RESEARCH ARTICLE

Efficacy and Tolerance of Pegaspargase-Based Chemotherapy in Patients with Nasal-Type Extranodal NK/T-Cell Lymphoma: a Pilot Study

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Abstract

Nasal-type extranodal natural killer (NK)/T-cell lymphoma (ENKL) is a highly invasive cancer with a poor prognosis. More effective and safer treatment regimens for ENKL are needed. Pegaspargase (PEG-Asp) has a similar mechanism of action to L-asparaginase (L-Asp), but presents lower antigenicity. The aim of the present research was to evaluate the safety profile and the latent efficacy of a PEG-Asp-based treatment regimen in patients with ENKL. Data collected from 20 patients with histologically confirmed ENKL, admitted to the Third Affiliated Hospital of Sun Yat-Sen University from January 2009 to August 2013, were included in the study. All patients received 2500 IU/m^2/IM PEG-Asp on day 1 of every 21-day treatment cycle. Patients received combination chemotherapy with CHOP (n=5), EPOCH (n=7), GEMOX (n=7) or CHOP with bleomycin (n=1). After 2-5 treatment cycles (median, 4 cycles) of PEG-Asp-based chemotherapy, five patients (25%) showed a complete response (CR), and the overall response rate (ORR) was 60%. Grade 3/4 neutropenia occurred in fourteen patients (70%). Grade 3 alanine aminotransferase (ALT) elevation was observed in two. Grade 1-2 non-hematological toxicity consisted of activated partial thromboplastin time (APTT) elongation (n=9), hypofibrinogenemia (n=6), hypoproteinemia (n=17), hyperglycemia (n=3), and nausea (n=6). No allergic reactions were detected. No treatment related death was reported. Our results suggested that PEG-Asp-based chemotherapy presented an acceptable tolerance and a potential short-term outcome in patients with nasal-type ENKL.

Keywords: Nasal - type extranodal NK/T - cell lymphoma - pegaspargase - response rate - safety - L-asparaginase

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Introduction

Extranodal natural killer (NK)/T-cell lymphoma (ENKL) is a highly invasive tumor with a short doubling time, and poor prognosis. ENKL is relatively rare in the United States and Europe, where it accounts for less than 1% of all non-Hodgkin's Lymphoma (NHL) cases. It is more common in Asia, Central America and South America, where it accounts for 3-8% of all NHL cases (Wang et al., 2009; Chakrabarti et al., 2010; Liu et al., 2011; Padhi et al., 2012; Tahmasby et al., 2013; Xu et al., 2014). The optimal first-line therapy for ENKL is evolving. The 5-year survival rates of limited stage ENKL treated with radiotherapy alone or with combination chemotherapy are both below 50% (Li et al., 2006; Zhang et al., 2013; Binesh et al., 2014). The main treatment for late stage ENKL is chemotherapy. Chemotherapy based on the CHOP regimen is the most frequently used, but the response rate is low, and the 5-year survival rate is only 7–25% (Li et al., 2004). Treatment failure may involve the multidrug resistance gene associated P-glycoprotein (Pgp). Pgp acts as a pump, combining with chemotherapeutic drugs and thereby decreasing their intracellular concentration. Therefore, other chemotherapeutic agents should be considered for the treatment of late stage ENKL.

In 2010, the National Comprehensive Cancer Network (NCCN) guideline added regimens based on L-asparaginase (L-Asp) and steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE). Chemotherapy regimens based on L-Asp have been reported to have a CR of 55.6%, a partial response (PR) of 26.7%, and an ORR of 82.2% when used in the treatment of relapsed or refractory ENKL; and the 3-year and 5-year survival rates for both are 66.9% (Yong et al., 2009). However, L-Asp treatment has two main disadvantages: the need for frequent intramuscular injection, and a very high rate of allergic reactions (Woo et al., 2000), which have become the key limiting factors

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of its use. A polyethylene glycol-modified version of L-Asp, pegaspargase (PEG-Asp), was developed in the 1990s with the aim of reducing its immunogenicity (Alfieri et al., 1995). PEG-Asp appears to be safe and effective in patients with acute lymphoblastic leukemia (ALL) (Dinndorf et al., 2007; The Cooperation Group of Phase II Clinical Trial of PEG-Asp, 2008; Silverman et al., 2010); however, the safety and potential efficacy of PEG-Asp in patients with ENKL was not systematically evaluated for future design of relevant clinical trials.

