MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 4297-4311
DOI: 10.12659/MSM.897650

Received: 2016.01.19
Accepted: 2016.03.11
Published: 2016.11.11

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

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Yan Xu
BCDE Jin Wang
BCDE Wanggang Zhang
BCDE Jie Liu
BCD Xingmei Cao
BCD Aili He
BCD Yinxia Chen
BC Liufang Gu
BC Bo Lei
BC Pengyu Zhang
ABCDEG Xiaorong Ma

Department of Hematology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shanxi, P.R. China

Corresponding Author: Xiaorong Ma, e-mail: xrma941@sina.com
Source of support: This work was supported by the 2013 Science and Technology Research and Development Project of Shanxi Province (No. 2013K12-06-03)

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

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/897650

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Background

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-Plasmacytic 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,

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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/m^2 cyclophosphamide, 30 mg/m^2 pirarubicin, vinorelbine 25 mg/m^2, and 10 mg dexamethasone, on days 1 and 8. In the CHOP-E regimen, 100 mg/m^2 etoposide were added on days 1 and 3. The MAED regimen included 6 mg/m^2 mitomycin and 100 mg/m^2 etoposide on days 1 and 3, and 100 mg/m^2 cytarabine and 10 mg dexamethasone on days 1 and 5. The MMED regimen included 6 mg/m^2 mitomycin, 100 mg/m^2 methotrexate, and 100 mg/m^2 etoposide on days 1 and 3, and dexamethasone 10 mg on days 1 and 5. The EPOCH regimen included 100 mg/m^2 etoposide added on days 1 and 3, vinorelbine 25 mg/m^2, 75 mg/m^2 doxorubicin, and 750 mg/m^2 cyclophosphamide on days 1 and 8. The SMILE regimen (dexamethasone, methotrexate, ifosfamide, etoposide, and L-asparaginase) was alternated with the A+B regimens 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 <1.0×10^9/L or blood platelet counts were 50×10^9/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 2.0×10^9/L were administered subcutaneous injection of G-CSF. Patients with platelet counts below 50×10^9/L were administered recombinant human thrombopoietin and hemostatic therapy. When the platelet count fell below 20×10^9/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 (>10^3 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

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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 78.6% (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.* and 22.9%, 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.

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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 (%)				0.698	0.423
Male	22 (59.5%)	12 (66.7%)	10 (71.4%)		
Female	15 (40.5%)	6 (33.3%)	4 (28.6%)		
B symptoms, n (%)				0.950	0.891
Yes	11 (29.7%)	6 (33.3%)	4 (28.6%)		
No	26 (70.3%)	12 (66.7%)	10 (71.4%)		
Performance status, n (%)				0.981	0.947
ECOG 0-1	31 (83.8%)	15 (83.3%)	12 (85.7%)		
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%)	5 (27.8%)	3 (21.4%)		
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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Table 1 continued. 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)
Primary sites involvement, n (%)				0.889	0.700
Nasal cavity	27 (73.0%)	12 (66.7%)	10 (71.4%)		
Other sites	10 (27.0%)	6 (33.3%)	4 (28.6%)		
Ki-67 index, n (%)				0.883	0.657
≤6%	17 (46.0%)	7 (38.9%)	6 (42.9%)		
>60%	20 (54.1%)	11 (61.1%)	8 (57.1%)		

* The normal upper limit of LDH is 300 IU/L, LDH >300 IU/L refers to elevation; ** EBV infection is indicated by $>10^3$ IU/ml. NA – not applicable.

Table 2. Short-term efficacy and EBV infection.

Group		EBV+ (%)	EBV– (%)	P
High-intensity	CR	41.7% (5/12)	88.0% (22/25)	0.006
	PR	25.0% (3/12)	4.0% (1/25)	0.091
	RR	66.7% (8/12)	92.0% (23/25)	0.073
6–8 courses	CR	40.0% (2/5)	76.9% (10/13)	0.268
	PR	20.0% (1/5)	7.7% (1/13)	0.490
	RR	60.0% (3/5)	84.6% (11/13)	0.533
<6 courses	CR	40.0% (2/5)	77.8% (7/9)	0.266
	PR	20.0% (1/5)	11.1% (1/9)	NA
	RR	60.0% (3/5)	88.9% (8/9)	0.505

RR – remission rate; CR – complete remission; PR – partial remission.

