

Long-term outcomes of upfront concurrent chemoradiotherapy followed by P-GDP regimen in newly diagnosed early stage extranodal nasal-type NK/T cell lymphoma

A prospective single-center phase II study

Fang Zhu, MD, PhD^a, Tao Liu, MD, PhD^a, Huaxiong Pan, MD^b, Yin Xiao, MD, PhD^a, Qiuhui Li, MMed^a, Xinxiu Liu, MMed^a, Wangbing Chen, MD, PhD^a, Gang Wu, MD, PhD^a, Liling Zhang, MD, PhD^{a,*}

Abstract

The optimal treatment strategy of newly diagnosed stage I/II, extranodal nasal-type natural killer/T cell lymphoma (NKTCL) remains unclear. This prospective phase II trial was conducted to explore the short-term and the long-term efficacy and safety of upfront concurrent chemoradiotherapy (CCRT) followed by pegaspargase, gemcitabine, dexamethasone, cisplatin (P-GDP) regimen in patients newly diagnosed with early stage NKTCL.

Thirty patients newly diagnosed with stage I/II NKTCL were enrolled from January 2013 to December 2016, and treated as the following strategy: upfront CCRT with cisplatin weekly (25 mg/m²) for 5 weeks, followed by 3 cycles of P-GDP regimen chemotherapy (pegaspargase 2500IU/m² capped at 3750IU, intramuscular on day 4, gemcitabine 850mg/m² intravenous on days 1 and 8; dexamethasone 40mg/day intravenous on days 1 to 4; and cisplatin 20mg/m² intravenous on days 1–3) 3 weeks after the completion of CCRT. The objective response rate (ORR) and the complete response (CR) rate were the primary endpoints, and the secondary endpoints were the overall survival (OS), progression-free survival (PFS), and the adverse event (AE).

The median follow-up period was 51.5 months (range, 5–78months). The ORR was 93.3% (28/30) and all these 28 patients attained CR at the end of the treatment. Two patients suffered from lymphoma associated hemophagocytic syndrome (LAHS) during the period of consolidation chemotherapy and died within 2 months. The 5-year OS was 93.3%, and the 5-year PFS was 89.4%. Mucositis was the most common grades 3/4 nonhematologic AEs (10%, 3/30) of CCRT. During the P-GDP chemotherapy, vomiting (6.7%, 2/30), neutropenia (43.3%, 13/30) and thrombocytopenia (23.3%, 7/30) were the major grades 3/4 toxicities during chemotherapy. No treatment-related deaths occurred.

The upfront CCRT followed by P-GDP regimen chemotherapy is an effective and well-tolerated first-line treatment strategy for patients diagnosed with early stage NKTCL. Further investigation of larger sample size is warranted.

Abbreviations: 3DCRT = three-dimensional conformal radiotherapy, AE = adverse event, CCRT = concurrent chemoradiotherapy, CR = complete response, CT = computed tomography, EBV = Epstein-Barr virus, ECOG = Eastern Cooperative Oncology Group, G-CSF = granulocyte colony-stimulating factor, GDP = gemcitabine, dexamethasone, and cisplatin, GP = gemcitabine, cisplatin, IMRT = intensity-modulated radiation therapy, L-Asp = L-asparaginase, LAHS = lymphoma associated hemophagocytic syndrome, LDH = lactate dehydrogenase, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, NKTCL = natural killer/T cell lymphoma, ORR = objective response rate, OS = overall survival, P-GDP = pegaspargase, gemcitabine, dexamethasone, cisplatin, P-gp = P-glycoprotein, PD = disease progression, PEG-Asp =

Editor: Jianxun Ding.

Trial registration: This study is retrospectively registered at www.chictr.org.cn (ChiCTR-OPC-15006263) on April 17, 2015.

The authors report no conflicts of interest.

Ethics approval and consent to participate: All participants provided written informed consent. This study protocol was approved by the institute review board of Tongji Medical College, Huazhong University of Science and Technology.

Data availability: The data used to support the findings of this study is available from the corresponding author upon request.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

^a Cancer Center, ^b Department of pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

* Correspondence: Liling Zhang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 430022 Wuhan, China (e-mail: lily-1228@hotmail.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

How to cite this article: Zhu F, Liu T, Pan H, Xiao Y, Li Q, Liu X, Chen W, Wu G, Zhang L. Long-term outcomes of upfront concurrent chemoradiotherapy followed by P-GDP regimen in newly diagnosed early stage extranodal nasal-type NK/T cell lymphoma: A prospective single-center phase II study. *Medicine* 2020;99:33(e21705).

Received: 1 May 2020 / Received in final form: 6 June 2020 / Accepted: 30 June 2020

<http://dx.doi.org/10.1097/MD.00000000000021705>

pegaspargase, PET-CT = positron emission tomography-computed tomography, PFS = progression-free survival, PR = partial remission, RT = radiotherapy.