Thus, in this study, we retrospectively reviewed data from 20 patients with ENKL treated with PEG-Asp contained chemotherapy in our center located in the epidemic area of ENKL. The safety profile and potential efficacy of this drug was systematically evaluated to facilitated future clinical trials of PEG-Asp contained strategy.

Materials and Methods

Ethics Statement

This retrospective study was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-Sen University and adhered to the tenets of the Declaration of Helsinki.

Clinical data

Data collected from 20 patients with histologically confirmed ENKL admitted to the Third Affiliated Hospital of Sun Yat-Sen University from January 2009 to August 2013 were included in this study. The following clinical data were collected retrospectively: age, sex, B symptoms, ECOG performance status (PS), primary site of involvement, Ann Arbor stage, serum lactate dehydrogenase (sLDH), Ki-67 expression, treatment regimens, treatment response and date of last follow-up.

Treatment protocols

All patients received PEG-Asp (2500 IU/m^2/IM) on day 1 of every 21-day treatment cycle with no skin test or drug pretreatment. The CHOP regimen consisted of cyclophosphamide (750 mg/m^2, IV, day 1); pirarubicin (40 mg/m^2, IV, day 1); vincristine (1.4 mg/m^2, IV, day 1) and prednisone (100 mg, oral, days 1-5). The EPOCH regimen consisted of etoposide (50 mg/m^2); epidoxorubicin (12 mg/m^2) and vincristine (0.4 mg/m^2) dissolved in 500 mL saline and administered as a continuous IV drip for 24 hours on days 1-4; cyclophosphamide (750 mg/m^2, IV, day 5) and prednisone (60 mg/m^2, oral, days 1-5), were also administered. The GEMOX regimen consisted of gemcitabine (0.8-1 g/m^2) and oxaliplatin (75 mg/m^2). Each treatment cycle lasted 21 days. For the CHOP-like regimen, 15 mg bleomycin was added on days 1-3. Patients with stage I-II disease, with the nasal cavity or nasopharynx as the primary site, received local radiotherapy after the chemotherapy.

Evaluation standards

The response to treatment was assessed by computed tomography (CT) scans of the chest and abdomen or positron emission tomography (PET) scans after every cycle of PEG-based chemotherapy. Treatment effects were evaluated according to the National Comprehensive Cancer Network (NCCN, USA) clinical practice guideline (modified in 2007) on NHL (Cheson et al., 2007). Clinical course was categorized as complete response (CR), partial response (PR), stable 10sease (SD), or progressive disease (PD). Progression-free survival (PFS) was determined as the time from the date of the first administration of PEG-Asp to the date of disease progression, or death by any cause. Overall survival (OS) was measured as the time from the date of the first administration of PEG-Asp to the date of death or the last follow-up visit.

Adverse effects

Adverse effects were evaluated according to the grading criteria for acute and subacute toxic reactions of anticancer drugs formulated by the National Cancer Institute Common Toxicity Criteria (version 3.0). The grading scale used was 1-5.

Statistical methods

Fisher's exact test was employed to evaluate the prognostic value of specific factors including stage, B symptoms, sLDH, Ki-67 and age. The relationships between these factors and PFS and OS were determined by Kaplan-Meier analysis. All P-values quoted are two-sided, and the level of significance was set at $p<0.05$. Statistical analyses were performed using SPSS v.17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Patient characteristics and previous treatment regimens are listed in Table 1. The median age of the patients was 46.5 years (range 14-73 years). Their disease status was: newly diagnosed (n=14, 70%), recurrent disease of remission (n=2, 10%) and refractory disease after first-line chemotherapy (n=4, 20%). At the time of diagnosis, eight patients (40%) had stage I-II disease and twelve patients (60%) had stage III-IV disease. Fourteen of the 20 patients had upper aerodigestive tract primary disease, including of the nasal cavity, nasopharynx and tonsils; two had skin primary disease; and four patients had gastrointestinal tract primary disease. Ten patients (50%) had systemic B symptoms; four patients (20%) had a PS >1; thirteen patients (65%) had an elevated level of sLDH; thirteen patients (65%) had a high Ki-67 expression (≥65%). The median follow-up period was 18 months (2.3-28.5 months).