Multivariate analysis

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

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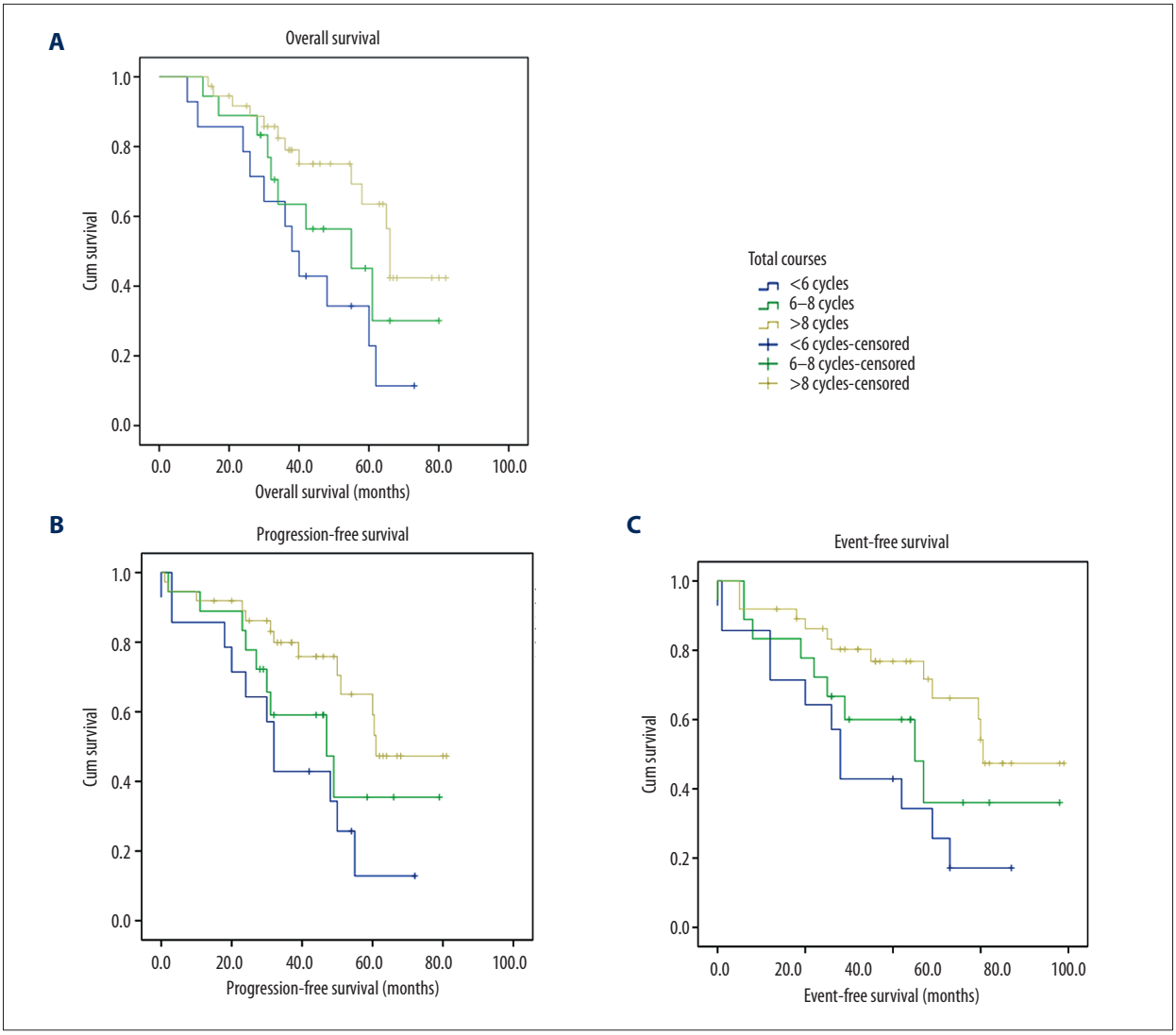

Figure 1. Kaplan-Meier curves for 5-year overall survival (**A**), progression-free survival (**B**), and event-free survival (**C**).

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/IIE 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,

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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.