Keywords: NK/T-cell lymphoma, pegaspargase, chemotherapy, radiotherapy

1. Introduction

Extranodal natural killer/T cell lymphoma (NKTCL) is a rare and aggressive subtype of lymphoid malignancy with poor prognosis according to the 2016 World Health Organization classification of lymphoma,^[1] which is associated with Epstein-Barr virus (EBV) infection closely.^[2] The incidence rate of NKTCL showed certain geographic variation, which is lower in North America and Europe than that in East Asia and Latin America.^[3] NKTCL accounts for 12% to 17% of non-Hodgkin lymphoma, and 47% to 50% of peripheral T cell lymphoma in China.^[4] About two-thirds of patients newly diagnosed with NKTCL initially have stage I or II localized in the nasal cavity and its adjacent site such as oropharynx, Waldeyer ring, and so on.^[5]

However, the optimal treatment strategy for newly diagnosed early stage NKTCL remains controversial. It is a lack of randomized controlled prospective trials to establish the standard treatment because of the low incidence rate. Accumulating evidence confirmed that radiotherapy (RT) is a vital treatment option for untreated localized NKTCL.^[6] However, RT alone is not sufficient for patients with NKTCL because local relapse and systemic failures often occurred in those patients who only receive RT even when the disease in the early stage.^[7,8] So, systemic chemotherapy is necessary to reduce treatment failure in patients with early-stage NKTCL. Concurrent chemoradiotherapy (CCRT) has been confirmed to improve local disease control and reduce systemic failure, which has been reported by some clinical trials for NKTCL.^[9] Many clinical trials have reported the efficacy and safety of different treatment sequences including chemotherapy followed by RT,^[10] CCRT followed by chemotherapy,^[11,12] RT followed by chemotherapy,^[13] sandwich therapy,^[14,15] and so on. Based on these reported results, CCRT, sequential chemoradiotherapy, sandwich therapy, and clinical trial were recommended for patients with early-stage NKTCL who are fit for chemotherapy according to the National Comprehensive Cancer Network (NCCN) guideline in 2019.

The optimal chemotherapy regimen of NKTCL remains unclear. The response of anthracycline-based chemotherapies, which are the most common chemotherapy regimens in the treatment of lymphoma, is poorer in NKTCL than that in B-cell lymphomas.^[10,16] The resistance to anthracycline-based regimens of NKTCL may be related to the highly expressed P-glycoprotein (P-gp) in tumor cells.^[17] L-asparaginase (L-Asp)-based chemotherapy regimens have been proved to be more effective than anthracycline-based chemotherapy in NKTCL.^[10,18] However, the high incidence of serious hypersensitivity reaction of L-Asp limited the clinical application in the treatment of NKTCL.^[19] Pegaspargase (PEG-Asp) is a modified form of native *E coli* asparaginase in which the enzyme is covalently linked to polyethylene glycol, which preserves nearly 50% of the initial activity and decreases the immunogenicity of L-Asp greatly, thus reducing the incidence rate of hypersensitivity reaction significantly.^[20,21]

GP (gemcitabine, cisplatin) as a combined chemotherapy regimen has been used to treat solid tumors widely for many years

such as lung cancer. GDP (gemcitabine, dexamethasone, and cisplatin) was confirmed to be effective in lymphoma, particularly in relapsed and refractory lymphoma. In our previous study, P-GDP (PEG-Asp, gemcitabine, dexamethasone, and cisplatin) had shown high efficacy and well tolerance in newly diagnosed NKTCL.^[22]

Therefore, we designed a novel treatment strategy that patients with early-stage NKTCL received upfront CCRT with weekly administration of cisplatin and followed by systemic chemotherapy with P-GDP regimen. We evaluated the short-term and long-term efficacy and toxicities of this treatment strategy to explore a more effective and better-tolerated treatment strategy for newly diagnosed localized nasal NKTCL at a single institution.

2. Patients and methods

2.1. Patients

All 30 enrolled patients were newly diagnosed with extranodal nasal type NKTCL based on the histologic features and immunophenotypes by pathologists were classified to stage I or II according to Ann Arbor staging system and were treated in the Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science, and Technology from January 2013 to December 2016. All participants provided written informed consent before any related treatment began, and this study protocol was approved by the institute review board of Tongji Medical College, Huazhong University of Science and Technology.

All enrolled patients were required to be more than 18 years old and less than 75 years old, to have at least one evaluable lesion, to have the Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2, and to have expected survival time >12 weeks. Besides, all patients had an adequate hematologic function, hepatic function, renal function, and normal coagulation function as described elsewhere.^[23]

Patients were ineligible if they had known hypersensitivity to any component of the treatment regimen. The patients should be excluded if non-nasal sites were involved by NKTCL, such as the central nervous system or gastrointestinal tract even if the lesion was localized.

2.2. Treatment protocol

The treatment scheme comprised CCRT with 5 courses of cisplatin (DDP, 25 mg/m², intravenous, weekly) followed by 3 cycles of P-GDP chemotherapies 3 weeks after the completion of CCRT, which was shown in Figure 1. All patients received intensity-modulated radiation therapy (IMRT) by using 6MV photons which are generated from a linear accelerator. The radiation volume was defined according to guideline described by Yahalom et al.^[24] The prescription dose to the gross lesions was 56 Gy, and to the high risk and low risk of clinical target volume was 54 Gy and 50.4 Gy, respectively, in 27 fractions in 6 weeks. Three weeks after the completion of CCRT, all participants

