Efficacy of a pegaspargase-based regimen in the treatment of newly-diagnosed extranodal natural killer/T-cell lymphoma

L. LI[‡], C. ZHANG[‡], L. ZHANG, X. LI, J. J. WU, Z. C. SUN, X. R. FU, X. H. WANG, Y. CHANG, R. WANG, Y. J. QIU, M. Z. ZHANG*

Department of Oncology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, P. R. China

*Correspondence: mingzhi_zhang2013@outlook.com
[‡]Contributed equally to this work.*

Extranodal natural killer (NK)/T-cell lymphoma (ENKL) is an aggressive neoplasm with poor prognosis. Currently, there is no consensus on the optimal treatment of this disease. In this study, we report the efficacy of a pegaspargase (PEG-Asp)-based chemotherapy, a DDGP regimen (PEG-Asp, dexamethasone, cisplatin, gemcitabine), for the treatment of newly-diagnosed ENKL. From August 2010 to May 2012, 12 patients with newly-diagnosed stage II – IV ENKL were initially treated with a DDGP regimen in our center. Ten patients (10/12, 83.3%) achieved complete response (CR) and two (2/12, 16.7%) achieved partial response (PR). The objective overall response rate (ORR) was 100%. Three patients (3/12, 25.0%) relapsed, and as a result, two died of disease. Eight patients (8/12, 66.7%) were alive with no evidence of disease (NOD) after a median follow-up of 19 months (range 16 – 31 months). Hematologic toxicity was the most frequent toxicity reported in this study. Grade 3/4 leukopenia and neutropenia were common and both occurred in eight patients (8/12, 66.7%), respectively. Additionally, six patients (6/12, 50.0%) experienced grade 3/4 thrombocytopenia and three (3/12, 25.0%) experienced grade 3/4 anemia. However, no patient died of hematologic toxicity. Our results demonstrate the significant efficacy and safety profile of a DDGP regimen in the treatment of newly-diagnosed ENKL, and indicate the potential of this regimen as a first-line therapy against this disease.

Key words: pegaspargase, extranodal NK/T-cell lymphoma, non-Hodgkin's lymphoma, medical oncology

Extranodal natural killer/T-cell lymphoma (ENKL), nasal type, is a rare type of non-Hodgkin's lymphoma (NHL) that accounts for less than 2% of all NHLs and occurs more frequently in Asia and South America than in Europe and North America [1]. ENKL is highly associated with Epstein-Barr virus (EBV) and is considered to originate from natural killer (NK) cells or, occasionally, from subsets of γδ or αβ cytotoxic T cells [2]. It has two clinical entities, nasal and extra nasal ENKL. Although these two entities differ in clinical presentation, treatment, and prognosis [3,4], they have the same histological and immunophenotypical properties and are therefore classified in the same category according to the World Health Organization (WHO) classification of lymphomas [5].

For the treatment of ENKL, conventional chemotherapies for other aggressive lymphomas, such as CHOP regimens and CHOP-like regiments (cyclophosphamide, vincristine, adriamycin, prednisone), usually provide poor clinical outcomes due to the frequent multidrug resistance caused by ENKL tumor cell expression of P-glycoprotein (P-gp) [6]. According to a previous report, the complete response (CR) rate of the CHOP regimen alone in newly-diagnosed ENKL patients was less than 33%, and two-year disease-free survival (DFS) and overall survival (OS) rates were 23% and 44%, respectively [7]. Currently, there is no consensus on the optimal treatment of

Abbreviations: ALL, acute lymphoblast leukemia; ALT, aminotransferase; APTT, activated partial thromboplastin time; BUN, blood urea nitrogen; CHOP regimen, cyclophosphamide + vincristine + adriamycin + prednisone; CR, complete response; DDGP regimen, pegaspargase + dexamethasone + cisplatin + gemcitabine; EBV, Epstein-Barr virus; ECG, electrocardiogram; ENKL, extranodal natural killer/T-cell lymphoma; DFS, disease-free survival; DOD, died of disease; IPI score, International Prognostic Index score; L-ASP, L-asparaginase; NHL, non-Hodgkin's lymphoma; NOD, no evidence of disease; NR, no response; ORR, overall response rate; OS, overall survival; PEG, polyethylene glycol; PEG-Asp, pegaspargase; P-gp, P-glycoprotein; PR, partial response, RT, radiotherapy; TC, total cholesterol; WHO, World Health Organization

ENKL, and no therapy is considered standard. Physicians are actively looking for new chemotherapeutic regimens with high efficacy and low toxicity for the treatment of ENKL, and the identification of such a regimen would be an important initial step in improving treatment outcomes.