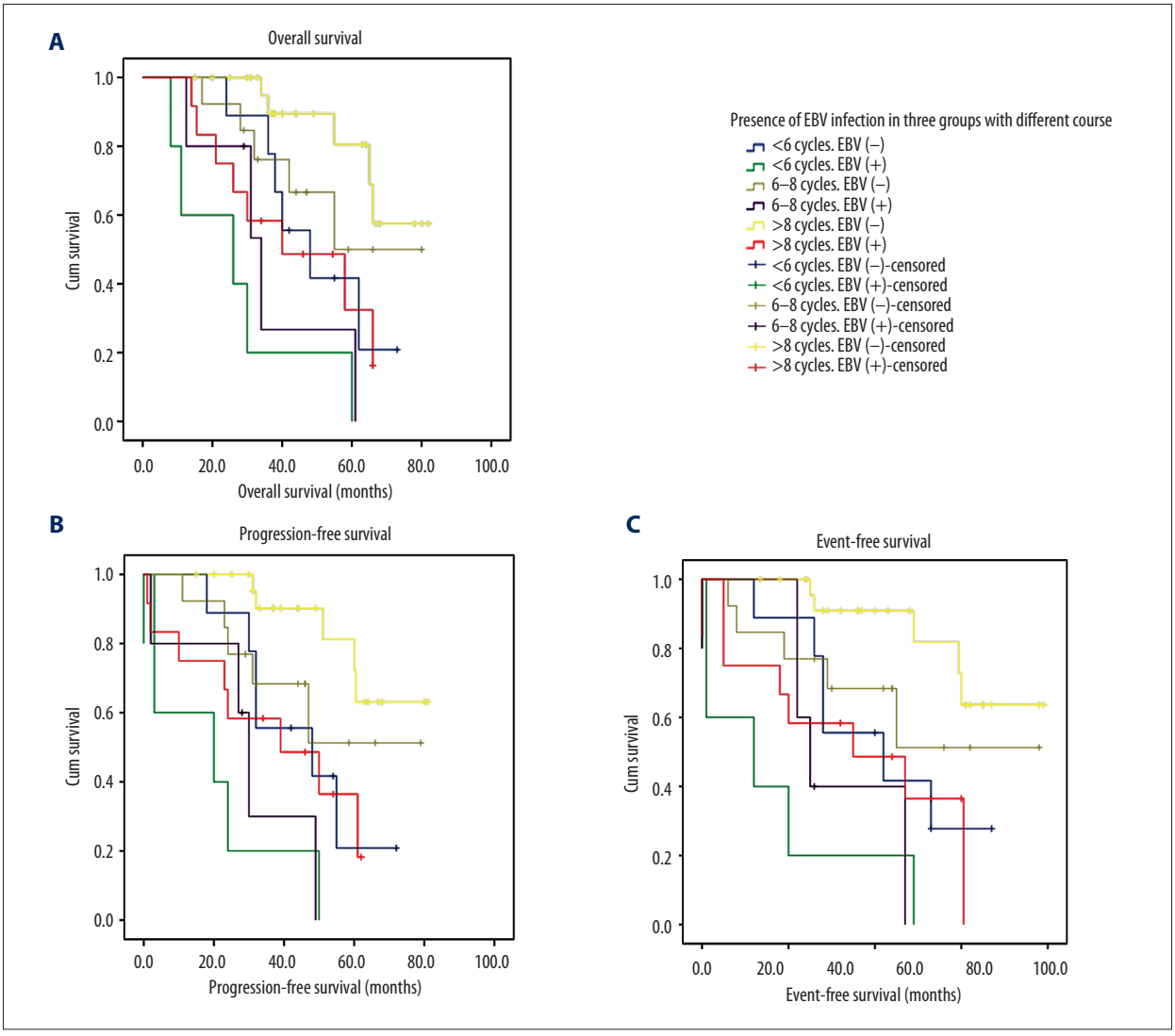

Figure 2. Kaplan-Meier curves for 5-year overall survival (**A**), progression-free survival (**B**), and event-free survival (**C**) according to EBV infection and chemotherapy.

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].