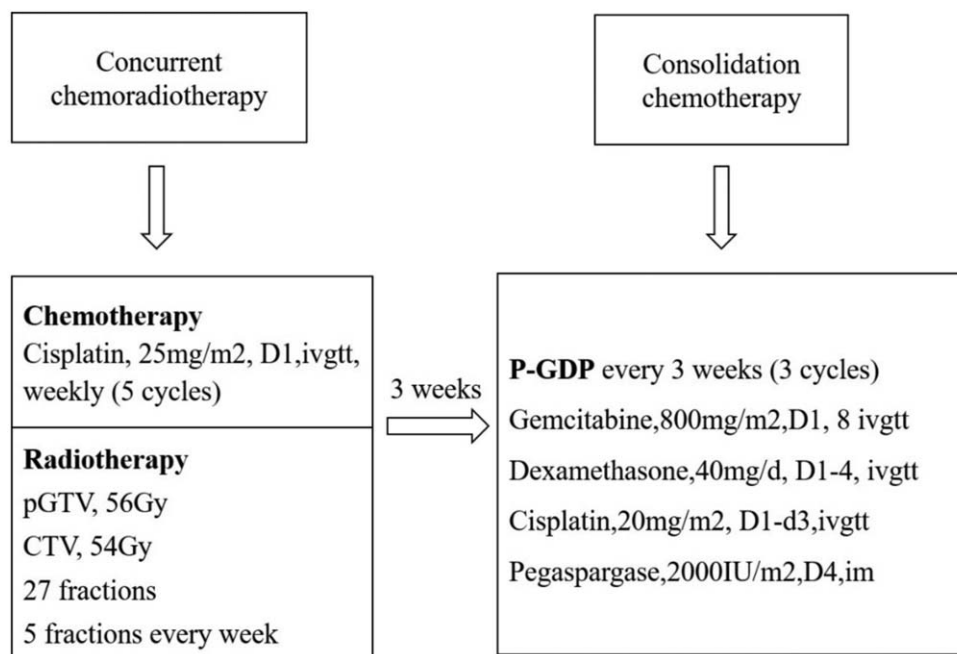


Figure 1. Treatment protocol: All enrolled patients received upfront CCRT with cisplatin weekly for 5 weeks, and followed by 3 cycles of P-GDP regimen consolidation chemotherapy 3 weeks after the completion of CCRT. CCRT=concurrent chemoradiotherapy, P-GDP=pegaspargase, gemcitabine, cisplatin, dexamethasone

received P-GDP chemotherapy every 3 weeks for up to 3 cycles. The P-GDP regimen was administrated as follows: pegaspargase 2500 IU/m² (capped at 3750 IU), intramuscular on day 4, gemcitabine 850 mg/m² intravenous on days 1 and 8; dexamethasone 40 mg/day intravenous on days 1 to 4; and cisplatin 20 mg/m² intravenous on days 1 to 3.

When patients suffered grade 2 to 4 hematologic toxicities, granulocyte colony-stimulating factor (G-CSF) or thrombopoietin would be used as indicated, and the chemotherapy would be delayed until the toxicity resolved to grade 0 to 1. When the creatinine clearance was <40 mL/min, any chemotherapies should be delayed and was restarted until the creatinine clearance recovered to >40 mL/min. The patients should be withdrawn from the study if the delay in administering the following chemotherapy cycle exceeded 2 weeks.

2.3. Evaluation

Before enrollment all patients should complete the baseline evaluation during 14 days including endoscopic examination of the nasal and the oral cavities by otorhinolaryngologists, computed tomography (CT) scan, or magnetic resonance imaging (MRI) of the nasopharynx and cervical region, CT scan from the chest to the pelvis, or positron emission tomography-computed tomography (PET-CT) scan including the whole body, and the bone marrow biopsy. Other examinations included taking a medical history, physical examination, the complete blood count, serum biochemistry, and the coagulation function. Besides, EBV DNA in peripheral blood also was checked to determine the EBV viral load by Quantitative polymerase chain reaction. All these examinations were performed at baseline, after completion of CCRT, during the period of receiving consolidation chemotherapy, and they

were repeated every 3 months after the completion of all treatment to identify disease progression.

We assessed the treatment response according to the WHO criteria. The treatment response rate was the primary endpoint including CR and PR. The secondary endpoints were survival time including the OS, PFS, AEs. OS was defined as the time from the date of enrollment to the date of death because of any cause or last follow-up. PFS was defined as the time from the date of enrollment to the date of confirmed disease progression. The AEs were evaluated according to the National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0.

2.4. Statistical analysis

We calculated the sample size of this study with reference to Kim et al's study^[25] according to Simon's optimal 2-stage design based on the CR rates of the localized NKTCL after radiotherapy. We assumed a target and a lower activity level of 0.90 (p1) and 0.70 (p0), respectively. A minimum of 27 patients was necessary in total. This design provided a probability of 0.05 of accepting a treatment worse than p0 and a probability of 0.20 for rejecting a treatment better than p1. If we assumed that the dropout rate is 10%, a total of 30 patients was needed. The calculating of PFS and OS by using the Kaplan-Meier method. Survival curves were observed by using the log-rank test. Cox regression analysis was used for multivariate analysis of factors related to survival time. All tests were 2-sided and a *P* value of <0.05 was considered significant.

3. Results

3.1. Characteristics of patients

A total of 30 patients were enrolled in this prospective phase II study from January 2013 to December 2016. The characteristics

of all patients were summarized in Table 1. The median age was 38.5 years (range 19–71 years), and the male to female ratio was 1.7:1. Eighteen patients (60%) were in stage I. Twelve patients (40%) were in stage II. B symptoms were present in 20 patients (66.7%). The increased lactic dehydrogenase (LDH) was observed in 26 patients (86.7%). The load of EBV-DNA increased in 21 patients (70%).

3.2. Response

Thirty patients completed CCRT according to the treatment protocol without interruption. 22 (73.3%) patients completed three cycles of chemotherapy, 4 (13.3%) patients had 2 cycles of chemotherapy, 2 (6.7%) patients only received 1 cycle of chemotherapy because of disease progression (PD) during the period of treatment, and 2 (6.7%) patients refused to continue chemotherapy after CCRT. A total of 76 cycles of chemotherapy were administered. All patients were assessable for response. The response rate was shown in Figure 2. Twenty-two (73.3%) patients achieved CR and 8 (26.7%) had a partial response (PR) after CCRT, 28 patients achieved CR at the end of the treatment, with 2 PD combined with LAHS during receiving consolidation chemotherapy. At the end of therapy, the overall response rate (ORR) was 93.3%.

Table 1
Clinical characteristics of enrolled patients.