Recently, several studies have reported the remarkable efficacy and safety of L-asparaginase (L-ASP)-based regimens in patients with newly-diagnosed or relapsed/refractory ENKL [8-10]. However, serious hypersensitivity reactions can occur in hypersensitive patients, who account for 10% of the patient population and thus limit the clinical application of L-Asp-based regimens [11]. An additional disadvantage, the short plasma half-life of L-Asp causes frequent dosing that is an inconvenience to patients and clinicians. Pegaspargase (PEG-Asp) is a modified form of native *E. coli* asparaginase in which the enzyme is covalently linked to polyethylene glycol (PEG). The modification retains nearly 50% of the initial activity but greatly decreases the immunogenicity of L-Asp, thus significantly reducing the risk of hypersensitivity reactions [12-14]. Furthermore, PEG-Asp has 5- to 10-fold increase in plasma half-life when compared with L-Asp, which allows for a considerable reduction in the frequency of drug administration for patients [15].

PEG-Asp has been approved for the treatment of acute lymphoblast leukemia (ALL) and already become the first-line agent for ALL [16]; however, there are quite few reports on the application of PEG-Asp or PEG-Asp-based regimens to the treatment of ENKL. Here, we retrospectively report our experience in employing a new PEG-Asp-based regimen in the treatment of 12 Chinese patients with newly-diagnosed ENKL at various stages.

Patients and methods

Twelve patients with newly-diagnosed ENKL were treated in the Lymphoma Center of the First Affiliated Hospital of Zhengzhou University from August 2010 to May 2012. All patients were fully informed about the nature and possible toxicities of the treatment protocol and signed the informed consent form. The inclusion criteria were: (1) histopathologic diagnosis of ENKL based on both morphological and immunohistological criteria as stated in the WHO classification of lymphomas [5]; (2) proven NK/T-cell type by immuneohistochemistry (cytoplasmic CD3ε+, CD20-phenotype, a cytotoxic

profile, and markers of EBV by in situ hybridization); (3) primary tumor site was in the nasopharyngeal region or another extra nodal site. All patients were independently reviewed and confirmed by two expert pathologists.

The pretreatment staging procedures included obtaining a history and physical examination, routine blood tests, and serum chemistry profile. Computed tomography (CT) scans of the head, neck, thorax, and abdomen were performed to determine the extent of the primary lesion. In addition, bone marrow aspiration and biopsy were also carried out.

All patients received a PEG-Asp-based regimen (DDGP regimen) consisting of PEG-Asp (Pegaspargase Injection, Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China), dexamethasone (Dexamethasone Acetate Injection, Chengdu Tiantaishan Pharmaceutical Co., Ltd., Chengdu, China), cisplatin (Cisplatin Injection, Qilu Pharmaceutical Co., Ltd., Ji'nan, China), and gemcitabine (Gemzar®, Eli Lilly, Indianapolis, USA). The specific details of the DDGP regimens are shown in Table 1. The cycle length was 21 days.

Response criteria. CT and magnetic resonance imaging (MRI) scans were employed to evaluate the treatment response every cycle and 1 month after the end of treatment according to adapted Cheson's standard criteria [17]. Complete response (CR) was defined as no evidence of residual disease; partial response (PR) was defined as a reduction of at least 50% of the pretreatment tumor burden; no response (NR) was defined as less than 50% tumor burden reduction or disease progression.

Assessment of toxicity of DDPG regimen. The toxicity of the DDPG regimen was assessed at each cycle from the first day of the regimen until one month after the last treatment. Adverse reactions were monitored by routine physical examination, biochemistry and hematological tests, urinalysis, and electrocardiogram (ECG); and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

Data collection. Data from all patients were retrospectively collected with approval from the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

Statistical analysis. A univariate analysis to identify clinical factors predictive of treatment response was performed using Fisher's exact test on SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered sufficient for statistical significance.

