Extended Course and Increased Dose of Initial Chemotherapy for Extranodal Nasal Type Natural Killer/T (NK/T)-Cell Lymphoma in Patients <60 Years Old: A Single-Center Retrospective Cohort Study

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Background: Extranodal NK/T-cell lymphoma (ENKTL) of the nasal type is highly invasive and relatively resistant to chemotherapy. This study aimed to assess the efficacy and safety of an extended chemotherapy regimen with increased dose intensity.

Material/Methods: This was a retrospective cohort study of 69 patients <60 years old with an ECOG score 0–2 treated for ENKTL at the Second Affiliated Hospital of Xi’an Jiaotong University between January 2004 and December 2013. The outcomes were compared between patients who received >8 courses of high-intensity chemotherapy (n=37) vs. 6–8 courses (n=18) and <6 courses (n=14) of conventional chemotherapy. Regimens included improved CHOP, CHOP-E, EPOCH, MAED, MMED, SMILE, and Hyper-CVAD with an increased dose intensity in the >8 courses group.

Results: The mean follow-up was 52 months (8 to 82 months). Remission rate did not differ significantly when compared among the 3 groups after 3 courses of chemotherapy (83.8%, 77.8%, and 78.6%, respectively, overall P=0.834), but the 5-year overall survival (OS) differed significantly (63.5%, 45.1%, and 22.9%, respectively, overall P=0.030), as did progression-free survival (PFS) (59.1%, 36.0%, and 15.1%, respectively, overall P=0.020), disease-free survival (DFS) (54.1%, 35.5%, and 12.9%, respectively, overall P=0.022), and total relapse rate throughout follow-up (37.04%, 50.0%, and 88.89%, respectively, overall P=0.027). There were no differences in adverse effects among the 3 groups.

Conclusions: These results suggest improved OS, PFS, DFS, and relapse rate in young patients with ENKTL receiving >8 courses of high-intensity chemotherapy.

MeSH Keywords: Drug Therapy • Lymphoma, Extranodal NK-T-Cell • Survival

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Extranodal NK/T-cell lymphoma of nasal type (ENKTL) is difficult to diagnose, is highly invasive, and exhibits poor sensitivity to chemotherapy [1]. ENKTL is likely to relapse despite treatments and distant metastases are often observed, resulting in poor prognosis. The geographical distribution of ENKTL differs significantly, and it is far more common in Asia, Central America, and South America compared with other parts of the world [2,3]. In 2010, ENKTL was reported to account for 6.9% of all non-Hodgkin’s lymphoma (NHL) in China, and accounted for 28.2% of T cell and NK cell lymphomas [4].

Although the disease manifests itself as focal lesions in about two-thirds of ENKTL patients, prognosis is still poor [5]. Currently, there is no internationally recognized first-line chemotherapy regimen for ENKTL. The traditional treatment protocols include radiotherapy, chemotherapy, and comprehensive therapy (radiotherapy + chemotherapy), but the 3-year overall survival (OS) is only 40–50%, even in patients with stage I/II focal lesions [6–8], suggesting that the traditional cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based regimens fail to achieve a satisfactory efficacy. Therefore, the selection of appropriate treatment regimens for ENKTL remains a clinical challenge.

Combined chemo-radiotherapy, shortened chemotherapy intervals, and high-intensity regimens have been reported to improve the prognosis of patients with ENKTL, but no study has reported the specific number of courses of chemotherapy associated with the best efficacy, and clinicians have to rely on their personal experience. Most published studies of ENKTL chemotherapy efficacy applied ≤6 courses of chemotherapy combined with radiotherapy, but the relapse rate can still be as high as 50% [9].

L-asparaginase-based combination chemotherapy regimen of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE regimen) and radiotherapy have been recommended [10], but long-term follow-up revealed that asparaginase may induce significant adverse effects, including hypofibrinogenemia and acute pancreatitis, and this regimen is still associated with a high long-term relapse rate [11]. Reports have confirmed that increasing the number of chemotherapy courses might affect the efficacy and long-term survival of diffuse large B lymphoma [12,13], but it is still unknown whether these results are applicable to other pathological types of NK/T lymphoma. The lack of prospective studies limits the possibility of selecting an appropriate number of courses of chemotherapy to optimize the relapse rate.

Therefore, this retrospective study aimed to investigate whether chemotherapy regimens with increased courses and dose intensity in young patients (<60 years old) with ENKTL can improve efficacy, relapse, and survival. These results could help providing guidance for clinical chemotherapy.

Material and Methods

Patients

This single-center retrospective cohort study included 69 patients treated at the Department of Hematology of the Second Affiliated Hospital of Xi’an Jiaotong University between January 2004 and December 2013. Inclusion criteria were: 1) <60 years old; 2) Eastern Cooperative Oncology Group (ECOG) score of 0–2; and 3) diagnosed with ENKTL according to the diagnostic criteria of the World Health Organization (WHO) Taxonomy of Hemopoiesis and Lympho-Plasmacytoid Diseases (2001) [14,15], which were the current criteria during the study period. Exclusion criteria were: 1) recurrent NHL; 2) secondary lymphoma after chemotherapy or radiotherapy; 3) primary central nervous system (CNS) NHL; 4) human immunodeficiency virus or acquired immunodeficiency syndrome-related lymphoma; 5) malignant tumors after transplantation; 6) severe acute or chronic infection; 7) pregnancy or lactation; 8) psychosis; or 9) dysfunction of the heart, liver, or kidney not associated with chemotherapy. All patients who did not complete the planned treatment were also excluded. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi’an Jiaotong University, and patients or their guardians provided written informed consent.

Data collection

All patients were comprehensively assessed before chemotherapy, including electrocardiogram, echocardiogram, computed tomography (CT) of the nasal cavity, brain, chest, abdomen, and pelvis, and lymph node B-mode ultrasound of superficial organs.