Characteristic	No	%
Age, y (range, 19–71)		
median	38.5	
>60	3	10
≤60	27	90
Sex		
Male	19	63.3
Female	11	36.7
ECOG performance status		
0	29	96.7
1	1	3.3
Ann Arbor stage		
IE	18	60
IIE	12	40
B symptoms		
Present	20	66.7
Absent	10	33.3
EBV-DNA (baseline)		
Normal	9	30
Increased	21	70
Serum LDH		
Normal	26	86.7
Increased	4	13.3
ESR		
Normal	21	70
Increased	9	30
Anemia		
Present	10	33.3
Absent	20	66.7
Platelet count		
Normal	25	83.3
Increased	5	16.7
IPI		
0/1	21	70
2	9	30

EBV=Epstein-Barr virus, ECOG=Eastern Cooperative Oncology Group, ESR=erythrocyte sedimentation Rate, IPI=international prognostic index, LDH=lactate dehydrogenase.

3.3. Survival

All patients were followed up to October 1, 2019, with the median follow-up time of 51.5 months (range, 5–78 months). As shown in Figure 2, 5-year OS was 93.3%, and 5-year PFS was 89.4%, respectively. Two (6.7%) patients experienced disease progression combined with LAHS during consolidation chemotherapy and died soon. Up to the end of follow-up, 2 (6.7%) patients died, 27 (90.0%) patients survived without disease progression. During the period of follow-up, 1(3.3%) patient suffered from disease progression in the facial skin which was outside the margin of the radiation field and LAHS with the PFS of 42 months. Anti-programmed death 1 (PD-1) antibody pembrolizumab was administered and the response was PR. As of the write-up of this manuscript, the patient still alive with an overall survival time of 56 months.

Besides, the value of LDH, the presence of B symptoms, staging, EBV-DNA, the scores of ECOG, the presence of B symptom, and age had not significantly relationship with the survival time in this study.

3.4. Toxicity

The treatment-related toxicities were shown in Table 2. The grade 1/2 AEs were frequent during the period of treatment. Radiation-related mucositis was the most common grade 3 nonhematologic toxicity (3/30, 10%) during the period of CCRT. The major AEs to P-GDP chemotherapy included myelosuppression, digestive tract symptoms, liver dysfunction, and coagulation dysfunction. Hematological toxicities of P-GDP chemotherapy were common including anemia, neutropenia, and thrombocytopenia. There was 1 (3.3%) patient with grade 1 pancreatitis and 4 (13.3%) patients with upper extremity deep venous thrombosis during the period of consolidation chemotherapy. All toxicities were tolerable and went away after all treatment. No significant late toxicities were observed during the period of follow-up. No treatment-related deaths happened.

4. Discussion

The induction of CR though the first-line treatment is very important, which is associated with the survival time closely in the patients newly diagnosed with localized NKTCL. Radiotherapy has been confirmed to be the most important treatment modality for localized NKTCL since the 1990s.^[26] Li et al revealed that the IMRT has better local control and a lower incidence of late xerostomia to three-dimensional conformal radiotherapy (3DCRT) in patients with localized NKTCL by comparing the treatment response, AEs and prognosis of patients treated with IMRT or 3DCRT.^[27] It is difficult to define the radiation target volume in NKTCL because of the presence of secondary inflammation in the region of the tumor. Yahalom et al suggested that the delineation of the clinical target volume for lymphoma located in the nasal cavity and the paranasal sinus should be based on the physical examination, nasopharyngeal fiberoptic, and imaging findings including CT scan, MRI, and FDG-PET/CT and the extended involved-site RT including the entire involved cavity and adjacent structures were recommended to improve the local control rates in the International Lymphoma Radiation Oncology Group guidelines.^[24] Many studies have reported that high-dose RT was related to superior disease local control for nasal type NKTCL.^[28,29] Huang et al reported that the 5-year OS and PFS were higher in patients with localized

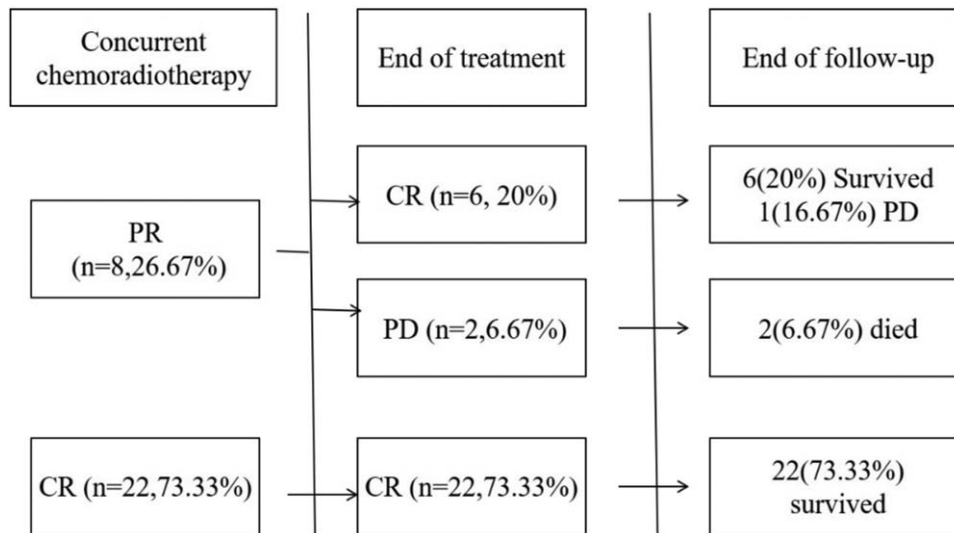


Figure 2. Treatment response and prognosis in patients: Summary of treatment outcomes and treatment failures. CR=complete response, PR=partial response, PD=progressive disease.