Results

Baseline characteristics of patients. The baseline characteristics of the 12 patients (six males and six females) are listed in Table 2. The median age was 54.5 years (range 28 - 64 years). At diagnosis, nine patients (9/12, 75.0%) had nasal presentation and three (3/12, 25.0%) had extra nasal presentation. For the nine patients with nasal presentation, the primary site was the nasal cavity; for the three patients with extra nasal presentation, the primary sites were the right colon, tonsil,

Table 1. The DDGP regimen used in this study.

Agents	Dose	Route	Timing of treatment
PEG-asparaginase	2500 IU/m^2	IM	Day 1
Gemcitabine	800 mg/m^2	IV	Day 1 and day 8
Cisplatin	20 mg/m^2	IV	Days 1-4
Dexamethasone	12 mg/m^2	IV	Days 1-5

Abbreviations: IM, intramuscularly; IV, intravenously
Cycles were repeated every 21 days

Table 2. Patient characteristics, treatment, and response.

No.	Sex	Age, year	Stage/Primary site	IPI score	Systemic B symptoms	Elevated serum LDH level	Cycle number	Consolidation therapy after remission	Treatment response [a]
1	M	58	IV/Nasal cavity	2	N	N	3	RT, 50 Gy	CR
2	M	28	III/Right colon	2	Y	N	3	-	CR
3	M	39	II/Tonsil	2	N	N	5	RT, 50 Gy	CR
4	F	44	II/Pharyngeal jaw	1	N	N	3	RT, 45 Gy	CR
5	M	57	II/Nasal cavity	1	Y	N	3	RT, 40 Gy	CR
6	M	57	III/Nasal cavity	3	N	Y	2	-	PR
7	M	35	III/Nasal cavity	2	Y	N	6	-	CR
8	F	52	II/Nasal cavity	1	N	N	3	RT, 50 Gy	CR
9	F	64	IV/Nasal cavity	3	Y	Y	6	-	CR
10	F	34	III/Nasal cavity	1	Y	N	6	-	CR
11	F	60	II/Nasal cavity	1	N	N	2	RT, 50 Gy	PR
12	F	60	IV/Nasal cavity	2	N	Y	6	-	CR

Abbreviations: IPI, the International Prognostic Index; LDH, lactate dehydrogenase; M, male; F, female; N, No; Y, Yes; RT, radiotherapy; CR, complete response; PR, partial response

[a] Treatment response indicates the response that was assessed one month after the end of treatment

and pharyngeal jaw, respectively. At the time of inclusion, five patients (5/12, 41.7%) had stage II disease and seven (7/12, 58.3%) had stage III or IV disease. Systemic B symptoms were present in five patients (5/12, 41.7%) and the elevation of serum lactate dehydrogenase (LDH) levels were observed in three patients (3/12, 25.0%).

Treatment outcomes. The median cycle number of the DDGP regimen in the 12 patients was three (range two to six). All patients had an objective response to the regimen. The resulting treatment responses are shown in Table 2. One month after the end of treatment, ten patients (10/12, 83.3%) achieved CR and two (2/12, 16.7%) patients achieved PR. The overall response rate (ORR) was 100%. Seven patients (7/12, 58.3%) received irradiation as consolidation therapy after remission. In order to explore the clinical factors predictive of response, we performed a univariate analysis and found that the clinical factors including sex, age, stage of disease, International Prognostic Index (IPI) score, systemic B symptoms, and elevated serum LDH level were not predictive of the response to DDGP regimen in our patients.

The results of the long-term outcomes to DDGP regiment are presented in Table 4. The median follow-up for overall patients was 17 months (range 10 – 31 months). Eight patients (8/12, 66.7%) were alive with no evidence of disease (NOD) after a median follow-up of 19 months (range 16 – 31 months). One patient (1/12, 8.3%) was alive with PR. Three patients (3/12, 25%) relapsed 6, 7, and 7.5 months after completing treatment with DDGP regimen, respectively. Of the three relapsed patients, one (1/12, 8.3%) was alive with disease recurrence and two (2/12, 16.7%) died of disease (DOD).