Chemotherapy

The choice of chemotherapy was made by the treating physician after a comprehensive evaluation of the patient and the disease. Patients who received high-intensity chemotherapy received >8 courses of improved CHOP (doxorubicin was replaced by pirarubicin, vincristine was replaced by vinorelbine, and oral prednisone was replaced by intravenous injection of dexamethasone); CHOP with additional etoposide (CHOP-E); mitomycin and etoposide alternating with cytarabine and dexamethasone (MAED); mitomycin, methotrexate, and etoposide alternating with dexamethasone (MMED); etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH); SMILE; or hyperfractionated cyclophosphamide, vincristine, doxorubicin,
and dexamethasone (Hyper-CVAD) regimen [10,16]. The improved CHOP regimen was preferred in all patients for the induction phase (first year); the delay between courses was 2-4 weeks, according to the patient’s condition. The other regimen, with increased dose intensity, were alternatively used in the consolidation phase (years 2–3). The order for the selection of chemotherapy regimen was: CHOP, CHOP-E, EPOCH, MAED, MMED, SMILE, and Hyper-CVAD [10,16]. Patients receiving the high-intensity regimen underwent at least 8 courses of chemotherapy and a maximum of 16. Based on the recommendations of 6-8 cycles CHOP/RCHOP for diffuse large B-cell lymphoma treatment [16] and the use of 1-6 cycles of chemotherapy [17], we felt it was appropriate to stratify patients according to the treatment they received, so the patients were divided into 3 groups of >8 courses (high-intensity group), 6-8 courses, and <6 courses.

Patients who were not considered for the high-intensity regimen received a maximum of 8 courses of chemotherapy, either CHOP or SMILE [16,17]. The dose was lowered by 25% in case of life-threatening grade 4 toxicity. For analysis purposes, these patients were further categorized as 6–8 courses and ≤5 courses.

The improved CHOP regimen consisted of 750 mg/m² cyclophosphamide, 30 mg/m² pirarubicin, vincristine 25 mg/m², and 10 mg dexamethasone, on days 1 and 8. In the CHOP-E regimen, 100 mg/m² etoposide were added on days 1 and 3. The MAED regimen included 6 mg/m² mitomycin and 100 mg/m² etoposide on days 1 and 3, and 100 mg/m² cytarabine and 10 mg dexamethasone on days 1 and 5. The MMED regimen included 6 mg/m² mitomycin, 100 mg/m² methotrexate, and 100 mg/m² etoposide on days 1 and 3, and dexamethasone 10 mg on days 1 and 5. The EPOCH regimen included 100 mg/m² etoposide added on days 1 and 3, vincristine 25 mg/m², 75 mg/m² doxorubicin, and 750 mg/m² cyclophosphamide on days 1 and 8. The SMILE regimen (dexamethasone, methotrexate, ifosfamide, etoposide, and L-asparaginase) was alternated with the A+B regimen of Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone).

After each course of chemotherapy, the next course was administered after 2 to 4 weeks. If white blood cell counts were <1.0×10⁹/L or blood platelet counts were 50×10⁹/L, the next course was delayed until the blood cells were restored.

**Radiotherapy**

Local radiotherapy was performed after 3 courses of chemotherapy in patients stage I-II according to the National Comprehensive Cancer Network (NCCN) guidelines [10,16]. Intensity-modulated radiation therapy was administered at 54 Gy in 27 fractions, once daily for 5 days.

**Symptomatic supportive treatment**

Patients with peripheral blood white blood cell counts less than 2.0×10⁹/L were administered subcutaneous injection of G-CSF. Patients with platelet counts below 50×10⁹/L were administered recombinant human thrombopoietin and hematopoietic therapy. When the platelet count fell below 20×10⁹/L or patients exhibited hemorrhage tendency, platelet suspension was infused. Patients with hemoglobin lower than 60 g/L and poor cardiopulmonary compensation were infused with red blood cell suspension. Patients with grade 4 myelosuppression were admitted into a sterile laminar flow ward and were given antibiotics, antifungals, and G-CSF. Patients with high blood Epstein-Barr virus (EBV) DNA titers (>10⁹ IU/ml) were given ganciclovir and foscarnet [18]. Here, it was not indicated that EBV was the evaluator factor for etiology. According to most relevant studies, EBV virus infection worsens the NK/T lymphoma prognosis. So for the patients with EBV virus infection, the administration of antiviral treatment is necessary and is beneficial to improve long-term survival.

**Follow-up**

Outpatient follow-up was performed every 3 months for the first 2 years, and then every 6 months. Symptoms, vital signs, survival, and quality of life were recorded. Routine blood tests and liver and kidney function tests were performed, as well as EBV titers, lymphocyte subsets, and electrocardiogram. Assessment of outcomes included measurement of size, number, distribution, and characteristics of lymphomas based on palpation of lymph nodes or lumps, B-ultrasound, X-ray, CT, and positron emission tomography (PET)-CT. This was a retrospective cohort study and all of the available patient data obtained in the study period were enrolled and analyzed. There was no calculation of sample size. In the initial study phase, the patients’ data were input into the database, and then the data were arranged and analyzed. Full sets of data were available for all patients and no patient was lost to follow-up. This high degree of compliance reflects the good compliance for tumor patients, the use of a specialized department and hospital, and timely telephone calls to remind the patients to attend follow-up.