Treatment effects

The median number of PEG-Asp-based chemotherapy cycles received was four (range 2-5). Among the patients, five received combination chemotherapy with the CHOP regimen, seven with EPOCH, seven with GEMOX, and one with a CHOP-like regimen (CHOP + bleomycin). Five patients (25%) showed a CR and seven patients (35%) achieved a PR. The overall response rate (ORR; CR+PR) was 60% (12/20). Univariate analysis showed that the potential prognostic factors (staging, B symptoms, sLDH,

Table 1. General Characteristics of 20 Patients with ENKL Treated with PEG-Asp-Based Chemotherapy

Patient No.	Age	Sex	AA stage at diagnosis	Disease state	Primary site of involvement	B-symptom	PS	sLDH	Ki-67 (%)	Previous treatment	Regimen	Courses	Response	PFS (m)	OS (m)
1	59	F	IV	Newly diagnosed	Adrenal gland; nasal cavity	Weight loss	1	Normal	80	N	EPOCH+ PEG-Asp	2	SD	6.3	8.9
2	37	M	IV	Newly diagnosed	Nasal cavity; pancreas	N	1	Elevated	50	N	EPOCH+ PEG-Asp	3	PR	10.5	15.4
3	63	M	IIE	Newly diagnosed	Nasopharynx	Fever	1	Elevated	60	N	CHOP+ PEG-Asp	2	CR	12.5	28.5
4	26	M	IV	Newly diagnosed	GI tract	Weight loss	1	Elevated	75	N	EPOCH+ PEG-Asp	4	SD	8.2	14.8
5	58	M	IE	First relapse	GI tract	Weight loss	0	Normal	70	CHOP+ BLM; GEMOX+ L-Asp; GEMOX	GEMOX+ PEG-Asp	3	PR	14.3	21.6
6	14	M	IIE	Newly diagnosed	Nasopharynx	N	1	Normal	70	N	GEMOX+ PEG-Asp	3	CR	8.2	8.2
7	32	F	IV	Refractory	Skin; liver	Fever	2	Elevated	80	CHOP	CHOP+ PEG-Asp	4	PD	1.9	2.3
8	73	F	IV	Refractory	Nasopharynx; Bone marrow	N	1	Elevated	80	GEMOX+ L-Asp	GEMOX+ PEG-Asp	3	PR	2.6	6.2
9	46	F	IE	First relapse	Nasopharynx	N	1	Elevated	NE	GEMOX+ PEG*3 followed by radiotherapy	GEMOX+ PEG-Asp	5	CR	16.5	16.5
10	22	M	IIE	Newly diagnosed	Tonsil	Fever	1	Normal	80	N	CHOP+ BLM+P EG-Asp	5	PR	14.4	14.4
11	52	M	III	Newly diagnosed	Nasopharynx	N	1	Elevated	60	N	CHOP+ PEG-Asp	4	PR	4.5	11.4
12	47	M	IIE	Newly diagnosed	GI tract	N	0	Normal	50	N	EPOCH+ PEG-Asp	5	CR	13.5	13.5
13	31	F	III	Newly diagnosed	Nasopharynx	Fever	1	Elevated	60	N	EPOCH+ PEG-Asp	4	SD	6.2	10.9
14	49	F	IV	Newly diagnosed	Nasopharynx Bone marrow	Weight loss	2	Elevated	75	N	CHOP+ PEG-Asp	3	PR	4.5	7.8
15	60	M	IV	Refractory	Nasopharynx	N	1	Elevated	80	CHOP	GEMOX+ PEG-Asp	3	PR	2.5	7.1
16	54	M	IV	Refractory	Nasopharynx	N	1	Normal	80	CHOP+ BLM	GEMOX+ PEG-Asp	5	SD	3.6	5.2
17	35	M	IE	Newly diagnosed	GI tract	Fever	2	Elevated	70	N	GEMOX+ PEG-Asp	5	CR	20.1	20.1
18	65	M	IIE	Newly diagnosed	Nasal cavity	Fever	2	Elevated	75	N	CHOP+ PEG-Asp	4	SD	3.7	3.7
19	31	F	IV	Newly diagnosed	Skin	N	1	Normal	85	N	EPOCH+ PEG-Asp	2	PD	1.6	8.2
20	39	M	III	Newly diagnosed	Nasopharynx	N	1	Elevated	50	N	EPOCH+ PEG-Asp	4	SD	6.7	6.7