Example of DDGP regimen efficacy. Patient 1, a 58-year-old male, was diagnosed with ENKL, having a CD3ε+, CD2+, granzyme-B+ CD56+ phenotype, localized at the anterior nasal

antrum (Figure 1A). He had no local symptoms apart from nasal obstruction and was admitted without fever. He received three courses of the DDGP regimen and then underwent radiotherapy (50 Gy) as consolidation therapy. CT examination before and after radiotherapy showed the disappearance of tumor lesions (Figures 1B and 1C). Currently, he is still in

Table 3. Univariate analysis of response to the DDGP regimen.

Factors	Number of patients	Treatment response [a]		
		CR (%)	PR (%)	P value
Sex				
Male	6	5 (83.3)	1 (16.7)	1.000
Female	6	5 (83.3)	1 (16.7)	
Age				
<50	5	5 (100)	0 (0)	0.470
≥50	7	5 (71.4)	2 (28.6)	
Stage				
II	5	4 (80.0)	1 (20.0)	1.000
III and IV	7	6 (85.7)	1 (14.3)	
IPI score				
1	5	4 (80.0)	1 (20.0)	1.000
2-3	7	6 (85.7)	1 (14.3)	
Systemic B symptoms				
Yes	5	5 (100)	0 (0)	0.470
No	7	5 (71.4)	2 (28.6)	
Elevated serum LDH level				
Yes	3	2 (66.7)	1 (33.3)	0.455
No	9	8 (88.9)	1 (11.1)	

Abbreviations: CR, complete response; PR, partial response; IPI, the International Prognostic Index; LDH, lactate dehydrogenase

[a] Treatment response indicates the response that was assessed one month after the end of treatment
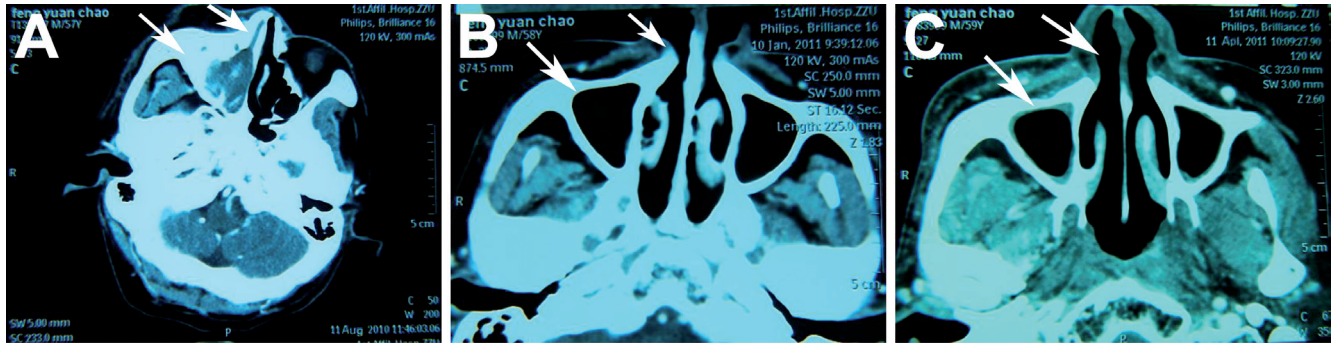
Figure 1. Efficacy of DDGP regimen in one representative patient (Patient 1, a 58-year-old male). (A) Axial CT image shows soft tissue masses (ENKL lesions) in the right nasal cavity, maxillary sinus, ethmoid sinus, and frontal sinus (indicated by white arrows) when he was admitted; (B) and (C) This patient received three courses of the DDGP regimen and then underwent radiotherapy (50 Gy) as consolidation therapy. CT images before (B) and after radiotherapy (C) show the disappearance of tumor lesions (indicated by white arrows). Currently, this patient is in CR with a follow-up of 31 months after the first course of the DDGP regimen

CR with a follow-up of 31 months after the first course of the DDGP regimen.