**Efficacy assessment**

Short-term efficacy was assessed after 3 courses of therapy, and graded according to the WHO guidelines [19] as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). The total remission rate (RR) was calculated as CR+PR, and ineffectiveness rate was calculated as SD+PD. Relapse was defined as the appearance of new lesions (lymph nodes or lumps, or bone marrow infiltration) after complete remission. Long-term efficacy was assessed using...
OS (defined as the time from start of treatments to death or last follow-up), 5-year progression-free survival (PFS; defined as the time from start of treatments to recurrence or death), 5-year event-free survival (EFS; defined as the time from start of treatments to any event leading to changes in treatments such as severe adverse effects, non-tolerance, disease progression, or death), and relapse during follow-up. All patients lost to follow-up were excluded.

**Adverse effects**

According to the chemotherapeutic toxicity grading guidelines issued by the WHO, adverse effects were classified into grade 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (life-threatening), according to the annotation from the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE) 4.0 [20].

**Statistical analysis**

The patients were categorized according to high-intensity chemotherapy vs. 6–8 courses of chemotherapy vs. <6 courses of chemotherapy. Patients were also stratified by systemic EBV infection (positive vs. negative). Continuous variables are presented as mean ± standard deviation and were analyzed using analysis of variance with the Tukey’s post hoc test. Categorical variables are presented as frequencies and were analyzed using the Fisher exact test. The Kaplan-Meier method was used to generate survival curves and calculate survival. The log-rank test was used to compare survival among groups. The Cox proportional hazard model was used to analyze the independence of variables in multivariate analysis. Statistical analyses were performed using SPSS 18.0 (IBM, Armonk, NY, USA). Two-sided P-values <0.05 were considered statistically significant.

**Results**

**Clinical characteristics**

This was a retrospective study of patients <60 years old with an ECOG score of 0-2 who received treatment for ENKTL at the Second Affiliated Hospital of Xi’an Jiaotong University between January 2004 and December 2013. A total of 69 patients were enrolled, of which 37 received high-intensity chemotherapy and 32 received conventional chemotherapy (control group). Of those patients in the control group, 18 received 6–8 courses of chemotherapy and 14 received <6 courses. The demographic and clinical characteristics were similar among all 3 groups (all P>0.05 by overall comparison) (Table 1). Supplementary Table 1 presents the individual characteristics of each patient.

**Short-term efficacy**

Efficacy was assessed after 3 courses of chemotherapy. In the high-intensity, 6–8 courses, and <6 courses groups, the RR was 83.8% (31/37), 77.8% (14/18), and 76.6% (11/14), respectively (overall P=0.834); the CR was 73.0% (27/37), 66.7% (12/18), and 64.3% (9/14), respectively (overall P=0.795); and the PR was 10.8% (4/37), 11.1% (2/18), and 11.1% (2/18), respectively (overall P=0.939).

Twenty-two patients tested positive for systemic EBV infection: 12, 5, and 5 in the high-intensity, 6–8 courses, and <6 courses groups, respectively. CR in the high-intensity group was significantly higher in patients with EBV infection compared to those without (41.7% and 88.0%, P=0.006) (Table 2). There were no differences between patients with/without active EBV infection in the other 2 groups.

**Long-term efficacy**

By September 30, 2014, the median follow-up ranged from 8 to 82 months (mean of 52 months). The high-intensity group received a median of 14 courses of chemotherapy (range: 9–16). The 6-8 courses group received a median of 6 courses (range: 6–8). The <6 courses group received a median of 3 courses (range: 3–5).

The 5-year OS in the high-intensity, 6-8 courses, and <6 courses groups was significantly different among groups (63.5% vs. 45.1% vs. 42.9%, respectively, overall P=0.030); as well as 5-year PFS (59.1% vs. 36.0% vs. 15.1%, respectively, overall P=0.020); 5-year EFS (54.1% vs. 35.5% vs. 12.9%, respectively, overall P=0.022); and relapse rates (37.0% vs. 50.0% vs. 88.9%, respectively, overall P=0.027) (Figure 1). Patients with stage III/IV seem to fare worse than patients with stage I/II, irrespective of chemotherapy, but the small number of patients in stage III/IV preclude any firm conclusions (Supplementary Figure 1).

Of the 22 patients with active EBV infection, only 6 recovered from the infection during follow-up for 3 to 15 months, but all 6 relapsed during follow-up. Eleven end-stage patients showed hemophagocytic syndrome (HLH) and an outbreak process, with rapid deterioration. They all died, within an average of 6 weeks. Ten of the 11 patients who developed HLH were EBV-infected.

The 5-year survival of patients with EBV was lower than that of patients without EBV infection among patients in the high-intensity group (P=0.01), but not in the other 2 groups (Table 3, Figure 2). This difference was also observed when all patients were analyzed together (Figure 3). Thirty-three patients died during follow-up: 11 of hemophagocytic syndrome, 16 of disease progression, 3 of heart failure, 2 of respiratory failure, and 1 of liver failure.
Table 1. Clinical characteristics of patients.

