

Polyethylene glycol conjugated asparaginase - CHOP in adult newly diagnosed extranodal NK/T-cell lymphoma: a multi-center prospective phase II study

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OBJECTIVES

Administration of L-asparaginase (L-ASP) is limited by hypersensitivity reactions mediated by anti-asparaginase antibodies. Native *Escherichia coli* L-asparaginase was conjugated to polyethylene glycol to formulate polyethylene glycol conjugated asparaginase (PEG-ASP) with decreased immunogenicity and increased circulating half-life. The efficacy and safety of PEG-ASP in adult extranodal natural killer NK/T-cell lymphoma is unclear. In this study, we investigated the efficacy and toxicity of PEG-ASP combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (PEG-L-CHOP regimen).

METHODS

The study was a prospective, multi-centre, open clinical trial. Patients with adult newly diagnosed ENKT and an ECOG performance status of 0 to 2 were eligible for enrollment. Treatment included 6 cycles of PEG-L-CHOP regimen: PEG-ASP 2500 IU/m² on days 2 (maximal dose 3750 IU), cyclophosphamide 750 mg/m² on days 1, doxorubicin 50 mg/m² on days 1, vincristine 1.4 mg/m² on days 1 (maximal dose 2 mg), and prednisone 60mg/m² on days 1 through 5 of a 21-day cycle. Radiotherapy was scheduled after 2–4 cycles of PEG-L-CHOP regimen, depending on stage and primary anatomic site. The primary endpoint was complete response (CR) rate.

Table 1. Clinical features and therapeutic efficacy in 33 patients with newly diagnosed adult ENK/T

Patients features	Patients (%)	CR (%)	NO CR (%)	P value
Age				
< 60 years	30 (90.9)	23(76.7)	7 (23.3)	1.000
≥ 60 years	3 (9.1)	2(66.7)	1 (33.3)	
Gender				
Male	19 (57.6)	16(84.2)	3 (15.8)	0.238
Female	14 (42.2)	9 (64.3)	5 (35.7)	
Primary site				
UNKTL	30 (90.9)	23(76.7)	7 (23.3)	1.000
EUNKTL	3 (9.1)	2 (66.7)	1 (33.3)	
An Arbor score				
I ~ II	21(63.6)	19(90.5)	2 (9.5)	0.015
III ~ IV	12(36.4)	6 (50.0)	6(50.0)	
B symptom				
Yes	12 (36.4)	9 (75.0)	3 (25.0)	1.000
No	21 (63.6)	16(76.2)	5 (23.8)	
ECOG				
0-1	27 (81.8)	21(77.8)	6(22.2)	0.6162
≥2	6 (18.2)	4 (66.7)	2(33.3)	
LDH				
increased	7 (21.2)	2(28.6)	5(71.4)	0.004
normal	26(78.8)	23(88.5)	3(11.5)	
IPI score				
0 ~ 1	22 (66.7)	21(95.5)	1(4.5)	<0.001
≥2	11 (33.3)	4 (36.4)	7(63.6)	
BM involvement				
Yes	4 (12.1)	3(75.0)	1(25.0)	1.000
No	29 (87.9)	22(75.9)	7(24.1)	
Lymph node involvement				
Yes	12 (36.4)	9 (75.0)	3 (25.0)	1.000
No	21 (63.6)	16(76.2)	5 (23.8)	
Extranodal involvement site				
0-1	26 (78.8)	22(84.6)	4(15.4)	0.042
≥2	7 (21.2)	3(42.9)	4(57.1)	
Allergy history				
Yes	1 (3.0)	0(0.0)	1(100.0)	0.242
No	32 (97.0)	25(78.1)	7(21.9)	

Table 2. Adverse reactions in the 33 patients with adult extranodal NK/T cell lymphoma

Adverse reactions	I	II	III	IV	Total (%) patients
Systemic reactions					
Allergic reaction	0	0	0	0	0 (0.0)
Infection	2	1	1	0	4 (12.1)
Hyperglycemia	3	0	0	0	3 (9.1)
Coagulation function					
Decreased fibrinogen	14	1	0	0	15 (45.5)
Prolonged APTT					*19(57.6)
Prolonged PT					*9 (27.3)
Thrombosis	0	1	0	0	1 (3.0)
Hemorrhage	0	0	0	0	0 (0.0)
Blood system					
Neutropenia	2	2	7	14	25 (75.8)
anemia	8	3	1	0	12 (36.4)
Thrombocytopenia	5	2	1	0	8 (24.2)
Gastrointestinal tract					
Abnormal liver function	17	2	3	0	22 (66.7)
Total bilirubin increase	11	0	0	0	11 (33.3)
Pancreatitis	0	0	0	0	0 (0.0)
Vomiting	4	4	0	0	8 (24.2)
Diarrhea	0	0	1	0	1 (3.0)
Cardiovascular system					
Arrhythmia	0	0	0	0	0 (0.0)
Hypotension	0	0	0	0	0 (0.0)
Cardiac insufficiency	0	0	0	0	0 (0.0)
Other events	1	1	0	0	2 (6.0)

RESULTS

A total of 33 eligible patients (from 6 centers in China) were enrolled. There were 19 male and 14 female with a median age of 39 years. The primary lesions were located in upper aerodigestive tract NK/T-cell lymphoma (UNKTL) in 30 patients (90.9%). Ann Arbor stage I~II, 21 patients (63.6%). B symptoms were observed in 12 patients (36.4%). IPI score was 1 or lower in 22 patients (66.7%). All patients underwent chemotherapy. 33 patients completed 170 cycles of chemotherapy, the median cycle of 6. 16 patients (48%) combined with radical radiotherapy. The overall response rate was 96.9% with 75.8% CR and 21.2% PR. OS at 1, 2, 3-year were 100%, 90.61% and 80.54%, respectively. The major adverse event was bone marrow suppression in 25 patients (75.8%) with 21 (63.6%) grade 3-4 neutropenia. Decrease of fibrinogen level in plasma was in 15 patients (45.5%). The other adverse events included liver dysfunction, and digestive tract toxicities. All patients were without the occurrence of allergic reaction. No treatment-related mortality were recorded.

CONCLUSIONS

PEG-L-CHOP for adult extranodal natural killer NK/T-cell lymphoma is effective and safe. The major advantage of PEG-ASP is less allergic reaction. The second is more prolonged effect and convenient. Each cycle of treatment need only 1 times , with good compliance of patients.

References

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