Toxicity. The toxicity profiles of the DDGP regimen are listed in Table 5. Only one patient (1/12, 8.3%) experienced mild allergic reactions. After oxygen inhalation, the symptoms including facial flushing and stuffiness disappeared in this patient. Hematologic toxicity was the most frequent toxicity in this study. All patients experienced varying degrees of leukopenia, neutropenia, thrombocytopenia, and anemia. Grade 3/4 leukopenia and neutropenia were common and both occurred in eight patients (8/12, 66.7%), respectively. Additionally, six patients (6/12, 50.0%) experienced grade 3/4 thrombocytopenia and three (3/12, 25.0%) experienced grade 3/4 anemia. However, no patient died of hematologic toxicity.

During the treatment, coagulation disorders occurring in patients included prolonged activated partial thromboplastin time (APTT), elevation of serum D-dimer levels, and venous thrombosis. Nevertheless, these adverse events were mild (grade 1/2) and no patients developed serious complications. For laboratory abnormalities, elevated alanine aminotransferase (ALT), total bilirubin, total cholesterol (TC), and blood urea nitrogen (BUN) were observed in two patients (2/12, 16.7%), but no patient experienced diabetes or pancreatitis.

Other toxicities included gastrointestinal and cardiac disorders. Eight patients (8/12, 66.7%) had varying degrees of nausea and vomiting. These symptoms were well controlled after the administration of serotonin receptor antagonists. Heart failure (grade 1/2) was observed in two patients complicated by heart diseases. After symptomatic treatment, significant recovery of cardiac functions was achieved in these patients.

Discussion

In this study, we have investigated the use of a PEG-Asp-based chemotherapy, a DDGP regimen, for the treatment of newly-diagnosed ENKL. In 12 patients, the ORR was 100%

Table 4. Long-term outcomes of the DDGP regimen

Patient No.	Follow-up, months	Relapse	Time of Relapse	Vital status at the end of follow-up
1	31	N	-	Alive, NOD
2	12	Y	7 months after completing treatment	DOD
3	30	N	-	Alive, NOD
4	24	Y	7.5 months after completing treatment	Alive with disease recurrence
5	26	N	-	Alive, NOD
6	10	Y	6 months after completing treatment	DOD
7	18	N	-	Alive, NOD
8	20	N	-	Alive, NOD
9	16	N	-	Alive, NOD
10	16	N	-	Alive, NOD
11	11	N	-	Alive with PR
12	16	N	-	Alive, NOD

Abbreviations: N, No; Y, Yes; NOD, no evidence of disease; DOD, died of disease; PR, partial response

(83.3% CR and 16.7% PR); and eight patients (8/12, 66.7%) were alive with NOD by the end of follow-up. Our results indicate that the DDGP regimen is effective in treating newly-diagnosed stage II – IV ENKL.

The enzyme L-Asp exerts its antitumor effects through the depletion of the essential amino acid L-asparagine, leading to inhibition of protein synthesis in tumor cells [18-21]. *In vitro* studies have demonstrated that L-Asp can induce apoptosis of chemotherapy-resistant tumoral NK cells, indicating it is not affected by multidrug resistance [22]. For the clinical use of L-Asp, Nagafuji et al. first reported the application of L-Asp in a patient with stage IV relapsed nasal natural killer/T-cell lymphoma after autologous peripheral blood stem cell transplantation [23]. Durable remission was achieved and this patient was alive with NOD at the time of the 18-month follow-up. Yong et al. first reported the clinical efficacy of L-Asp in patients with first-line CHOP-resistant ENKL [24]. Of a total of 33 patients, 17 achieved CR and the five-year OS rate was 55.9%. Recently, a series of clinical studies have confirmed the remarkable efficacy of L-Asp-based regimens for the treatment of newly-diagnosed, relapsed, or refractory ENKLs [25-30]. Table 6 summarizes the latest published results (within five years) of L-Asp-based regimens for these diseases.