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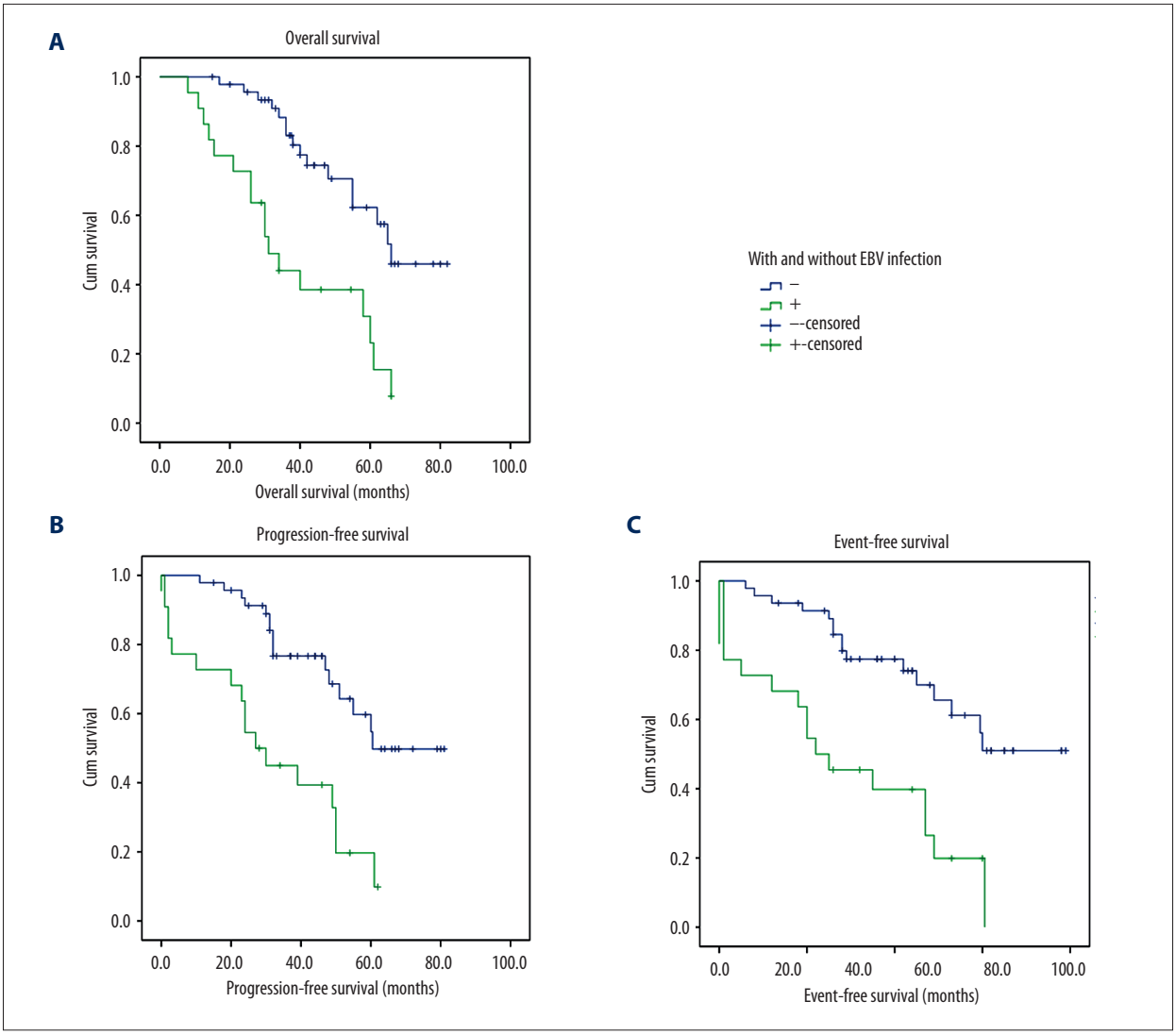

Figure 3. Kaplan-Meier curves for 5-year overall survival (**A**), progression-free survival (**B**), and event-free survival (**C**) according to EBV infection in all patients.

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.

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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
Thrombocyopenia	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
Interventions				
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	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

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.

