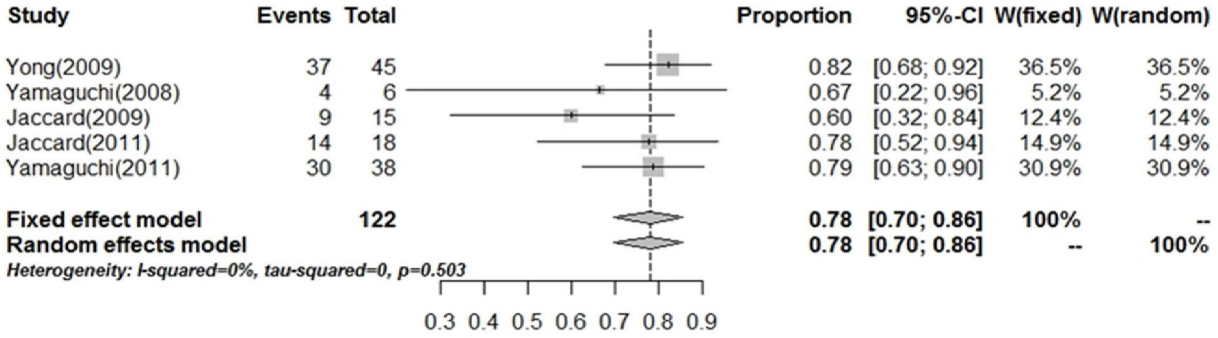


**Figure 2. Meta-analysis of overall response rate of patients undergoing L-asparaginase-based chemotherapy regimens. Forest plot of the overall response rate along with summary estimates and its 95% CI.**

**3. 3 Adverse Events:**The main adverse events of L-Asparaginase are leukopenia, liver dysfunction, anaphylactic reactions and infection(Table3)Since there was substantial heterogeneity clinically, it is not suitable to pool for summary estimate. The incidence rate of adverse events with respect to leukopenia, liver dysfunction, anaphylactic reactions and infection are 60%, 50. 8%, 11. 4%, 20. 4%, respectively.

**Table 3 Summary of adverse events associated with L-asparaginase based chemotherapy regimens**

| Study, year | N patients | Leukopenia | Liver dysfunction | Anaphylactic reactions | Infection |
|---|---|---|---|---|---|
| Yong et al, 2009 [15] | 45 | 15 | 23 | 2 | 0 |
| Yamaguchi et al, 2008 [23] | 6 | 6 | 2 | 0 | 0 |
| Jaccard et al, 2009 [16] | 15 | 4 | 4 | 3 | 3 |
| Jaccard et al, 2011 [22] | 18 | 11 | 11 | 4 | 5 |
| Yamaguchi et al, 2011 [17] | 38 | 38 | 22 | 5 | 17 |
| Summary | 122 | 74 (60%) | 62 (50. 8%) | 14 (11. 4%) | 25 (20. 4%) |

## 4 Discussion

Natural killer (NK)-cell malignancies are uncommon lymphoid neoplasms with an aggressive course and dismal prognosis. Owning to the low frequencies of this disease and scarcity of clinical trials, optimum treatment remain undefined. For stage I–II nasal NK-cell lymphomas, radiotherapy is the conventional initial treatment, with overall response rate ranged from 60 to 80%[6]. Kim SJ et al performed a concurrent chemoradiotherapy trial and 77% patients achieved CR with a 2-year overall survival (OS) at 78%, while 37% of patients relapsed[19]. However, about half of all patients will relapse[20]. High expression of P-glycoprotein(P-gp) may contribute to the high rate of refractory, which usually extruded many MDR dependent drugs out of neoplastic cells[10]. Chemotherapy is the sole approach for advanced, relapsed or refractory NK-cell malignancies, while conventional anthracycline-based regimens give grim outcome with CR rates less than 15%[5,6,9]. Therefore investigating effective therapeutic regimens unaffected by P-glycoprotein to improve the poor outcome seems to be imperious.

L-asparaginase has been demonstrated efficient in reducing activity on NK-cell tumours and inducing apoptosis of tumoural NK cells in vitro, whereas various anti-tumour agents currently used presented no activity[13]. L-asparaginase are insensitive to the multidrug resistance pathway. The specific antitumoral mechanism has been assumed that L-asparaginase digests serum L-asparagine and depletes asparagines of NK cells, where asparagine synthetase expression is low[21]. Clinically, Yong et al first examined the efficacy of L-asparaginase in extranodal NK/T-cell lymphoma. In this trial, 50% of patients with refractory NK-cell lymphoma achieved complete response when treated with L-Asparaginase-Based chemotherapy(L-asparaginase 6000 U/$m^2$ on days 1–7, vincristine 1. 4 mg/$m^2$ on day 1 and dexamethasone 10 mg on days 1–7, with 28-day cycles), compared to 0% in the none-Lasparaginase group[14]. Yamaguchi conducted a prospective study of SMILE (L-asparaginase, dexamethasone, etoposide, methotrexate, ifosfamide) chemotherapy for advanced relapsed or refractory natural killer NK-cell lymphomas, resulting in a CR rate of 50% and OR rate of 67% after two courses[23]. Reyes VE Jr et al reported two patients with extranodal NK/T-cell lymphoma who achieved complete response after receiving single Pegaspargase therapy, even though they were refractory to CHOP[24]. In addition, some other prospective or retrospective trials have also demonstrated the remarkable outcome of L-Asparaginase based chemotherapy regimen. These protocols generally comprise L-Asparaginase and other MDR independent drugs, such as methotrexate, ifosfamide. Since sample sizes included in these trials are relatively small, we perform this systematic review and meta-analysis to detemine the efficacy of L-Asparaginase-based chemotherapy regimens for for advanced、relapsed or refractory NK/T-cell lymphomas. Fixed-effects analysis demonstrated the summary CR rate 52%(95% CI =42% to 61%), summary OR rate 78%(95% CI = 70% to 86% ). Only two retrospective trials reported 3-year overall survival (OS) rates. In the trial conducted by Yong et al, both 3-year and 5-year OS rates were 66. 9%[15]. However, recently Mohamad et al[25] presented a case with advanced ENKTL who progressed despite receiving a fairly intensive L-asparaginase based therapy. The patient achieved complete response after receiving a novel treatment regimen B-GIFOX (bortezomib, gemcitabine, ifosfamide and oxalipaltin) with minimal toxicity.

In terms of adverse events, leukopenia and liver dysfunction were the most common ones, occur in 60% and 50. 8% patients. Sometimes they were fatal in patients who developed severe infectious. The effective way to cope with myelosuppression and relative complications is early G-CSF support. For those who are in poor condition, less intensive L-asparaginase chemotherapies are better choices.

In this meta-analysis, there were several limitations. First, all studies included are not randomized, double-blinded, controlled trials. This may decrease the quality of meta-analyses. Secondly, the courses of chemotherapy and the assessment criteria of tumor response are different among these trials. In addition, certain patients treated with chemotherapy are followed by local radiotherapy or stem cell transplantation, thus evaluations of the efficacy of L-Asparaginase-based chemotherapy are not accurate.

In conclusion, L-Asparaginase-based chemotherapy regimens significantly improve treatment outcome for patients with advanced, relapsed or refractory NK-cell malignancies. Prospective trials are expected to determine optimal treatment modalities.

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