Although L-Asp-based regimens demonstrated to be significantly effective in treating ENKL, hypersensitivity reactions to L-Asp, considered to be associated with the immunogenicity of L-Asp and reported to occur in 3% to 78% of patients, are of great concern because they are a potentially fatal complication during treatment [31-33]. To overcome this issue, the *E. coli* L-Asp is modified by conjugation with PEG to produce PEG-Asp, which has a significant decrease in immunogenicity and high increase in drug stability. Currently, PEG-Asp, as an effective alternative for patients hypersensitive to the native enzyme, is being increasingly applied as a primary treatment regimen for leukemia [13,34,35]. Nevertheless, the application of PEG-Asp alone or PEG-Asp-based regimens for treating lymphoma has been rarely reported. Within the most recent five years, only one report exists on the clinical efficacy of PEG-Asp against ENKL [26]. For the two patients with stage I refractory ENKL, CR was achieved in both cases and one was alive with NOD by the end of follow-up (Table 6). Additionally, Zhang et al. reported that a DDGP regimen produced a high response rate and low recurrence rate in patients with subcutaneous panniculitis-like T-cell lymphomas, and its hematologic toxicity was well tolerated [36]. These findings indicate that PEG-Asp may be effective for the treatment of ENKL and thus warranted further investigation.

In this study, a DDGP regimen showed impressive clinical efficacy in the patients with newly-diagnosed stage II-IV ENKL. The ORR was 100% and the CR rate was 83.3%, which were similar as well as better compared to results reported in previous studies on L-Asp-based regimens [8, 30]. Eight patients were alive in continuous CR by the end of the follow-up, highlighting the favorable long-term outcome of this

Table 5. Toxicity profiles of the DDGP regimen

Toxicity	All grades	Grades 3/4
Immune system disorders		
Allergic reactions	1	0
Hematologic toxicities		
Leukopenia	12	8
Neutropenia	12	8
Thrombocytopenia	12	6
Anemia	12	3
Coagulation disorders		
Prolonged APTT	4	0
Serum D-dimer elevation	4	0
Venous thrombosis	3	0
Laboratory abnormalities		
ALT elevation	2	0
Serum bilirubin elevation	2	0
TC elevation	2	0
BUN elevation	2	0
Gastrointestinal disorders		
Nausea	8	1
Vomiting	8	0
Cardiac disorders		
Heart failure	2	0

Abbreviations: APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; TC, total cholesterol; BUN, blood urea nitrogen

regimen. Additionally, because of increased plasma half-life and reduced renal excretion, PEG-Asp in the DDGP regimen required much lower dosage and administration frequency than L-Asp in L-Asp-based regimens [37]. For example, the SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-Asp, etoposide) requires intravenous injection of L-Asp at a dose of 6000 IU/m^2 for six days in a 28-day cycle; while the DDGP regimen requires only one intramuscular injection of PEG-Asp at a dose of 2500 IU/m^2 in a 21-day cycle, thus greatly enhancing the convenience and compliance of patients.

With regard to the toxicity profile of the DDPG regimen, the incidence of allergic reactions caused by hypersensitivity to PEG-Asp was very low, which may be attributed to the low immunogenicity of PEG-Asp. Hematological toxicity was the major concern using a DDPG regimen, although no hematological toxicity-related death occurred in the present study. Hematological toxicity may be caused by the myelosuppressive effects of gemcitabine and cyclophosphamide [38], thus indicating hematological parameters should be carefully monitored in patients receiving this regimen in order to avoid any severe unpredictable complications. Coagulation disorders were another concern, but these were mild and none led to serious clinical complications. Venous thrombosis was observed in three patients, which might be triggered by the hypercoagulable state in cancer patients and the inhibition of the synthesis of anticoagulant proteins caused by asparaginase [11]. However, detailed mechanisms still need to be investigated.

Table 6. Literature review of the outcomes of PEG-Asp- or L-Asp-based regimen in the treatment of extranodal NK/T-cell lymphoma within five years