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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 synergic 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 Files

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	3	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

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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	6	2 CHOP, 2 SMILE, 2 CHOPE	Dead	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	F/20	I	6	4 CHOP, 1 SMILE, 1 CHOPE	Survival	33
24	M/35	I	6	2 CHOP, 2 SMILE, 2 CHOPE	Dead	55
25	M/38	I	6	2 CHOP, 2 SMILE, 2 CHOPE	Survival	80
26	M/39	II	6	3 CHOP, 1 SMILE, 2 CHOPE	Survival	29
27	F/48	I	6	4 CHOP, 1 SMILE, 1 CHOPE	Dead	42
28	M/48	I	6	2 CHOP, 2 SMILE, 2 CHOPE	Survival	59
29	F/44	I	6	3 CHOP, 2 SMILE, 1 CHOPE	Dead	61
30	M/50	II	6	3 CHOP, 1 SMILE, 2CHOPE	Dead	32
31	F/50	I	6	4 CHOP, 1 SMILE, 1 CHOPE	Survival	47
32	M/49	IV	6	4 CHOP, 1 SMILE, 1 CHOPE	Dead	12.5
33	F/49	II	9	2 CHOP, 2 SMILE, 1 CHOPE, 2 MAED, 2 MMED	Dead	55
34	F/51	I	12	3 CHOP, 2 SMILE, 2 CHOPE, 2 MAED, 2 MMED, 1 HyperCVAD	Survival	38
35	F/52	I	12	4 CHOP, 2 SMILE, 1 CHOPE, 2 MAED, 2 MMED, 1 HyperCVAD	Survival	20
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

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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, 1EPOCH	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

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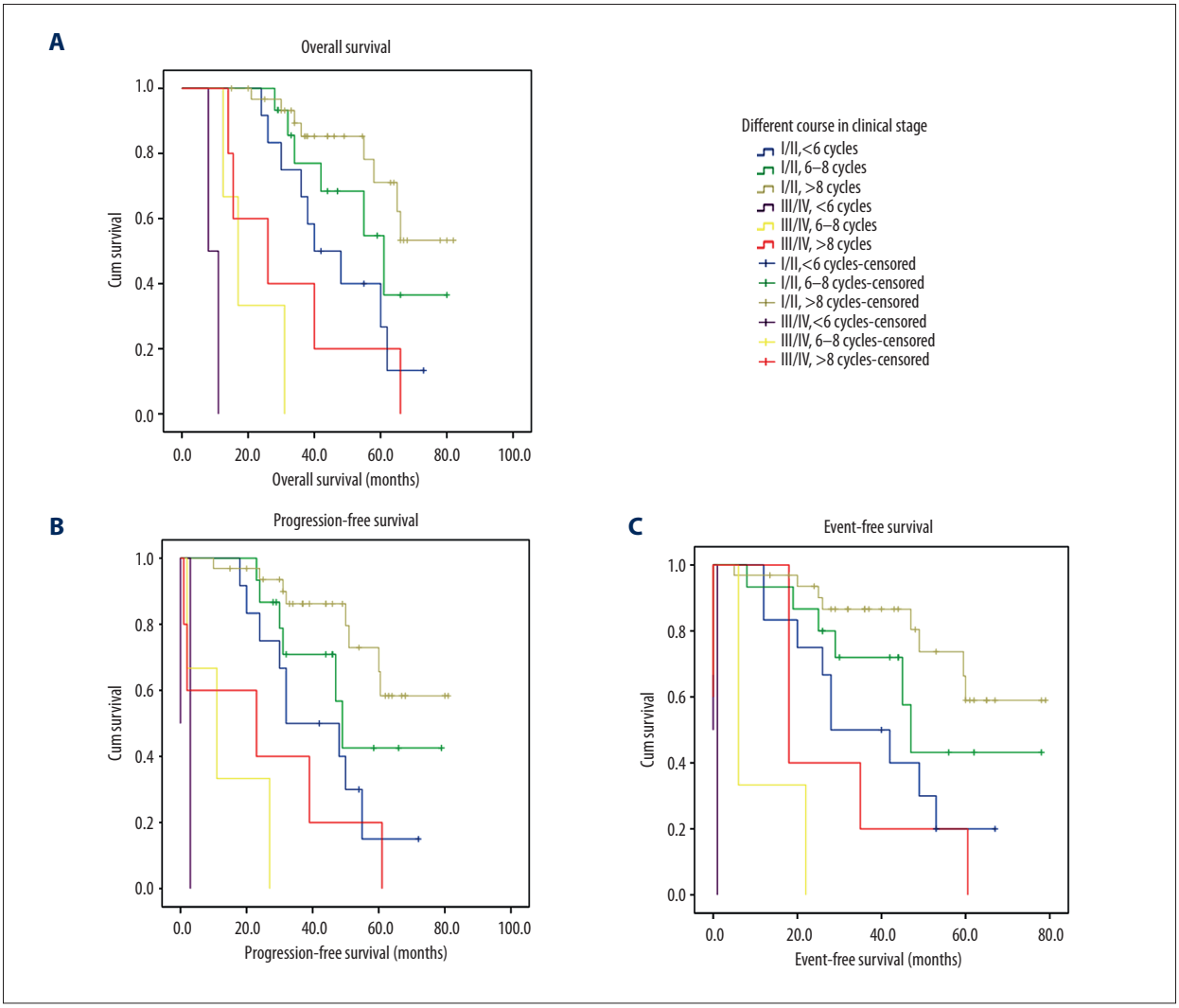
No	Sex/age (years)	Stage	Total chemotherapy courses	Treatments (number and types)	Outcome	Follow-up (months)
63	M/49	I	14	3 CHOP, 2 SMILE, 2 CHOPE, 3 MAED, 2 MMED, 1 HyperCVAD, 1 EPOCH	Survival	31
64	M/53	II	12	3 CHOP, 2 SMILE, 3 CHOPE, 1 MAED, 2 MMED, 1 HyperCVAD	Dead	30
65	M/57	III	9	3 CHOP, 2 SMILE, 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 CHOP, 2 SMILE, 1 CHOPE, 2 MAED, 1 HyperCVAD, 1 EPOCH	Dead	14
69	M/44	II	10	2 CHOP, 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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References:

1. Li S, Feng X, Li T et al: Extranodal NK/T-cell lymphoma, nasal type: A report of 73 cases at MD Anderson Cancer Center. Am J Surg Pathol, 2013; 37: 14–23
2. Au WY, Weisenburger DD, Intragumtornchai T et al: Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: A study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood, 2009; 113: 3931–37
3. Kwong YL: The diagnosis and management of extranodal NK/T-cell lymphoma, nasal-type and aggressive NK-cell leukemia. J Clin Exp Hematop, 2011; 51: 21–28
4. Li X, Li G, Gao Z, Zhou XY, Zhu X: The relative frequencies of lymphoma subtypes in China: A natiowide study of 10,002 cases by the Chinese Lymphoma Study Group, 2012
5. Lim ST, Hee SW, Quek R et al: Comparative analysis of extra-nodal NK/T-cell lymphoma and peripheral T-cell lymphoma: significant differences in clinical characteristics and prognosis. Eur J Haematol, 2008; 80: 55–60
6. Kim GE, Cho JH, Yang WI et al: Angiocentric lymphoma of the head and neck: Patterns of systemic failure after radiation treatment. J Clin Oncol, 2000; 18: 54–63
7. Kim WS, Song SY, Ahn YC et al: CHOP followed by involved field radiation: Is it optimal for localized nasal natural killer/T-cell lymphoma? Ann Oncol, 2001; 12: 349–52
8. Cheung MM, Chan JK, Lau WH et al: Early stage nasal NK/T-cell lymphoma: Clinical outcome, prognostic factors, and the effect of treatment modality. Int J Radiat Oncol Biol Phys, 2002; 54: 182–90
9. Lee J, Kim CY, Park YJ, Lee NK: Sequential chemotherapy followed by radiotherapy versus concurrent chemoradiotherapy in patients with stage I/II extranodal natural killer/T-cell lymphoma, nasal type. Blood Res, 2013; 48: 274–81
10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Hodgkin's Lymphoma. Version 1.2014. Fort Washington: National Comprehensive Cancer Network, 2014
11. Liang R: Advances in the management and monitoring of extranodal NK/T-cell lymphoma, nasal type. Br J Haematol, 2009; 147: 13–21
12. Pfreundschuh M, Schubert J, Ziepert M et al: Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: A randomised controlled trial (RICOVER-60). Lancet Oncol, 2008; 9: 105–16
13. Schmitz N, Nickelsen M, Ziepert M: Aggressive chemotherapy (CHOEP-14) and rituximab or high-dose therapy (MegaCHOEP) and rituximab for young, highrisk patients with aggressive B-cell lymphoma: results of the MegaCHOEP Trial of the German High – Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Blood, 2009; 114: Abstr 404
14. Chan JK: The new World Health Organization classification of lymphomas: the past, the present and the future. Hematol Oncol, 2001; 19: 129–50
15. World Health Organization. WHO Taxonomy of Hemopoiesis and Lympho-Plasmacytic Diseases. Lyons: ARC Press, 2001
16. Zelenetz AD, Abramson JS, Advani RH et al: NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's lymphomas. J Natl Compr Canc Netw, 2010; 8: 288–334
17. Guo Y, Lu JJ, Ma X et al: Combined chemoradiation for the management of nasal natural killer (NK)/T-cell lymphoma: elucidating the significance of systemic chemotherapy. Oral Oncol, 2008; 44: 23–30
18. Sun L, Che K, Zhao Z et al: Sequence analysis of Epstein-Barr virus (EBV) early genes BARF1 and BHRF1 in NK/T cell lymphoma from Northern China. Virol J, 2015; 12: 135
19. Cheson BD, Pfistner B, Juweid ME et al: Revised response criteria for malignant lymphoma. J Clin Oncol, 2007; 25: 579–86
20. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events, Version 4.0.2009. Bethesda: National Institutes of Health, 2009
21. Kiyomiya K, Satoh J, Horie H et al: Correlation between nuclear action of anthracycline anticancer agents and their binding affinity to the proteasome. Int J Oncol, 2002; 21: 1081–85
22. Mori M, Kitamura K, Masuda M et al: Long-term results of a multicenter randomized, comparative trial of modified CHOP versus THP-COP versus THP-COPE regimens in elderly patients with non-Hodgkin's lymphoma. Int J Hematol, 2005; 81: 246–54
23. Galano G, Caputo M, Tecce MF, Capasso A: Efficacy and tolerability of vinorelbine in the cancer therapy. Curr Drug Saf, 2011; 6: 185–93
24. Webb MS, Saltman DL, Connors JM, Goldie JH: A literature review of single agent treatment of multiply relapsed aggressive non-Hodgkin's lymphoma. Leuk Lymphoma, 2002; 43: 975–82
25. Bostrom BC, Sensel MR, Sather HN et al: Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. Blood, 2003; 101: 3809–17
26. Yamaguchi M, Tobinai K, Oguchi M 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: 4044–46
27. Wang L, Wang ZH, Chen XQ et al: 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: 348–55
28. Lin N, Song Y, Zheng W et al: A prospective phase II study of L-asparaginase-CHOP plus radiation in newly diagnosed extranodal NK/T-cell lymphoma, nasal type. J Hematol Oncol, 2013; 6: 44
29. Yamaguchi M, Tobinai K, Oguchi M 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: 5594–600
30. Ma HH, Qian LT, Pan HF et al: Treatment outcome of radiotherapy alone versus radiochemotherapy in early stage nasal natural killer/T-cell lymphoma. Med Oncol, 2010; 27: 798–806
31. Barrionuevo C, Zaharia M, Martinez MT et al: Extranodal NK/T-cell lymphoma, nasal type: study of clinicopathologic and prognosis factors in a series of 78 cases from Peru. Appl Immunohistochem Mol Morphol, 2007; 15: 38–44
32. Huang Y, de Leval L, Gaulard P: Molecular underpinning of extranodal NK/T-cell lymphoma. Best Pract Res Clin Haematol, 2013; 26: 57–74
33. Au WY, Pang A, Choy C et al: Quantification of circulating Epstein-Barr virus (EBV) DNA in the diagnosis and monitoring of natural killer cell and EBV-positive lymphomas in immunocompetent patients. Blood, 2004; 104: 243–49
34. Suzuki R, Yamaguchi M, Izutsu K et al: Prospective measurement of Epstein-Barr virus-DNA in plasma and peripheral blood mononuclear cells of extranodal NK/T-cell lymphoma, nasal type. Blood, 2011; 118: 6018–22
35. Kwong YL, Anderson BO, Advani R et al: Management of T-cell and natural-killer-cell neoplasms in Asia: Consensus statement from the Asian Oncology Summit 2009. Lancet Oncol, 2009; 10: 1093–101
36. Janka GE, Schneider EM: Modern management of children with haemophagocytic lymphohistiocytosis. Br J Haematol, 2004; 124: 4–14
37. Henter JI, Horne A, Arico M et al: HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer, 2007; 48: 124–31
38. Li YX, Yao B, Jin J et al: Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol, 2006; 24: 181–89
39. Lee J, Suh C, Park YH et al: Extranodal natural killer T-cell lymphoma, nasal-type: A prognostic model from a retrospective multicenter study. J Clin Oncol, 2006; 24: 612–18

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