| Characteristics          | High-intensity (n=37) | 6–8 courses (n=18) | <6 courses (n=14) | P (comparison between the three groups) | P (high-intensity group vs. <6 courses group) |
|--------------------------|-----------------------|--------------------|-------------------|-----------------------------------------|-----------------------------------------------|
| Age (years), median (range) | 49 (18–59)           | 48 (20–59)         | 42 (18–57)        | 0.822                                   | 0.584                                         |
| Gender, n (%)            |                       |                    |                   |                                         |                                               |
| Male                     | 22 (59.5%)            | 12 (66.7%)         | 10 (71.4%)        | 0.698                                   | 0.423                                         |
| Female                   | 15 (40.5%)            | 6 (33.3%)          | 4 (28.6%)         |                                         |                                               |
| B symptoms, n (%)        |                       |                    |                   |                                         |                                               |
| Yes                      | 11 (29.7%)            | 6 (33.3%)          | 4 (28.6%)         | 0.950                                   | 0.891                                         |
| No                       | 26 (70.3%)            | 12 (66.7%)         | 10 (71.4%)        |                                         |                                               |
| Performance status, n (%)|                       |                    |                   |                                         |                                               |
| ECOG 0-1                 | 31 (83.8%)            | 15 (83.3%)         | 12 (85.7%)        | 0.981                                   | 0.947                                         |
| ECOG 2                   | 6 (16.2%)             | 3 (16.7%)          | 2 (14.3%)         |                                         |                                               |
| LDH >UNV*, n (%)         |                       |                    |                   | 0.811                                   | 0.576                                         |
| Yes                      | 9 (24.3%)             | 3 (16.7%)          | 3 (21.4%)         |                                         |                                               |
| No                       | 28 (75.7%)            | 15 (83.3%)         | 11 (78.6%)        |                                         |                                               |
| Ann Arbor Stage, n (%)   |                       |                    |                   | 0.996                                   | 0.985                                         |
| I                        | 19 (51.4%)            | 9 (50.0%)          | 6 (42.9%)         |                                         |                                               |
| II                       | 13 (35.1%)            | 6 (33.3%)          | 6 (42.9%)         |                                         |                                               |
| III                      | 3 (8.1%)              | 2 (11.1%)          | 1 (7.1%)          |                                         |                                               |
| IV                       | 2 (5.4%)              | 1 (5.6%)           | 1 (7.1%)          |                                         |                                               |
| IPI score, n (%)         |                       |                    |                   | 0.851                                   | 0.685                                         |
| 0–1                      | 27 (73.0%)            | 13 (72.2%)         | 9 (64.3%)         |                                         |                                               |
| 2                        | 7 (18.9%)             | 3 (16.7%)          | 2 (14.3%)         |                                         |                                               |
| 3                        | 1 (2.7%)              | 1 (5.6%)           | 2 (14.3%)         |                                         |                                               |
| 4–5                      | 2 (5.4%)              | 1 (5.6%)           | 1 (7.1%)          |                                         |                                               |
| NK/T-cell PI score [39], n (%) | NA              |                    |                   | 0.997                                   |                                               |
| 0                        | 10 (27.0%)            | 13 (72.2%)         | 12 (20.9%)        |                                         |                                               |
| 1                        | 12 (32.4%)            | 6 (33.3%)          | 5 (35.7%)         |                                         |                                               |
| 2                        | 8 (21.6%)             | 4 (22.2%)          | 3 (21.4%)         |                                         |                                               |
| 3–4                      | 7 (18.9%)             | 3 (16.7%)          | 3 (21.4%)         |                                         |                                               |
| EBV infection**, n (%)   |                       |                    |                   | 0.887                                   | 0.916                                         |
| Negative                 | 25 (67.6%)            | 13 (72.2%)         | 9 (64.3%)         |                                         |                                               |
| Positive                 | 12 (32.4%)            | 5 (27.8%)          | 5 (35.7%)         |                                         |                                               |
| Nodal involvement, n (%) |                       |                    |                   | 0.879                                   | 0.618                                         |
| Yes                      | 14 (37.8%)            | 8 (44.4%)          | 6 (42.9%)         |                                         |                                               |
| No                       | 23 (62.2%)            | 10 (55.6%)         | 8 (57.1%)         |                                         |                                               |

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The multivariate analysis revealed that the total number of chemotherapy courses, the chemotherapy strategy, and NK score were independent prognostic factors affecting OS, PFS, and EFS (Table 4).

Safety and toxicity

The rate of adverse effects was recorded during follow-up, and higher rates of many adverse events were reported in the high-intensity group compared with the other 2 groups (Table 5). Nevertheless, the reported adverse events were controllable and the main outcomes (including chemotherapy-related mortality) were similar among groups.

Discussion

This was a single-center retrospective cohort study of the outcomes of chemotherapy in patients less than 60 years of age diagnosed with ENKTL. Although the RR did not differ significantly among groups, the 5-year OS, PFS, and DFS were significantly better in patients who received high-intensity chemotherapy, and the RR was significantly lower in this group. The rate of adverse effects did not differ significantly among the 3 groups.

Compared with the traditional CHOP regimens, in our improved CHOP regimen, the doxorubicin was replaced by pirarubicin, vincristine was replaced by vinorelbine, and oral prednisone was replaced by intravenous injection of dexamethasone. The potential advantages of this regimen include: (1) pirarubicin is a synthetic anthracycline antitumor antibiotic. Compared with doxorubicin, the fat solubility of pirarubicin is increased due to structural changes, which enable it to quickly enter cells but be excluded slowly, leading to a high concentration in the...
cells and increased anti-tumor activity [21]. The incidence of cardiac toxicity was 1.5% in elderly NHL patients receiving pirarubicin and 14.2% for those receiving doxorubicin in combination chemotherapy [22]. Therefore, it is applicable to more patients, and it is safe in elderly patients. (2) Vinorelbine is a semi-synthetic vinca alkaloid compound with broad-spectrum anti-tumor activity, and has lower neurotoxicity compared with other vinca alkaloids [23]. In addition, monotherapy efficiency of vinorelbine can be up to 38% in NHL patients who had received failure treatment with vinca alkaloid chemotherapy drugs [24]. (3) Dexamethasone is a long-term glucocorticoid, which can more effectively reduce CNS infiltration or relapse and reduce adverse effects of chemotherapy better than prednisone [25]. Furthermore, we produced new combinations of drugs according to different mechanisms, no cross-resistance, and other principles, such as MMED and MAED regimens, as well as produced multidrug resistance genes (MDR), aiming to improve the efficacy in treating hematological malignant tumors.