NKTCL receiving the dose of RT ≥ 54 Gy.^[30] Some retrospective studies suggested that a minimum RT dose of 50Gy must be administered to treat nasal NKTCL. In this study, we contoured the radiation target volume according to the International Lymphoma Radiation Oncology Group guidelines. All enrolled patients received the IMRT with the prescription dose of CTV 54 Gy to improve the local control and reduce the AEs related to radiotherapy. However, some studies reported that RT alone is not enough because of the high incidence rate of systemic failure.^[31]

Recently, CCRT showed a better response in treating localized nasal type NKTCL compared to RT alone, which improved the local and systemic control. The reported strategies of CCRT in some prospective clinical trials were reviewed in Table 3, which included RT combined with a two-thirds dose of DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin),^[23,32] RT combined with DEP (dexamethasone, etoposide, cisplatin) followed by DVIP,^[12] and RT with weekly cisplatin administrated followed by different combined chemotherapy regimens such as VIPD (etoposide, ifosfamide, cisplatin, dexamethasone),^[25] MIDDLE(methotrexate, ifosfamide, dexamethasone, L-asparagi-

nase, etoposide),^[33] VIDL (etoposide, ifosfamide, dexamethasone, L-asparaginase),^[34] GDP(gemcitabine, dexamethasone, cisplatin),^[35] and so on. The simultaneous initiation of RT and chemotherapy may improve the treatment response and reduce the systemic failure, but combined with the increasing risk of the hematologic and nonhematologic toxicities. Considering the high risk of AEs, we designed the CCRT to combined RT with weekly cisplatin administrated in this study. All patients completed the CCRT with a 73.3% (22/30) CR rate and a 26.8% (8/30) PR rate, and without intolerable AEs. Mucositis related to radiation was the most common grade 3 non-hematologic toxicity (3/30, 10%), and recovered in 2 weeks after completion of the CCRT.

Chemotherapy is an important component in the treatment of localized extranodal nasal type NKTCL, too. However, in contrast to other types of lymphoma, NKTCL showed intrinsic resistance to anthracyclines-based chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-like chemotherapy, which could not provide a survival benefit to the patients with NKTCL.^[10,16] Increasing evidence has demonstrated that high expression of multidrug-

Table 2
Treatment-related adverse events.

Adverse events	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Hematologic				
Anemia	15 (50%)	7 (23.3%)	4 (13.3%)	1 (3.3%)
Neutropenia	4 (13.3%)	10 (33.3%)	11 (36.7%)	2 (6.7%)
Thrombocytopenia	9 (30%)	8 (26.7%)	3 (10%)	4 (23.3%)
Nonhematologic				
Nausea/vomiting	18 (60%)	8 (26.7%)	2 (6.7%)	0
ALT/AST elevation	11 (36.7%)	4 (13.3%)	0	0
Increased BUN/Cr	0	0	0	0
Hypofibrinogenemia	14 (46.7%)	4 (13.3%)	1 (3.3%)	0
Mucositis	9 (30%)	18 (60%)	3 (10%)	0

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN= blood urea nitrogen, Cr=creatinine.

Table 3 Prospective phase II trials of CCRT followed by nonanthracycline chemotherapy for newly diagnosed localized NKTCL.

Authors	No	RT dose, Gy	Chemo regimen	Response			Survival			Adverse effects			
				ORR	CR	PFS	OS	Grade 3/4 neutropenia	Grade 3/4 thrombocytopenia	Grade 3/4 mucositis	Treatment-related death		
Simultaneous application of RT and chemotherapy													
Yamaguchi et al ^[30]	27	50	2/3DeVIC	81%	77%	2-y: 67%	2-y: 78%	93%	11%	30%	None		
Tsai et al ^[12]	33	50.4	DEP-CCRT/DVIP	81%	63%	2-y: 64%; 5-y: 60%	5-y: 73%; 5-y: 66%	85%	21.2%	36.4%	Pancreatitis (n = 1) Infection (n = 1)		
RT with weekly cisplatin followed by chemotherapy													
Ke et al ^[34]	32	56	GDP	90.6%	84.4%	3-y: 84.4%	3-y: 87.5%	43.3%	46.7%	NA	Infection (n = 1)		
Yoon et al ^[32]	28	36-44	MIDLE	85.7%	82.1%	3-y: 74.1%	3-y: 81.5%	91.3%	13%	0	Acute kidney injury and pneumonia (n = 1)		
Kim et al ^[22]	30	40-52.8	VIPD	83.3%	80.1%	3-y: 85.2%	3-y: 86.3%	41.4%	24.1%	0	Infection (n = 2)		
Kim et al ^[33]	30	40-50	VIDL	—	87%	5-y: 60%	5-y: 73%	80%	13.3%	36.7%	None		
Present study	30	54	P-GDP	93.3%	93.3%	3-y: 93.6%; 5-y: 89.4%	3-y: 93.6%; 5-y: 93.6%	43.3%	23.3%	10%	None		

CCRT = concurrent chemoradiotherapy, CR = complete response, DEP = dexamethasone, etoposide, cisplatin, DeVIC = dexamethasone, etoposide, ifosfamide, carboplatin, DVIP = dexamethasone, etoposide, ifosfamide, cisplatin, GDP = gemcitabine, cisplatin, GDP = gemcitabine, cisplatin, dexmethasone, MIDLE = methotrexate, etoposide, ifosfamide, dexmethasone, L-asparaginase, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, P-GDP = pegaspargase, gemcitabine, cisplatin, dexmethasone, VPD = etoposide, ifosfamide, cisplatin, dexmethasone, VIDL = dexmethasone, L-asparaginase, VIDL = etoposide, ifosfamide, dexmethasone.