Author, year (reference)	Total number of cases	Stage (number of cases)	Previous treatment (number of cases)	Regimen	Response	Long-term outcomes
Berk V, et al. 2008 [19]	1	Stage IV	CHOP	L-Asp + VCR + PDNN	CR	NOD
Yamaguchi M, et al. 2008 [10]	6	Newly diagnosed stage IV (3); first relapse (2); refractory to the 1st-line therapy (1)	N/A (3), CHOP-like (2), DeVIC + RT (1)	SMILE	3 CR + 1 PR + 1 NE + 1 NR	1 DUD + 5 NE
Jaccard A, et al. 2009 [25]	15	All cases were relapsed or refractory; stage I (1); stage II/IIE (4); stage IV (10)	CHOP or CHOP-like (12)	L-Asp associated with DXM, MTX, or VLB	7 CR + 2 PR + 3 NR + 3 NE	5 NOD + 6 DOD + 4 DUD
Yong W, et al. 2009 [18]	45	All cases were relapsed or refractory; I/II (33); III/IV (12)	CHOP or CHOP-like (17)	L-Asp-based salvage regimen	55.6% CR + 26.7% PR	Five-year OS rate was 66.9%
Reyes VE Jr, et al. 2010 [26]	2	Stage IAE, refractory, (1); stage IE, refractory, (1)	CHOP + RT (2)	PEG-Asp alone	2 CR	1 NOD + 1 DOD
Yamaguchi M, et al. 2011 [27]	38	Newly diagnosed stage IV (20); first relapse (14); refractory to the 1st-line therapy (4)	N/A (20), CHOP-like (14), DeVIC + RT (4)	SMILE	17 CR + 13 PR + 1 NR + 4 PD + 3 ED	One-year OS rate was 55%
Jaccard A, et al. 2011 [28]	19	All cases were relapsed or refractory; stage IE/IIE (12); stage IV (7)	CHOP or CHOP-like (17), RT (9)	DXM + MTX + L-Asp	11 CR + 3 PR + 4 NR + 1 NE	8 NOD + 10 DOD + 1 DUD
Kwong YL, et al. 2012 [9]	87	Newly diagnosed: stage I (12), stage II (5), stage IV (26); relapsed/refractory: stage I (13), stage II (8), stage III (2), stage IV (21)	CHOP or CHOP-like (30); CHOP or CHOP-like + RT (7); CCRT (5)	SMILE	66% CR + 15% PR	Five-year OS rate was 50% and 4-year DFS rate was 64%
Jiang M, et al. 2012 [8]	26	Newly diagnosed: stage IE (20), IIE (6)	N/A	L-Asp + VCR + PDN	21 CR + 2 PR + 3 PD	Two-year OS rate was 88.5%, and 2-year PFS rate was 80.6%
Ahn HK, et al. 2013 [29] [a]	1	IVB, relapsed	CCRT followed by VIDL; MIDLE	L-Asp + GEM	Death	PFS: 0.6 month; OS: 0.6 month
Wang L, et al. 2013 [30]	27	Newly diagnosed: stage IE (18), IIE(9)	N/A	GEM + L-Asp + OXA	20 CR + 6 PR	4 DOD. Two-year OS and PFS rates were 86%.

[a] Twenty patients were reported in this literature but only one received an L-Asp-based regimen

Abbreviations: CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; DeVIC, carboplatine + etoposide + ifosfamide + dexamethasone; SMILE, dexamethasone + methotrexate + ifosfamide + L-asparaginase + etoposide; CCRT, concurrent chemoradiotherapy; VIDL, etoposide + ifosfamide + L-Asp + dexamethasone; MIDLE, methotrexate + ifosfamide + dexamethasone + L-Asp + etoposide; VCR, vincristine; PDNN, prednisolone; DXM, dexamethasone; MTX, methotrexate; VLB, vinblastine; PDN, prednisone; GEM, gemcitabine; OXA, oxaliplatin; RT, radiotherapy; CR, complete response; PR, partial response; ED, early death; NE, not evaluated; NR no response; NOD, no evidence of disease; DOD, died of disease; DUD, dead unrelated to disease; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival

In conclusion, our study shows significant efficacy and safety of PEG-Asp-based DDGP regimen in treating patients with newly-diagnosed stage II-IV ENKL, and indicates the potential of this regimen as a first-line therapy against this disease. The retrospective nature, small sample size, and short follow-up period suggest that our findings need to be further investigated using a prospective study with a larger patient group and longer follow-up period. Furthermore, the efficacy of DDGP regimen against relapsed or refractory ENKL is still unclear. A clinical study is now in progress to evaluate its efficiency in the treatment of this disease.

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