

ESHAP Salvage Therapy for Relapsed or Refractory Non-Hodgkin's Lymphoma

The ESHAP regimen, a combination of the chemotherapeutic drugs etoposide, methylprednisolone (solumedrol), high-dose cytarabine (ara-C), and cisplatin, has been shown to be active against refractory or relapsed non-Hodgkin's lymphoma (NHL) in therapeutic trials. We undertook this study to determine whether this regimen would be effective and tolerable in Korean patients. A total of 40 patients with refractory or relapsed NHL (8 indolent and 32 aggressive) were enrolled in this study. The overall response rate was 70% (95% confidence interval; 59.8-89.7%); 22.5% of patients achieved a complete response and 47.5% a partial response. The median survival duration was 12 months (95% confidence interval; 5.9-18.1 months) and the median duration of progression-free survival was 9 months (95% confidence interval; 1.1-16.9 months). The median survival duration of patients with relapsed NHL was longer than that of patients with refractory lymphoma (15 months vs 4 months, $p=0.02$). Myelosuppression was the most frequent complication and treatment-related mortality was noted in two patients. These results suggest that the ESHAP regimen is effective in patients with relapsed NHL who have a sensitive disease. The role of ESHAP chemotherapy in discriminating patients who are more likely to benefit from a subsequent transplant should be evaluated in the future.

Key Words : Lymphoma, Non-Hodgkin; Salvage Therapy; Recurrence

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INTRODUCTION

Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of lymphoproliferative malignancies with differing patterns of responses to treatment (1). A combination chemotherapy regimen such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) is effective for patients with aggressive NHL, but nearly 50% of patients do not go into complete remission (CR) and approximately 10% to 20% of patients with CR eventually experience relapses (2). For those who are refractory to the first-line therapy or relapse at a later time need additional therapy, but the long-term prognosis is dismal.

As a new way of cure, high-dose chemotherapy (HDC) with hematopoietic stem cell transplantation (HSCT) has become the gold standard as compared to the conventional salvage therapy (3). However, patients with an old age, poor performance status, or prior history of chemotherapy resistance are not candidates for this approach, and an effective salvage regimen for these patients is needed. For patients with a primary refractory disease, a recent study emphasizes the importance of chemosensitivity in determining the outcome of HDC with HSCT (4). It is suggested that patients with primary refractory aggressive NHL should be treated with

second-line chemotherapy, and HDC with HSCT should be a treatment option for patients with a chemosensitive disease. Considering this point, to find an effective salvage regimen for refractory or relapsed NHL is important.

ESHAP is a combination chemotherapy regimen consisting of etoposide, methylprednisolone, cytosine arabinoside, and cisplatin, and its efficacy and feasibility in relapsed or refractory NHL was reported by Velasquez et al. (5) for the first time, and followed by others (6, 7). However, few studies have been reported on the effects of an ESHAP regimen in Korean patients. To determine the effect and tolerability of ESHAP chemotherapy as a salvage regimen for the Korean patients, we undertook this retrospective study.

MATERIALS AND METHODS

Eligibility

Between January 1996 and February 2000, 40 patients who visited the Korea University Anam and Guro Hospital were enrolled in this study. All patients had evaluable NHL that was primary refractory or had relapsed after one doxorubicin-based regimen. Inclusion criteria were: histologic diag-

nosis of NHL, refractory or relapsing after one or more chemotherapy regimens; age younger than 75 yr; performance status less than 2; normal hepatic, renal, and bone marrow functions; and signed informed consent. They were graded according to the Ann Arbor classification and international prognostic index (IPI), and the disease was reclassified according to the REAL classification. We only distinguished between indolent and aggressive forms of lymphoma in the results and for discussion.

Treatment

The ESHAP regimen consisted of etoposide (40 mg/m², days 1-4), methylprednisolone (500 mg, days 1-5), ara-C (2 g/m², day 5), and cisplatin (25 mg/m², days 1-4), using its original schedule with dose modifications (5). Cycles were repeated every 3-4 weeks, provided that a minimum of 1.0 × 10⁹/L absolute neutrophil count (ANC) and 100 × 10⁹/L platelets had been reached.