resistant P-gp in tumor cells plays an important role in the drug-resistance of NKTCL.^[17] P-gp is responsible for the intracellular decrease of various cytotoxic drugs, which is an ATP-dependent drug efflux pump and results in tumor multidrug resistance.^[36] Some studies have reported that L-Asp exhibits outstanding antitumor activity to NK cell tumors in vitro and in vivo through a unique antitumor mechanism that is not affected by P-gp. L-Asp-based chemotherapy regimens, such as SMILE (dexamethasone, methotrexate, ifosfamide, l-asparaginase, etoposide) and AspaMetDex (L-asparaginase, methotrexate, dexmethasone), are effective for early-stage, advanced-stage, and relapsed/refractory NKTCL.^[18,37,38] However, the serious hypersensitivity reactions of L-Asp can occur in 32.5% to 75% patients, thus limiting the clinical application of L-Asp-based chemotherapy regimens.^[19] Besides, the short plasma half-life of L-Asp causes frequent dosing that is an inconvenience to the patients and the clinicians. Peg-Asp, a form of *Escherichia coli*-Asp that is linked to polyethylene glycol, has been confirmed to be effective in NKTCL with less AEs and a longer half-life than that of L-Asp. In a prospective multicenter study, 619 patients with relapsed/refractory aggressive lymphoma were randomly assigned to chemotherapy with GDP or DHAP (dexamethasone, cytarabine, and cisplatin). Similar ORRs, event-free survival, and OS were observed, and GDP regimen was associated with less AEs and preserved quality of life.^[39] In another prospective clinical trial, a total of 44 patients diagnosed with refractory or relapsed Hodgkin lymphoma were randomly divided into 2 groups equally. One group was treated with GDP and the other group was treated with ESHAP (etoposide, methyl prednisolone, cisplatin, and cytarabine). The results showed that similar response rates were obtained (59.1% vs 53.5%).^[40] In a clinical trial of P-GDP chemotherapy in the treatment of newly diagnosed advanced stage and relapsed/refractory NKTCL, Wang et al reported that the ORR was 83% with 41.5% CR rate. The 2-year PFS rate and the 2-year OS rate were 45.4% and 54.7%, respectively. The P-GDP regimen has been confirmed to be effective both in early-stage and advanced-stage NKTCL in our previous retrospective study.^[22] Considering the well effectiveness of Peg-Asp and GDP in the treatment of NKTCL, we determined the P-GDP regimen to be the following consolidation chemotherapy in this prospective study.

In our study, the CR rate was 93.3%, and the ORR was 93.3% at the end of all treatment. The median follow-up time was 51.5 months (range 5–78months). The OS rates at 1, 3, and 5 years were 93.3%, 93.3%, and 93.3%, and the 1-, 3-, and 5-year PFS rates of all patients were 93.3%, 93.3%, 89.4%, respectively, which were shown in Figure 3. Grade 3/4 neutropenia (43.4%) and grade 3/4 thrombocytopenia (23.3%) during the following consolidation chemotherapy were common. Other commonly grade 1/2 side effects include gastrointestinal disorders such as nausea and vomiting, liver dysfunction, coagulation dysfunction, which all could be well controlled with supportive treatment. There was 1 patient suffering from mild pancreatitis after receiving the first cycle of P-GDP chemotherapy. The application of G-CSF in time is an important support treatment for patients experiencing grade 3/4 neutropenia during and after chemotherapy. Other support treatments such as antiemetic drugs, platelet transfusion, and infection prevention were also important during the treatment. Compared with several previous prospective phase II clinical studies focused on stage I/II NKTCL patients (Table 3), these results showed the AEs were similar to others. However, the response rate and survival rates of this study were superior to others.

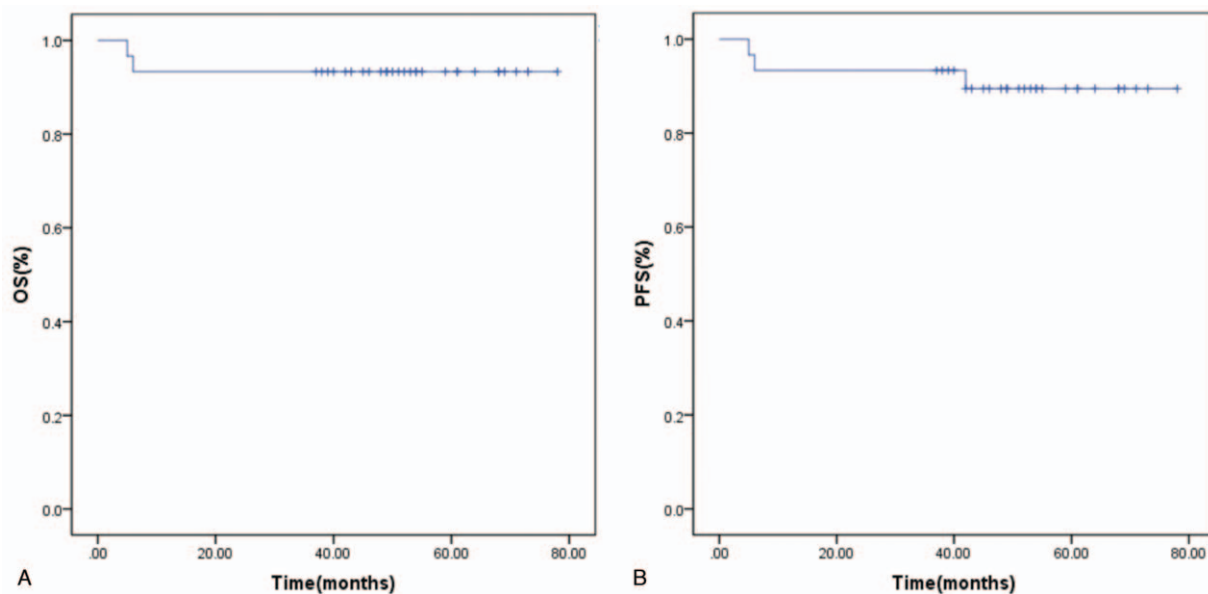


Figure 3. Survival curves: The OS rates at 1, 3, and 5 years were 93.3%, 93.3%, and 93.3%. The 1-, 3-, and 5-year PFS rates were 93.3%, 93.3%, 89.4%, respectively. OS=overall survival, PFS=progression-free survival.

