THERAPEUTIC EFFICACY OF L-ASPARAGINASE IN THE TREATMENT OF REFRACTORY MIDFACIAL PERIPHERAL T-CELL NON-HODGKIN'S LYMPHOMA

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ABSTRACT

Objective: To improve the efficacy of refractory midfacial peripheral T-cell non-Hodgkin's lymphoma (MPTC-NHL) with L-asparaginase (L-ASP) based salvage chemotherapy. Methods: 21 patients with refractory MPTC-NHL were analyzed. 11patients (L-ASP group) received L-asparaginase based salvage chemotherapy consisting of L-asparaginase, vincristine and dexamethosone. 10 patients (control group) received salvage combination chemotherapy without L-asparaginase. Results: Complete remission rates were 45.6% for L-ASP group and 0.0% for control group ($P<0.05$). Overall response rates (CR+PR) were 63.6% for L-ASP group and 10.0% for control group, respectively ($P<0.05$). 2-year survival rates were 45.5% for L-ASP group and 0.0% for control group ($P<0.05$). The major adverse effects of L-ASP were leukopenia, elevation of serum bilirubin and hyperglycemia. Conclusion: The preliminary clinical study shows that the L-ASP based salvage chemotherapy may improve the response rate and 2-year survival rate of the patients with refractory MPTC-NHL. It is necessary to continue the study further.

Key words: Efficacy L-asparaginase, Treatment, Midficial peripheral T-cell non-Hodgkin's lymphoma

Primary midficial peripheral T-cell non-Hodgkin's lymphoma (PMPTC-NHL) of the nasal cavity, paranasal sinuses, palate and nasopharynx occurs relatively high among Orientals. The incidence comprises approximately 3% of NHL in Hong Kong Chinese.[1] Previously, PMPTC-NHL has been designated by the names of lethal midline granuloma, midline reticulosis or polymorphic reticulosis, but recently it is considered as a distinct clinicopathological entity of NHL because the lesions show NK/T or T cell immunotype.[1,2] The patients, especially those with advanced disease and B symptoms, seems to have a poor prognosis despite aggressive radiotherapy and chemotherapy.

We reported the treatment results of L-asparaginase based salvage chemotherapy in the patients with refractory PMPTC-NHL in this paper.

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MATERIALS AND METHODS

Twenty-one patients with refractory PMPTC-NHL were enrolled in this study from January 1990 to February 2000 at the department of Medical Oncology, Beijing Cancer Hospital, Peking University. The diagnosis of the patients was confirmed with biopsy-proven. Cytological spectrum was broad, ranging from small, medium-size to large cells or a mixture of these cells. Some cells had clear cytoplasm or irregular nuclei. All the lesions exhibited an immunophenotype of LCA (CD_{45})+, CD_{45RO}+, CD_{43}+, CD_{45RA}-, CD_{20}-. The expression of CD_{56} and EBV was not evaluated. Angiocentric growth and focal necrosis presented in 14 patients of the 21 patients (66.7%). For the purpose of the study, all the eligible patients were refractory cases who failed to attain CR or deteriorated with local radiotherapy and CHOP-like combination chemotherapy.

Age was between 12 and 68 years, median 40 years. 14 were men, 7 women (male female were 2:1). Patients were staged according to the Ann Arbor system. Clinical staging (CS) procedures included complete physical examination, full blood counts, blood biochemistry, chest

tomograms, ultrasonic examination of the stomach, liver, spleen, and celiac lymph nodes, bone marrow aspirate, electrocardiography, computed tomography of the chest. Work-up showed that 2 patients (9.5%) were CS I, II, 19 cases (90.5%) CS III, IV. 18 cases (85.7%) had fever. According to the international non-Hodgkin's lymphoma prognostic index (IPI) model,[3] 2 patients (9.5 %) were assigned to low risk group and low intermediate risk group, 19 patients (90.5%) high intermediate group and high risk group.

Eleven patients (L-ASP group) were treated with L-ASP based salvage chemotherapy. The regimen was as follows: L-ASP 5000 IU /m^2 IV infused in 500 ml of 5% dextrose solution over 30 minutes daily on days 1 through 7.Skin test to L-ASP must be negative prior to drug administration. Dexamethosone 10 mg IV daily on days 1 through 7. Vincristine 1 mg /m^2 IV on day 1. Cycles were repeated every 21–28 days. The patients of L-ASP group received 4–6 cycles of L-ASP based regimen .10 patients （control group ） received salvage combination chemotherapy without L-ASP , consisting of Ifosfamide, Etopside, Cisplatin or Ara-c etc.

In this study, tumor response was assessed with WHO criteria.[4] Overall survival (OS) curves were established using Kaplan-Meier method. Log-rank method was used to compare the OS curves. X^2 test was used to test response rates and other individual clinical characteristics. The study was non-randomized, but the clinical characteristics of the L-ASP group and control group were similar as seen in Table 1.