Evaluation

The response to salvage therapy was assessed after a minimum of two courses of chemotherapy. The standard WHO response criteria were used to assess the response to treatment, and toxicity was also reported using the WHO criteria. The response duration was calculated from the date the response was confirmed to the date the progressive disease was first

observed. Overall survival (OS) was calculated from the first day of the first cycle of the ESHAP therapy to death or the last date the patient was known to be alive. Overall survival curves were plotted with the Kaplan-Meier method.

RESULTS

Patients

A total of 40 patients (36 males and 4 females) aged from 17 to 73 yr (median 43) were enrolled. Patient characteristics are listed in Table 1. Of these patients, 36 (70%) had a WHO performance status grade 0 or 1 and four patients had grade 2. Before the first ESHAP cycle, the disease status was primary refractory in 9 (22.5%) patients, and relapse in 31 (77.5%) patients. Patients with stage II were 17 (42.5%), and those with stage III and IV were 16 (40%) and 7 (17.5%), respectively. The histologic type was indolent in 8 (20%) patients and aggressive in 32 (80%) patients.

Response to ESHAP chemotherapy

The 40 enrolled patients received a total of 154 courses of treatment; the median number of courses per patient was 3.85, with a range of one to eight. Complete response (CR) was achieved in 9 (22.5%) patients and partial response (PR) in 19 (47.5%) patients. Therefore, the overall response rate was 70% (95% confidence interval; 59.8-89.7%) (Table 2). Among nine patients with a refractory disease, none attained CR and four patients achieved PR. The median survival dura-

Table 1. Patient characteristics

Characteristics	No (%)
Number of patients	40
Median age (range) (yr)	43 (17-73)
Male/Female	36/4
WHO performance status	
0-1	36 (90)
2	4 (10)
Serum LDH level	
Normal	28 (70)
Increased	12 (30)
Disease status	
Relapsed	31 (77.5)
Refractory	9 (22.5)
Stage	
Stage II	17 (42.5)
Stage III	16 (40.0)
Stage IV	7 (17.5)
Histology	
Indolent	8 (20)
Aggressive	32 (80)
IPI risk group	
Low	17 (42.5)
Low-intermediate	14 (35.0)
High-intermediate	5 (12.5)
High	4 (10.0)

LDH; lactate dehydrogenase. IPI; international prognostic index.

Table 2. Treatment response in patients with NHL receiving ESHAP chemotherapy

Characteristics	No. (%)
No. of patients	40
Response (%)	
Complete response	9 (22.5)
Partial response	19 (47.5)
Stable disease	5 (12.5)
Progressive disease	7 (17.5)
Total treatment cycles	154
Median	4
Median duration of survival (months)	12
Range	2-53

Table 3. Major toxicities of ESHAP chemotherapy

WHO Grade	Number of cycles (%) (n=154)	
	3	4
Neutropenia	65 (42.2)	35 (22.7)
Thrombocytopenia	61 (39.6)	22 (14.3)
Nausea/Vomiting	50 (32.5)	10 (6.5)
Mucositis	23 (14.9)	7 (4.5)

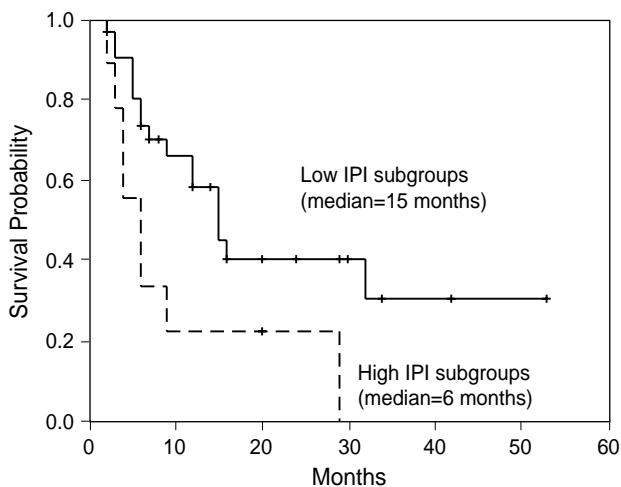


Fig. 1. Overall survival of relapsed/refractory NHL patients according to IPI subgroups.

tion was 12 months (95% confidence interval; 5.9-18.1 months) and the median duration of progression-free survival was 9 months (95% confidence interval; 1.1-16.9 months). We analyzed the survival duration according to the disease status. As a result, the median survival duration of patients with relapsed NHL was longer than that of patients with refractory lymphoma (15 months vs 4 months, $p=0.02$). We also analyzed the overall survival and progression-free survival according to the IPI risk group. The low risk IPI subgroups (low and low-intermediate) showed longer duration of overall survival than the high risk IPI subgroups (high-intermediate and high) (median: 15 months vs 6 months, $p=0.02$) (Fig. 1). The progression-free survival was also longer in the low risk subgroups (median: 11 months vs 0 months, $p=0.02$) (Fig. 2).