Yang et al reported that the presence of B symptoms and extensive disease (stage I/II with local invasiveness) were associated with poor PFS and extensive disease was related to poor OS significantly in early-stage nasal NKTCL.^[41] However, there was no relationship between the value of LDH, the presence of B symptoms, staging, EBV-DNA, the scores of ECOG, the presence of B symptom, and age with PFS and OS in this study. It might be related to the small sample size in our study.

Two patients died during the period of the following consolidation chemotherapy in this study because of disease progression combined with hemophagocytic syndrome. According to Chang's retrospective study of 57 patients with LAHS, LAHS may occur at any stage of NKTCL. It may be the initial presentation of NKTCL, as well as a complication during the treatment. The study demonstrated 43 (75.4%) patients diagnosed with LAHS associated with NKTCL, which meant that the most common type of lymphoma related to LAHS was NKTCL.^[42] Riviere et al^[43] reported that patients with hematologic malignancies-associated hemophagocytic syndrome had a poorer prognosis than other reasons such as infection. The median survival time of patients with LAHS related to NKTCL was 28 days. In the present study, the poor outcomes of LAHS were consistent with the previous reports.

In conclusion, our study demonstrated that CCRT with cisplatin weekly administrated followed by P-GDP chemotherapy had good short-term and long-term outcomes with the tolerable AEs in patients with localized nasal type NKTCL. This strategy may be one of the most recommendable options as the first-line treatment for localized nasal-type NKTCL. A larger number of sample size and a prospective randomized clinical trial will be needed to further evaluate the efficacy and safety of this treatment strategy.

5. Note

The preliminary results of this study were presented at the 13th International Conference on Malignant Lymphoma, Lugano, Switzerland, June 17-20, 2015

Acknowledgments

The authors thank all enrolled patients and their families as well as all the investigators in the Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Author contribution

Gang Wu, Liling Zhang and Fang Zhu designed research and analyzed the data. Tao Liu, Huaxiong Pan, and Yin Xiao collected the data. Wangbing Chen, Qiuhui Li and Xinxiu Liu performed analysis. Liling Zhang and Fang Zhu wrote the manuscript.

References

- [1] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127:2375–90.
- [2] Kimura H, Fujiwara S. Overview of EBV-associated T/NK-cell lymphoproliferative diseases. *Front Pediatr* 2018;6:417.
- [3] Haverkos BM, Pan Z, Gru AA, et al. Extranodal NK/T cell lymphoma, nasal type (ENKTL-NT): an update on epidemiology, clinical presentation, and natural history in North American and European cases. *Curr Hematol Malig Rep* 2016;11:514–27.
- [4] Yang QP, Zhang WY, Yu JB, et al. Subtype distribution of lymphomas in Southwest China: analysis of 6,382 cases using WHO classification in a single institution. *Diagn Pathol* 2011;6:77.
- [5] Tse E, Kwong YL. The diagnosis and management of NK/T-cell lymphomas. *J Hematol Oncol* 2017;10:85.
- [6] 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;24:181–9.
- [7] Vargo JA, Patel A, Glaser SM, et al. The impact of the omission or inadequate dosing of radiotherapy in extranodal natural killer T-cell lymphoma, nasal type, in the United States. *Cancer* 2017;123:3176–85.
- [8] 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.
- [9] Yamaguchi M, Suzuki R, Oguchi M. Advances in the treatment of extranodal NK/T-cell lymphoma, nasal type. *Blood* 2018;131:2528–40.