Table 1.Comparison of clinical characteristics between two groups of patients

Characteristics	L-ASP group		Control group	
	No. of patients	(%)	No. of patients	(%)
Sex				
Male	9	(81.8)	5	(50.0) *
Female	2	(18.2)	5	(50.0) *
Age Median (years)	35		42	
Primary sites of disease				
Nose, paranasal sinuses	5	(45.5)	3	(30.0) *
Nasopharynx,	5	(45.5)	6	(60.0) *
Palate	1	(9.1)	1	(10.0) *
Histological characteristics				
T-cell	11	(100.0)	10	(100.0) *
Angiocentric growth, focal necrosis	7	(63.6)	7	(70.0) *
Clinical stage of disease				
I, II	1	(9.1)	1	(10.0) *
III, IV	10	(81.8)	9	(90.0) *
Fever	9	(81.8)	9	(90.0) *
IPI model**				
Low risk group, low intermediate risk group;	1	(9.1)	1	(10.0) *
High intermediate risk group, High risk group	10	(90.9)	9	(90.0) *

**IPI model: International prognostic index model[6] *$P>0.05$

RESULTS

Treatment Response and Survival

Complete remission rates were 45.5% and 0.0% for L-ASP group and control group, respectively ($P<0.05$). Overall response rates were 63.6% and 10.0% for L-ASP group and control group ($P<0.05$). 2-year overall survival (OS) rate (45.5%) was higher for L-ASP group than that (0.0%) for control group ($P<0.05$). Median follow-up time was 24 months. The OS survival curves were listed in Figure 1.

Adverse Effects

The main adverse effect of L-ASP was leukopenia. 9 of 11 patients (81.8%) developed leukopenia. Toxicity was graded according to WHO criteria.[4] I grade of leukopenia accounted for 9.1% (1 of 11 cases), II grade 45.5% (5 of 11 cases), III grade 27.3% (3 of 11 cases). 5

of 11 cases (45.5%) occurred elevation of serum bilirubin. I grade of hyperbilubinemia developed in 4 patients (36.4%), II grade in 1 patient (9.1%). 2 patients (18.2%) had hyperglycemia (12.1 mmol/L, 17.2 MMOL/L). ALT elevation occurred in 1 patient (9.1%) (I grade), and BUN elevation in 1 patient (I grade). Hypoalbuminemia (I grade) occurred in 4 patients (36.4%). 1 patient developed allergic rash. Mild nausea and vomiting were also noted in most patients. No bleeding complication occurred. All the patients could tolerate the adverse effects with symptomatic treatment. There was no L-ASP related death.

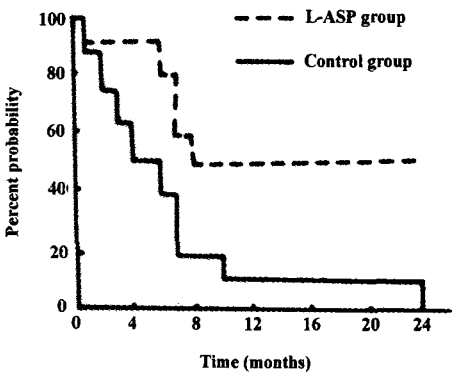

Fig. 1. Overall survival: L-ASP group versus control group

DISCUSSION

This series of patients with refractory PMPTC-NHL had a young median age of 40 years and marked male predominance. 90.5% of patients had CS III, IV diseases. 85.7% of the patients had fever. All of the lesions expressed T-cell associated markers and regarded as peripheral T-cell NHL. The drawback of the study was lack of evaluation of CD_{56} and EBV. 14 of the patients (66.7%) presented angiocentric tumor infiltration and focal necrosis. The histological features of the 14 patients corresponded to angiocentric lymphoma in REAL classification[5] or nasal lymphoma in WHO classification.[6] Clinically, the patients were characterized by rapid progression of disease and responded badly to CHOP-like chemotherapy. It was reported that patients with nasal NK/T-cell lymphoma, especially with CS III. IV diseases and B symptoms, often had poor prognosis and almost died within 2 years despite aggressive chemotherapy.[1, 2] In this clinical study, we used L-ASP based regimen as salvage chemotherapy. L-asparaginase has a different antitumor mechanism from alkylating agents, plant alkaloids and antitumor antibiotics etc. It is well known that L-asparaginase hydrolyzes asparagine. This results in rapid inhibition of protein synthesis and delayed inhibition of DNA and RNA synthesis to yield antitumor effects in certain tumor cells, especially lymphocytes lacking the enzyme L-asparagine synthase. Our preliminary results indicated that L-ASP based regimen possibly improve the response rates and 2-year survival rates in the treatment of refractory PMPTC-NHL. Owing to the rarity of PMPTC-NHL, it is necessary to collect more cases to make conclusion.

In this series, the major adverse effects of L-ASP were leukopenia, liver compromise, hyperglycemia. Acute serious hypersensitivity, acute pancreatitis and bleeding were not observed but reported in other papers. It should be emphasized that skin test to L-ASP must be performed before drug administration and L-ASP should only be used in hospitalized patients under close supervision. Appropriate agents for treating acute hypersensitive reaction must be available. Hyperglycemia can be treated with low dose regular insulin.

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