Yamaguchi et al. performed a long-term follow-up study of the JCOGO211 trial [26]. They showed that in 33 stage I/IIIE patients (ECOG score 0–2) undergoing radiotherapy and DevIC chemotherapy, the OS and PFS by Yamaguchi were 70% and 63%, which are similar to the present study (71.1% and 65.6%, respectively). Wang et al. studied 27 patients with newly diagnosed ENKTL patients receiving the GELOX chemotherapy; after a median follow-up of 27.4 months, OS and PFS were 86% [27]. It was previously reported that in patients with ENKTL treated with CHOP-L regimen combined with radiotherapy, the 2-year OS and PFS were 80.1% and 81.0%, respectively [28]. In patients with stage I/II ENKTL initially treated with CCRT+DevIC, the rate of complete remission was 77%, and 2-year OS and PFS were 78% and 67%, respectively [29]. In the present study,

Figure 1. Kaplan-Meier curves for 5-year overall survival (A), progression-free survival (B), and event-free survival (C).
the 2-year OS and PFS in the high-intensity group were higher, at 91.7% and 86.1%, respectively, which may indicate that increased dose intensity and improved regimens can improve outcome in severe ENKTL. Lee et al. [9] compared the efficacy of CCRT (1–6 courses) and SCRT (1-4 courses) treatment modes and found that neither the 3-year OS (59% and 75%, respectively) nor 3-year PFS (41% and 56%, respectively) differed significantly. The long-term efficacy of a longer treatment course in the present study was also higher, in agreement with a previous report by Ma et al. [30].

Table 3. Survival rate in patients with and without EBV infection.

| Survival | High-intensity (n=37) | 6–8 courses (n=18) | <6 courses (n=14) | All |
|----------|-----------------------|-------------------|------------------|-----|
|          | EBV– | EBV+ | P value | EBV– | EBV+ | P value | EBV– | EBV+ | P value | EBV– | EBV+ | P value |
| 5-year OS | 80.5 | 32.1 | 0.010 | 51.3 | 26.7 | 0.294 | 41.7 | 0.0 | 0.221 | 62.2 | 23.1 | <0.001 |
| 5-year PFS | 72.2 | 0.0 | <0.001 | 50.0 | 0.0 | 0.101 | 20.8 | 0.0 | 0.505 | 54.7 | 19.7 | <0.001 |

OS – overall survival; PFS – progression-free survival.

Figure 2. Kaplan-Meier curves for 5-year overall survival (A), progression-free survival (B), and event-free survival (C) according to EBV infection and chemotherapy.

the 2-year OS and PFS in the high-intensity group were higher, at 91.7% and 86.1%, respectively, which may indicate that increased dose intensity and improved regimens can improve outcome in severe ENKTL. Lee et al. [9] compared the efficacy of CCRT (1–6 courses) and SCRT (1-4 courses) treatment modes and found that neither the 3-year OS (59% and 75%, respectively) nor 3-year PFS (41% and 56%, respectively) differed significantly. The long-term efficacy of a longer treatment course in the present study was also higher, in agreement with a previous report by Ma et al. [30].
Table 4. Multivariate analysis of factors affecting OS, PFS, and EFS in patients with ENKTL.

| Factors                     | OS            | PFS           | EFS            |
|-----------------------------|---------------|---------------|----------------|
|                             | P value | RR | 95% CI     | P value | RR | 95% CI     | P value | RR | 95% CI     |
| Total chemotherapy courses  | 0.004    | 0.494 | (0.303, 0.803) | 0.004    | 0.497 | (0.307, 0.803) | 0.010    | 0.547 | (0.346, 0.864) |
| Chemotherapy strategy       | 0.006    | 0.495 | (0.301, 0.816) | 0.008    | 0.511 | (0.312, 0.837) | 0.017    | 0.558 | (0.346, 0.900) |
| NK score                    | 0.001    | 5.731 | (2.208, 14.877) | 0.000    | 6.258 | (2.375, 16.488) | 0.000    | 6.824 | (2.415, 19.279) |

OS – overall survival; PFS – progression-free survival; EFS – event-free survival; RR – relative risk; CI – confidence interval.
The etiology and pathogenesis of ENKTL are still unclear, but EBV has been implicated [31]. Huang et al. [32] hypothesized that EBV infection causes active NK cells in the nasal cavity to release cytokines (IL-2, IL-9, and IL-15), which reduce the expression of tumor suppressor genes, leading to malignant conversion of NKC cells and promotion of ENKTL progression. Early studies have confirmed that plasma EBV DNA titers are positively correlated with tumor loading and poor prognosis [33,34]. Therefore, continuously monitoring EBV levels in peripheral blood may show efficacy and/or act as an early indicator of relapse [35]. In this study, the efficacy of treatment in patients with low EBV titers was greater than that in patients with high EBV titers. Appropriately prolonging the course of chemotherapy course was associated with increased survival rate, and EBV became temporarily undetectable in some patients during therapy. Ten patients with EBV-related HLH exhibited quicker progression, shorter survival, and 100% mortality, and the main causes of death were bleeding, infection, failure of multiple organs, and DIC. Cytokines released after EBV infection play an important role in the pathogenesis of EBVHLH [36,37], causing uncontrolled activation of T lymphocytes and macrophages to attack otherwise healthy cells, causing clinical presentation of the manifestations of HLH.