*Abbreviaztion:F, female; M, male; AA stage, Ann Arbor stage; GI tract, gastrointestinal tract; N, none; PS, performance status; sLDH, serum lactate dehydrogenase; NE, not evaluated; CHOP, cyclophosphamide + pirarubicin + vincristine + prednisone; BLM, bleomycin; GEMOX, gemcitabine + oxaliplatin; L-asp, L-asparaginase; PEG-Asp, Pegaspargase; EPOCH, etoposide+epidoxorubicin+vincristine+cyclophosphamide+prednisone; CR, complete response; PR, partial response; PD, progressive disease; PFS, progressive-free survival; OS, overall survival; m, months

Ki-67 and age) were not associated with the response to PEG-Asp-based chemotherapy in our study ($p>0.05$).

The median PFS (mPFS) and median OS (mOS) of the 20 patients were 6.3 and 9.9 months, respectively. The PFS and OS of the twelve responders (CR+PR) were 11.5 and 13.95 months, respectively, which were significantly longer than the PFS and OS of the eight non-responders (SD+PD); 4.95 and 7.45 months, respectively; $p<0.05$; Figure 1). Univariate analysis indicated that stage was the only prognostic indicator for PFS and OS. Stage I-II patients had significantly improved PFS and OS rates compared with stage III-IV patients ($p<0.05$; Figure 2). The treatment responses and long-term outcomes of the patients are shown in Table 2.

Adverse effects

Following treatment, all patients experienced varying degrees of neutropenia. Grade 3/4 neutropenia occurred in fourteen patients (70%). Additionally, two patients experienced grade 3/4 anemia; two experienced thrombocytopenia; and six developed infection. Grade 3 alanine aminotransferase (ALT) elevation was observed in two patients. Grade 1-2 non-hematological toxicities consisted of activated partial thromboplastin time (APTT) elongation (n=9), hypofibrinogenemia (n=6), hypoproteinemia (n=17), hyperglycemia (n=3), and nausea (n=6). All liver function and coagulation abnormalities normalized within a week following treatment. No allergic reactions, pancreatitis, or thrombosis were observed.