- [10] Qi S, Yahalom J, Hsu M, et al. Encouraging experience in the treatment of nasal type extra-nodal NK/T-cell lymphoma in a non-Asian population. *Leuk Lymphoma* 2016;57:2575–83.
- [11] Michot JM, Mazeron R, Danu A, et al. Concurrent etoposide, steroid, high-dose Ara-C and Platinum chemotherapy with radiation therapy in localised extranodal natural killer (NK)/T-cell lymphoma, nasal type. *Eur J Cancer (Oxford, England: 1990)* 2015;51:2386–95.
- [12] Tsai HJ, Lin SF, Chen CC, et al. Long-term results of a phase II trial with frontline concurrent chemoradiotherapy followed by consolidation chemotherapy for localized nasal natural killer/T-cell lymphoma. *Eur J Haematol* 2015;94:130–7.
- [13] Huang Y, Yang J, Liu P, et al. Intensity-modulated radiation therapy followed by GDP chemotherapy for newly diagnosed stage I/II extranodal natural killer/T cell lymphoma, nasal type. *Ann Hematol* 2017;96:1477–83.
- [14] Jiang M, Zhang H, Jiang Y, et al. Phase 2 trial of “sandwich” L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. *Cancer* 2012;118:3294–301.
- [15] Jiang M, Zhang L, Xie L, et al. A phase II prospective study of the “Sandwich” protocol, L-asparaginase, cisplatin, dexamethasone and etoposide chemotherapy combined with concurrent radiation and cisplatin, in newly diagnosed, I/II stage, nasal type, extranodal natural killer/T-cell lymphoma. *Oncotarget* 2017;8:50155–63.
- [16] Kim BS, Kim TY, Kim CW, et al. Therapeutic outcome of extranodal NK/T-cell lymphoma initially treated with chemotherapy—result of chemotherapy in NK/T-cell lymphoma. *Acta Oncol (Stockholm, Sweden)* 2003;42:779–83.
- [17] Wang B, Li XQ, Ma X, et al. Immunohistochemical expression and clinical significance of P-glycoprotein in previously untreated extranodal NK/T-cell lymphoma, nasal type. *Am J Hematol* 2008;83:795–9.
- [18] Obama K, Tara M, Niina K. L-asparaginase-based induction therapy for advanced extranodal NK/T-cell lymphoma. *Int J Hematol* 2003;78:248–50.
- [19] Shinnick SE, Browning ML, Koontz SE. Managing hypersensitivity to asparaginase in pediatrics, adolescents, and young adults. *J Pediatr Oncol Nurs* 2013;30:63–77.
- [20] Muss HB, Spell N, Scudieri D, et al. A phase II trial of PEG-L-asparaginase in the treatment of non-Hodgkins lymphoma. *Invest New Drugs* 1990;8:125–30.
- [21] Escherich G, Zur Stadt U, Zimmermann M, et al. Co ALL Study Group Clofarabine in combination with pegylated asparaginase in the frontline treatment of childhood acute lymphoblastic leukaemia: a feasibility report from the CoALL 08-09 trial. *Br J Haematol* 2013;163:240–7.
- [22] Liu T, Zhu F, Xiao Y, et al. Pegaspargase, gemcitabine, dexamethasone, and cisplatin (P-GDP) combined chemotherapy is effective for newly diagnosed extranodal NK/T-cell lymphoma: a retrospective study. *Cancer Manag Res* 2018;10:5061–9.
- [23] 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 JCOG211. *J Clin Oncol* 2012;30:4044–6.
- [24] Yahalom J, Illidge T, Specht L, et al. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys* 2015;92:11–31.
- [25] Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma study. *J Clin Oncol* 2009;27:6027–32.
- [26] Jaffe ES, Chan JK, Su JJ, et al. Report of the Workshop on Nasal and Related Extranodal Angiocentric T/Natural Killer Cell Lymphomas, Definitions, differential diagnosis, and epidemiology. *Am J Surg Pathol* 1996;20:103–11.
- [27] Li YY, Lin HQ, Zhang LL, et al. Intensity-modulated radiotherapy has superior outcomes to three-dimensional conformal radiotherapy in patients with stage IE-IIE extranodal nasal-type natural killer/T-cell lymphoma. *Oncotarget* 2017;8:60504–13.
- [28] Isobe K, Uno T, Tamaru J, et al. Extranodal natural killer/T-cell lymphoma, nasal type: the significance of radiotherapeutic parameters. *Cancer* 2006;106:609–15.
- [29] Kim TH, Kim JS, Suh YG, et al. The roles of radiotherapy and chemotherapy in the era of multimodal treatment for early-stage nasal-type extranodal natural killer/T-cell lymphoma. *Yonsei Med J* 2016;57:846–54.
- [30] Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. *Int J Radiat Oncol Biol Phys* 2008;70:166–74.
- [31] Li YX, Liu QF, Wang WH, et al. Failure patterns and clinical implications in early stage nasal natural killer/T-cell lymphoma treated with primary radiotherapy. *Cancer* 2011;117:5203–11.
- [32] 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.
- [33] Yoon DH, Kim SJ, Jeong SH, et al. Phase II trial of concurrent chemoradiotherapy with L-asparaginase and MIDDLE chemotherapy for newly diagnosed stage I/II extranodal NK/T-cell lymphoma, nasal type (CISL-1008). *Oncotarget* 2016;7:85584–91.
- [34] Kim SJ, Yang DH, Kim JS, et al. Concurrent chemoradiotherapy followed by L-asparaginase-containing chemotherapy, VIDL, for localized nasal extranodal NK/T cell lymphoma: CISL08-01 phase II study. *Ann Hematol* 2014;93:1895–901.
- [35] Ke QH, Zhou SQ, Du W, et al. Concurrent IMRT and weekly cisplatin followed by GDP chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell lymphoma. *Blood Cancer J* 2014;4:e267.
- [36] Drenou B, Lamy T, Amiot L, et al. CD3- CD56+ non-Hodgkin's lymphomas with an aggressive behavior related to multidrug resistance. *Blood* 1997;89:2966–74.
- [37] Kwong YL, Kim WS, Lim ST, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. *Blood* 2012;120:2973–80.
- [38] Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. *Blood* 2011;117:1834–9.
- [39] Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol* 2014;32:3490–6.
- [40] Ramzi M, Rezvani A, Dehghani M. GDP versus ESHAP regimen in relapsed and/or refractory hodgkin lymphoma: a comparison study. *Int J Hematol Oncol Stem Cell Res* 2015;9:10–4.
- [41] Yang CW, Wang CW, Hong RL, et al. Treatment outcomes of and prognostic factors for definitive radiotherapy with and without chemotherapy for Stage I/II nasal extranodal NK/T-cell lymphoma. *J Radiat Res* 2017;58:114–22.
- [42] Chang Y, Cui M, Fu X, et al. Lymphoma associated hemophagocytic syndrome: a single-center retrospective study. *Oncol Lett* 2018;16:1275–84.
- [43] Riviere S, Galicier L, Coppo P, et al. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. *Am J Med* 2014;127:1118–25.