### Table 5. Adverse effects.

| Grade 3–4 adverse effects | High-intensity (n=37) | 6–8 courses (n=18) | <6 courses (n=14) | Overall P |
|---------------------------|-----------------------|-------------------|------------------|-----------|
| Aleucocytosis             | 364 (79.8%)           | 94 (78.3%)        | 31 (64.6%)       | 0.051     |
| Anemia                    | 148 (32.5%)           | 28 (23.3%)        | 12 (25.0%)       | 0.111     |
| Thrombocytopenia          | 130 (28.5%)           | 23 (19.2%)        | 9 (18.8%)        | 0.057     |
| Neutrocytopenia           | 320 (70.2%)           | 74 (61.7%)        | 28 (58.3%)       | 0.075     |
| Nausea and vomit          | 74 (16.2%)            | 13 (10.8%)        | 3 (6.3%)         | 0.08      |
| Dysfunction of liver      | 12 (2.6%)             | 0                 | 0                | 0.105     |
| Dysfunction of kidney     | 0                     | 0                 | 0                |           |
| Alopecia                  | 14 (3.1%)             | 4 (3.3%)          | 0                | 0.457     |
| Cardiac damage            | 0                     | 0                 | 0                |           |
| Peripheral neuritis       | 0                     | 0                 | 0                |           |
| Oral ulcer                | 74 (16.2%)            | 12 (10.0%)        | 5 (10.4%)        | 0.159     |
| Neutropenia with fever    | 49 (10.7%)            | 13 (10.8%)        | 4 (8.3%)         | 0.87      |
| Red blood cell transfusion|                       |                   |                  |           |
| Single patient            | 17 (45.9%)            | 6 (34.3%)         | 4 (28.5%)        | 0.442     |
| One course                | 10 (27.0%)            | 3 (16.6%)         | 2 (14.1%)        | 0.512     |
| Platelet transfusion      |                       |                   |                  |           |
| Single patient            | 8 (21.6%)             | 3 (17.1%)         | 2 (13.9%)        | 0.805     |
| One course                | 3 (8.1%)              | 1 (5.3%)          | 4.80%            | 0.943     |
| Antibiotics               |                       |                   |                  |           |
| Single patient            | 64.90%                | 50.00%            | 42.50%           | 0.298     |
| One course                | 24.30%                | 16.10%            | 13.20%           | 0.66      |
| Chemotherapy-related mortality |                  | 0                 | 0                |           |
| Acute pancreatitis        | 12 (2.6%)             | 3 (2.5%)          | 1 (2.1%)         | 0.973     |
| Hypofibrinogenemia        | 345 (75.7%)           | 80 (66.7%)        | 31 (64.6%)       | 0.055     |

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A large retrospective and multi-center study of 262 patients from South Korea reported that Ann Arbor stage, B symptoms, LDH levels, and regional lymph node involvement were independent prognostic factors in patients with ENKTL [12]. Based on these results, they established a prognostic model for patients with ENKTL, and reported that it predicted prognosis of ENKTL patients more accurately than the IPI score. A further study of 105 patients with early ENKTL reported that Ann Arbor staging, IPI score, and tumor invasion were independent prognostic factors of ENKTL [38]. Another retrospective study of 79 patients with stage I-IV ENKTL reported that Ann Arbor stage and PS score were associated with ENKTL prognosis [8].

In the present study, total number of chemotherapy courses, chemotherapy strategy, and NK score were independent prognostic indexes associated with OS, PFS, and DFS. Clearly, selection of chemotherapy regimen is crucial for ENKTL prognosis. In this study, short-term efficacy and long-term survival were improved using alternating chemotherapy with prolonged courses and improved regimens compared with the traditional regimens, and the reasons may include: (1) The dose was increased in the remission induction phase and administration was focused on the 1st and 8th days. (2) These drugs had synergetic effects, which tended to strengthen the therapeutic efficiency without cross-resistance, and had mild adverse effects, especially the mild cardiac toxicity of THP and neurotoxicity of NVB, which tended to improve the quality of life of patients and was conducive for consolidation therapy in the later stage. (3) Alternately applying chemotherapy regimens of CHOPE, MAED, MMED, TAED, improved SMILE, middle-dose cytarabine and L-asparaginase and Hyper-CVAD in the consolidation phase after remission induction was able to reduce the drug resistance of tumor cells. (4) Patients were admitted to the sterile laminar flow ward as soon as possible to receive supportive treatment, avoiding chemotherapy-related death. (5) The number of courses was appropriately prolonged, where it was above 8 in the first year, and 4–6 and 2–3 in the second and third years, respectively. Subsequent outpatient follow-up and regular recheck were conducted to achieve close monitoring and timely treatment.

Nevertheless, the present study is not without limitations. It was a small, single-center, retrospective, cohort study. Further large, randomized, and controlled studies are required to confirm whether this strategy can be considered as an optimized treatment regimen in initial treatment of young ENKTL patients. The patients in this study may have received many different chemotherapy regimens over time, and this is likely to have an influence on the efficacy of the regimens studied here. In addition, the wide variety of regimens may confound the results, so strictly controlled prospective trials are necessary. Finally, patients with active systemic EBV infection received ganciclovir and foscarnet, which could bias the results.

**Conclusions**

These results suggest improved OS, PFS, DFS, and relapse rate in young patients with ENKTL receiving >8 courses of high-intensity chemotherapy.

**Conflict of interest**

The authors declare that they have no conflicts of interest.