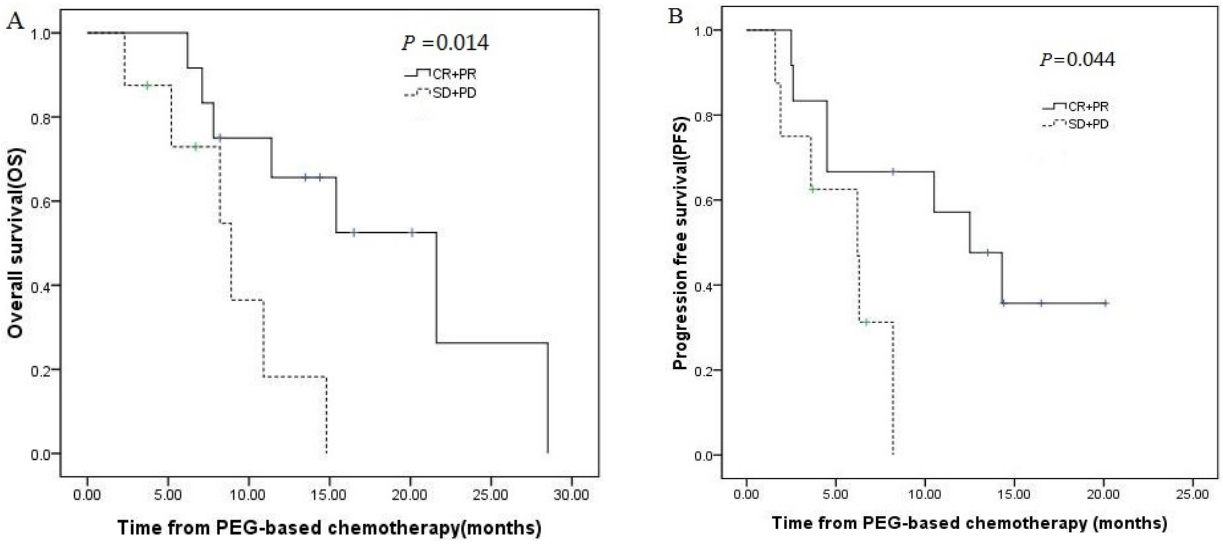

Figure 1. Overall Survival (A) and Progression-Free Survival (B) after PEG-Asp-Based Chemotherapy According to Treatment Response. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

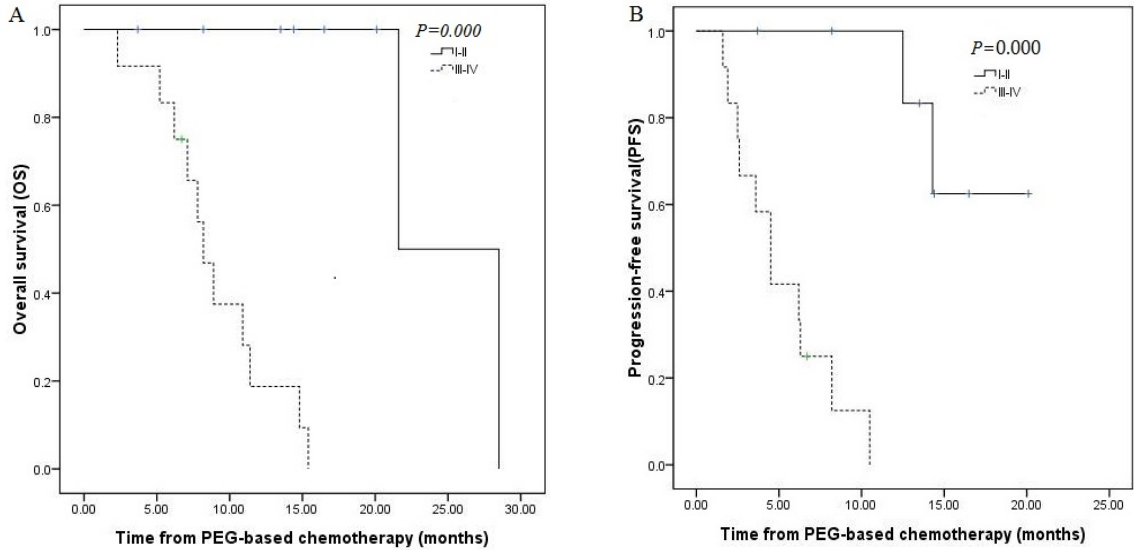

Figure 2. Overall Survival (A) and Progression-Free Survival (B) after PEG-Asp-Based Chemotherapy According to Stage (I-II vs. III-IV)

Table 2. The Response and Long-Term Outcome of PEG-Asp-Based Chemotherapy

Factors	Number of patients	ORR (%)	*P*-Value	mPFS (m)	*P*-Value	mOS (m)	*P*-Value
Staging							
Limited stage (stage I-II)	8	7 (87.5)		13.9		15.45	
Extensive stage (stage III-IV)	12	5 (41.7)	0.07	4.5	0	8	0
B symptoms							
Without B symptoms	10	7 (70.0)		5.6		12.65	
With B symptoms	10	5 (50.0)	0.65	7.25	0.805	8.2	0.494
sLDH							
Normal	7	4 (57.1)		8.2		10.9	
Elevated	13	8 (61.5)	1	6.2	0.496	8.9	0.88
Ki-67							
≥65%	13	7 (53.8)		4.5		8.2	
< 65%	6	4 (66.7)	1	8.6	0.621	12.45	0.203
Age							
>60	3	2 (66.7)		3.7		6.2	
≤60	17	10 (58.8)	1	7.45	0.527	10.9	0.512
Treatment response							
CR+PR	12	----	----	11.5		13.95	
SD+PD	8	----	----	4.95	0.044	7.45	0.0144

*Abbreviaztion: sLDH, serum lactate dehydrogenase; CR, complete remission; PR, partial remission; SD, stable disease; PD, progression disease;ORR, overall response rate; mPFS, median progressive-free survival; mOS, median overall survival; m, months

Table 3. Toxicity Profile of PEG-Asp-Based Chemotherapy

Adverse event	Grade of Toxicity					
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)	Total (%)
Neutropenia	1 (5%)	5 (25%)	6 (30%)	8 (40%)	0	20 (100%)
Anemia	3 (15%)	4 (20%)	2 (10%)	0	0	9 (45%)
Thrombocytopenia	5 (25%)	3 (15%)	2 (10%)	0	0	10 (50%)
Infection	0	0	6 (12%)	0	0	6 (12%)
APTT elongation	4 (20%)	5 (25%)	0	0	0	9 (45%)
Hypofibrinogenemia	3 (15%)	3 (15%)	0	0	0	6 (30%)
Hypoproteinemia	3 (15%)	14 (70%)	0	0	0	17 (85%)
ALT elevation	4 (20%)	8 (40%)	2 (10%)	0	0	14 (70%)
Hyperglycemia	0	3 (15%)	0	0	0	3 (15%)
Nausea	2 (10%)	4 (20%)	0	0	0	6 (30%)

*Abbreviaztion: APTT, activated partial thromboplastin time; ALT, alanine aminotransferase

No chemotherapy-related deaths occurred. The toxicity profiles of PEG-Asp-based chemotherapy are listed in Table 3.

Discussion

ENKL is known as one of the worst types of lymphoma due to unacceptable efficacy of current chemotherapy regimes. Treatment failure partially involved the multidrug resistance gene associated P-glycoprotein. L-Asp is an antitumor drug with a unique mechanism that is not affected by Pgp and presented acceptable efficacy in malignant lymphoid tumors, such as ALL and lymphoma that cannot synthesize asparagines (Yong et al., 2006). A few reports have reported the efficacy of L-Asp-based chemotherapy in Advanced, relapsed, or refractory ENKLs (Colombat et al., 2001; Obama et al., 2003; Jaccard et al., 2011; Yamaguchi et al., 2011; Lin et al., 2013). However, severe toxicity associated with highly immunogenicity of L-Asp significantly limited its universal usage. PEG-Asp, a new generation of L-Asp, presented improves tolerance and efficacy with reduced immunogenicity (Alfieri et al., 1995) .PEG-Asp appears to be safe and effective in patients with acute lymphoblastic leukemia (ALL) (Dinndorf et al., 2007; The Cooperation Group of Phase II Clinical Trial of PEG-Asp, 2008; Silverman et al., 2010). Thus, PEG-Asp could be a potential agent for ENKL. A few case reports and clinical studies with limited sample sizes have presented the potential efficacy in selected patients. However, these evidences could not warrant the universal usage of this drug in ENKL due to their shortage of reporting the overall safety profile in unselected patients. As far as we are aware, our study aiming at systemically evaluated the safety profile of PEG-Asp represented the largest number of continuous ENKL cases treated with PEG-Asp in the epidemic area, which provided reliable evidence for the design of future clinical trials.