### Supplementary Table 1. Description of each patient.

| No | Sex/age (years) | Stage | Total chemotherapy courses | Treatments (number and types) | Outcome | Follow-up (months) |
|----|----------------|-------|----------------------------|-------------------------------|---------|-------------------|
| 1  | M/23           | III   | 3                          | 2 CHOP, 1 SMILE               | Dead    | 11                |
| 2  | M/25           | I     | 4                          | 2 CHOP, 2 SMILE               | Survival| 42                |
| 3  | M/32           | II    | 3                          | 1 CHOP, 1 SMILE, 1 CHOPE      | Dead    | 30                |
| 4  | M/42           | II    | 4                          | 2 CHOP, 2 SMILE               | Dead    | 36                |
| 5  | M/42           | I     | 3                          | 2 CHOP, 1 SMILE               | Dead    | 60                |
| 6  | M/52           | I     | 2                          | 1 CHOP, 1 SMILE, 1 CHOPE      | Dead    | 62                |
| 7  | M/57           | II    | 3                          | 2 CHOP, 1 CHOPE               | Dead    | 24                |
| 8  | M/55           | I     | 3                          | 1 CHOP, 1 SMILE, 1 CHOPE      | Dead    | 38                |
| 9  | F/49           | II    | 5                          | 2 CHOP, 2 SMILE, 1 CHOPE      | Dead    | 40                |
| No | Sex/age (years) | Stage | Total chemotherapy courses | Treatments (number and types) | Outcome | Follow-up (months) |
|----|----------------|-------|-----------------------------|-------------------------------|---------|-------------------|
| 10 | F/18           | I     | 3                           | 1 CHOP, 1 SMILE, 1 CHOPE      | Dead    | 48                |
| 11 | M/46           | II    | 4                           | 1 CHOP, 1 SMILE, 2 CHOPE      | Survival| 55                |
| 12 | F/49           | I     | 3                           | 1 CHOP, 1 SMILE, 1 CHOPE      | Survival| 73                |
| 13 | M/27           | IV    | 3                           | 2 CHOP, 1 SMILE               | Dead    | 8                 |
| 14 | F/38           | II    | 4                           | 2 CHOP, 1 SMILE, 1 CHOPE      | Dead    | 26                |
| 15 | M/41           | I     | 7                           | 3 CHOP, 2 SMILE, 2 CHOPE      | Survival| 47                |
| 16 | M/49           | II    | 7                           | 3 CHOP, 1 SMILE, 3 CHOPE      | Dead    | 34                |
| 17 | M/48           | III   | 8                           | 3 CHOP, 2 SMILE, 3 CHOPE      | Dead    | 17                |
| 18 | F/57           | I     | 8                           | 3 CHOP, 2 SMILE, 3 CHOPE      | Survival| 29                |
| 19 | M/59           | III   | 7                           | 2 CHOP, 2 SMILE, 2 CHOPE      | Survival| 31                |
| 20 | F/25           | II    | 8                           | 2 CHOP, 3 SMILE, 3 CHOPE      | Survival| 44                |
| 21 | M/42           | II    | 8                           | 4 CHOP, 2 SMILE, 2 CHOPE      | Dead    | 28                |
| 22 | M/52           | II    | 8                           | 3 CHOP, 3 SMILE, 2 CHOPE      | Survival| 66                |
| 23 | M/35           | I     | 6                           | 4 CHOP, 1 SMILE, 1 CHOPE      | Survival| 33                |
| 24 | M/38           | I     | 6                           | 2 CHOP, 2 SMILE, 2 CHOPE      | Dead    | 55                |
| 25 | M/39           | II    | 6                           | 3 CHOP, 1 SMILE, 2 CHOPE      | Survival| 29                |
| 26 | M/48           | I     | 6                           | 4 CHOP, 1 SMILE, 1 CHOPE      | Dead    | 42                |
| 27 | M/48           | I     | 6                           | 2 CHOP, 2 SMILE, 2 CHOPE      | Survival| 59                |
| 28 | F/44           | I     | 6                           | 3 CHOP, 2 SMILE, 1 CHOPE      | Dead    | 61                |
| 29 | M/50           | II    | 6                           | 3 CHOP, 1 SMILE, 2CHOPE       | Dead    | 32                |
| 30 | F/50           | I     | 6                           | 4 CHOP, 1 SMILE, 1 CHOPE      | Survival| 47                |
| 31 | M/49           | IV    | 6                           | 4 CHOP, 1 SMILE, 1 CHOPE      | Dead    | 12.5              |
| 32 | M/49           | I     | 9                           | 2 CHOP, 2 SMILE, 1 CHOPE, 2 MAED, 2 MMED | Dead    | 55                |
| 33 | F/49           | II    | 12                          | 3 CHOP, 2 SMILE, 2 CHOPE, 2 MAED, 2 MMED, 1 HyperCVAD | Survival| 38                |
| 34 | F/51           | I     | 12                          | 4 CHOP, 2 SMILE, 1 CHOPE, 2 MAED, 2 MMED, 1 HyperCVAD | Survival| 20                |
| 35 | F/52           | I     | 12                          | 3 CHOP, 2 SMILE, 2 CHOPE, 2 MAED, 2 MMED, 1 HyperCVAD | Survival| 38                |
| 36 | M/54           | II    | 11                          | 3 CHOP, 1 SMILE, 2 CHOPE, 2 MAED, 2 MMED, 1 HyperCVAD | Dead    | 58                |
| 37 | M/57           | II    | 10                          | 2 CHOP, 2 SMILE, 1 CHOPE, 2 MAED, 2 MMED, 1 HyperCVAD | Survival| 15                |
| 38 | F/57           | II    | 14                          | 3 CHOP, 2 SMILE, 2 CHOPE, 3 MAED, 2 MMED, 1 HyperCVAD, 1 EPOCH | Survival| 40                |
| 39 | M/57           | I     | 13                          | 3 CHOP, 2 SMILE, 1 CHOPE, 1 EPOCH, 3 MAED, 2 MMED, 1 HyperCVAD | Survival| 37.5              |
| 40 | F/59           | III   | 12                          | 2 CHOP, 3 SMILE, 2 CHOPE, 2 MAED, 2 MMED, 1 HyperCVAD | Dead    | 66                |
| No | Sex/age (years) | Stage | Total chemotherapy courses | Treatments (number and types) | Outcome | Follow-up (months) |
|----|----------------|-------|----------------------------|-------------------------------|---------|-------------------|
| 41 | M/40           | I     | 12                         | 4 CHOP, 2 SMILE, 1 CHOPe, 1 MAED, 2 MMED, 1 EPOCH, 1 HyperCVAD | Survival | 25                |
| 42 | M/18           | I     | 9                          | 3 CHOP, 1 SMILE, 2 CHOPe, 2 MAED, 1 MMED | Dead    | 65                |
| 43 | M/24           | I     | 12                         | 2 CHOP, 2 SMILE, 2 CHOPe, 2 MAED, 2 MMED, 1 HyperCVAD, 1 EPOCH | Survival | 63                |
| 44 | M/28           | I     | 14                         | 4 CHOP, 2 SMILE, 2 CHOPe, 2 MAED, 2 MMED, 1 HyperCVAD, 1 EPOCH | Survival | 33                |
| 45 | F/28           | I     | 14                         | 2 CHOP, 2 SMILE, 2 CHOPe, 4 MAED, 2 MMED, 1 HyperCVAD, 1 EPOCH | Survival | 67                |
| 46 | M/31           | I     | 14                         | 3 CHOP, 2 SMILE, 2 CHOPe, 3 MAED, 2 MMED, 2 HyperCVAD | Survival | 68                |
| 47 | F/35           | II    | 14                         | 4 CHOP, 2 SMILE, 2 CHOPe, 2 MAED, 2 MMED, 2 EPOCH | Dead    | 66                |
| 48 | F/42           | II    | 12                         | 3 CHOP, 1 SMILE, 2 CHOPe, 3 MAED, 2 MMED, 1 HyperCVAD | Survival | 66                |
| 49 | F/43           | II    | 11                         | 3 CHOP, 2 SMILE, 1 CHOPe, 2 MAED, 2 MMED, 1 HyperCVAD | Dead    | 36                |
| 50 | F/49           | II    | 12                         | 2 CHOP, 2 SMILE, 1 CHOPe, 3 MAED, 3 MMED, 1 HyperCVAD | Survival | 44                |
| 51 | F/59           | II    | 12                         | 3 CHOP, 1 SMILE, 2 CHOPe, 3 MAED, 2 MMED, 1 EPOCH | Survival | 54.5              |
| 52 | F/52           | III   | 14                         | 5 CHOP, 2 SMILE, 2 CHOPe, 1 MAED, 2 MMED, 2 HyperCVAD | Dead    | 40                |
| 53 | F/54           | II    | 14                         | 3 CHOP, 3 SMILE, 2 CHOPe, 3 MAED, 2 MMED, 1 HyperCVAD | Survival | 46                |
| 54 | M/28           | I     | 14                         | 3 CHOP, 2 SMILE, 2 CHOPe, 4 MAED, 3 MMED | Survival | 30                |
| 55 | F/49           | I     | 14                         | 3 CHOP, 1 SMILE, 2 CHOPe, 3 MAED, 3 MMED, 1 HyperCVAD, 1 EPOCH | Survival | 64                |
| 56 | F/50           | I     | 14                         | 5 CHOP, 3 SMILE, 1 CHOPe, 2 MAED, 2 MMED, 1 HyperCVAD | Survival | 34                |
| 57 | M/48           | I     | 14                         | 2 CHOP, 2 SMILE, 2 CHOPe, 4 MAED, 3 MMED, 1 HyperCVAD | Survival | 80                |
| 58 | M/55           | I     | 14                         | 3 CHOP, 3 SMILE, 2 CHOPe, 3 MAED, 2 MMED, 1 HyperCVAD | Survival | 78                |
| 59 | M/57           | I     | 14                         | 3 CHOP, 2 SMILE, 1 CHOPe, 3 MAED, 3 MMED, 1 HyperCVAD, 1 EPOCH | Survival | 82                |
| 60 | M/38           | I     | 14                         | 2 CHOP, 2 SMILE, 2 CHOPe, 4 MAED, 3 MMED, 1 HyperCVAD | Survival | 49                |
| 61 | M/25           | I     | 14                         | 3 CHOP, 3 SMILE, 2 CHOPe, 3 MAED, 2 MMED, 1 HyperCVAD | Survival | 44                |
| 62 | M/26           | I     | 14                         | 2 CHOP, 3 SMILE, 2 CHOPe, 4 MAED, 2 MMED, 1 HyperCVAD | Survival | 37                |
| No | Sex/age (years) | Stage | Total chemotherapy courses | Treatments (number and types) | Outcome | Follow-up (months) |
|----|----------------|-------|----------------------------|--------------------------------|---------|--------------------|
| 63 | M/49           | I     | 14                         | 3 CHOP, 2 SMILE, 2 CHOPE, 3 MAED, 2 MMED, 1 HyperCVAD, 1 EPOCH | Survival | 31                 |
| 64 | M/53           | II    | 12                         | 3 CHOP, 2 SMILE, 3 CHOPE, 1 MAED, 2 MMED, 1 HyperCVAD | Dead    | 30                 |
| 65 | M/57           | III   | 9                          | 3 CHOP, 2 SMILE, 2 CHOPE, 1 MAED, 1 MMED | Dead    | 26                 |
| 66 | M/59           | II    | 10                         | 3 CHOP, 2 CHOPE, 1 MAED, 2 MMED, 2 HyperCVAD | Dead    | 34                 |
| 67 | M/59           | IV    | 9                          | 3 CHOP, 3 SMILE, 2 MAED, 1 MMED | Dead    | 15.5               |
| 68 | M/59           | IV    | 9                          | 2 CHOPE, 2 SMILE, 1 CHOPE, 2 MAED, 1 HyperCVAD, 1 EPOCH | Dead    | 14                 |
| 69 | M/44           | II    | 10                         | 2 CHOPE, 2 SMILE, 1 CHOPE, 2 MAED, 2 MMED, 1 HyperCVAD | Dead    | 21                 |

Supplementary Figure 1. Kaplan-Meier curve for 5-year overall survival (A), progression-free survival (B), and event-free survival (C) of different clinical stages.
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