In our study, PEG-Asp presented an acceptable toxicity profiles. Grade 3/4 toxicities were mainly hematological. Grade 3/4 neutropenia occurred in fourteen patients (70%). Additionally, two (20%) patients experienced grade 3 anemia; two (20%) experienced grade 3 thrombocytopenia; and six developed consequent infection. Hematologic toxicity could be caused by the myelosuppressive effects of the EPOCH, CHOP or GEMOX regimens. Grade 3 alanine aminotransferase (ALT) elevation occurred in two (20%) patients. All liver function and coagulation abnormalities normalized within a week following treatment. Significantly, no allergic reactions, pancreatitis, or thrombosis were detected. Besides, no chemotherapy-related deaths occurred. The superior safety profile of PEG-Asp relied on its pharmalogical behavior. It has a plasma half-life of about 5.5 days, substantially longer than that of L-Asp (approximately 20 hours). PEG-Asp is advantageous as it does not require a skin test, needs far fewer drug administrations, and can be delivered more conveniently (The Cooperation Group of Phase II Clinical Trial of PEG-Asp, 2008). The safety profile of PEG-Asp contained chemotherapy was acceptable and the dosage in our study could be a reasonable option for the future clinical trials in the setting.

Moreover, PEG-Asp presented decreased specific toxicities related to L-Asp. L-Asp may cause pancreatitis in 1-16% of patients (Alvarez et al., 2000). By contrast, commonly reported side-effects of PEG-Asp therapy include digestive tract reactions, liver function abnormalities, and hyperglycemia. Pancreatitis occurs in about 1% of patients and thrombosis in 4%. In the present study, one patient had acute pancreatitis before the chemotherapy. After the pancreatitis was resolved, PEG-Asp was added, starting from the second chemotherapy cycle. No pancreatitis was observed throughout the following four chemotherapy cycles. No PEG-Asp related allergic reactions, pancreatitis, or thrombosis were observed in this study. With the exception of allergic reactions, PEG-Asp and L-Asp have a similar toxicity profile (Graham et al., 2003; The Cooperation Group of Phase II Clinical Trial of PEG-Asp, 2008). Overall, PEG-Asp and combination chemotherapy were well tolerated by patients with ENKL.

Studies have demonstrated that PEG-Asp exhibits similar antitumor effects to L-Asp in the treatment of ALL (Avramis et al., 2002; Msdryyi et al., 2009). PEG-Asp has been recognized as an essential element in the treatment of ALL; but, few studies have reported its use in patients with non-Hodgkin lymphoma (NHL). Muss et al. (Muss et al., 1990), treated 21 patients with refractory NHL with PEG-Asp and noted two PRs. Tulpule et al. (Tulpule et al., 1998) treated five patients with AIDS-related lymphoma with PEG-Asp and three achieved CR. Reyes (Reyes et al., 2010) reported two patients in which PEG-Asp alone was

used to treat ENKL tolerant to a CHOP regimen, and both had a CR. Li (Li et al., 2014))demonstrate the significant efficacy and safety profile of a DDGP regimen (PEG-Asp, dexamethasone, cisplatin, gemcitabine) in the treatment of newly-diagnosed ENKL. Clinical studies that directly compare these two drugs in the treatment of lymphoma are now needed. Erik et al. (Teske et al., 1990), compared PEG-Asp with L-Asp in 42 dogs with spontaneous malignant lymphomas and found no difference in the estimated 1-year survival rates between these two groups (52% for PEG-Asp and 38% for L-Asp). These reports indicate that PEG-Asp alone or PEG-based chemotherapy may be promising for the treatment of lymphoma and ENKL. In the present study, the ORR was 60% and the CR rate was 25%. The mPFS and mOS of the 20 patients were 6.3 and 9.9 months, respectively. This treatment effect is similar to that of L-Asp combined chemotherapy (Teske et al., 1990;Jaccard et al., 2009).

A novel prognostic index incorporating B symptoms, clinical stage, serum LDH level and regional lymph node involvement has been described (Lee et al., 2006). Ki-67 expression has been also reported as a prognostic factor in patients with ENKL (Kim et al., 2007; Yasuda et al., 2009; Huang et al., 2014; He et al., 2014). However, in this study, univariate analysis indicated that stage was the only prognostic indicator for PFS and OS. Further investigations in a larger patient cohort are needed to identify the appropriate prognostic factors for ENKL.

Our results indicate that PEG-Asp-based chemotherapy is effective for the treatment of patients with ENKL that are newly diagnosed, first relapse after remission, or refractory to previous treatments. Further large-scale, prospective, and multi-center studies are now needed to evaluate the clinical significance of PEG-Asp-based regimens in the treatment of ENKL, and even other malignances.

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