Toxicity

The main toxicities encountered with ESHAP chemotherapy were hematologic toxicities (Table 3). WHO grades 3 and 4 neutropenia was observed in 65 (42.2%) and 35 (22.7%) cycles, respectively. Grade 3 and 4 thrombocytopenia was observed in 61 (39.6%) cycles and 22 (14.3%) cycles, respectively. Neutropenic fever was noted in 20 (13%) cycles. Other side effects were nausea, vomiting, and mucositis. Alopecia was detected in all patients. Treatment-related death was observed in 2 patients, and all were non-responders to ESHAP therapy. Sepsis associated with severe neutropenia was the cause of death.

DISCUSSION

The treatment of choice for patients with an advanced stage NHL is the combination chemotherapy either alone or fol-

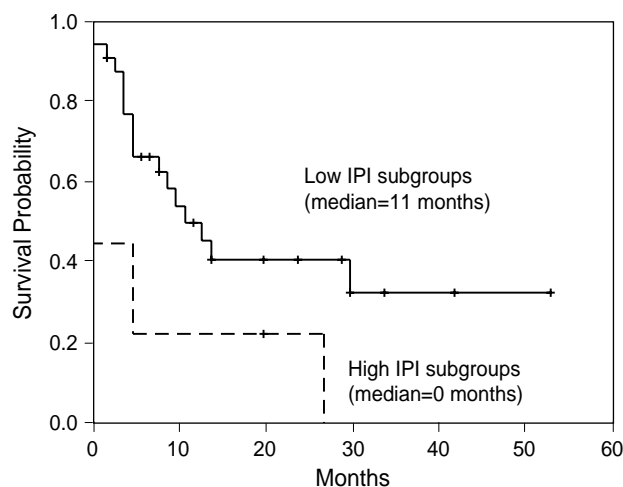


Fig. 2. Progression-free survival of relapsed/refractory NHL patients according to IPI subgroups.

lowed by involved-field radiotherapy (1, 8). Although the CHOP combination chemotherapy remains the best available regimen, the outcome of patients who do not attain response is poor and these patients should be included in phase II trials testing new strategies. The prognosis of partial responders is also poor, particularly for aggressive lymphomas, with only 0% to 25% of patients becoming long-term survivors (9). Thus it is clinically important to have an effective and well-tolerated salvage therapy. Previous studies for recurrent or refractory NHL involved IMVP-16 (ifosfamide, methotrexate, and etoposide) (10), MIME (methyl-gag, ifosfamide, methotrexate, and etoposide) (11), DHAP (cisplatin, ara-C, and dexamethasone) (12), and EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone) (13). The IMVP-16 study included NHL patients with various histologic types and the overall CR rate was 37%. Thirty-four patients had a diffuse large cell lymphoma and their long-term survival was 20%. The MIME regimen was used to treat 123 patients with aggressive lymphomas, including 94 with a diffuse large cell histology. The CR rate for the aggressive histologies was 32% and the survival rate was approximately 20%. The DHAP study included 90 patients and 77 had an aggressive histology. Survival rate among the entire group was approximately 25%. The EPOCH regimen included 74 patients and 56 patients had an aggressive lymphoma. The CR rate was 27%. Thus, the four studies are very similar in their results.

In our series, we demonstrated that the ESHAP regimen could achieve an overall response rate of 70% (28/40) in patients with relapsed or refractory NHL, and this is similar to the results from the previous ESHAP trials (5-7). However, none of the 9 patients with a refractory disease attained CR; 4 patients attained PR and the remaining 5 had a progressive disease. Among 4 patients with PR, three relapsed during the follow-up period (duration: 5, 7, and 9 months,

respectively) and only one showed a progression-free survival (duration: 29 months); therefore, this regimen was not effective in refractory NHL. The major toxicities were neutropenia and thrombocytopenia and two patients died of sepsis associated with neutropenia. Although the overall response rate was high, the duration of progression-free survival was relatively short (9 months) and the response of the primary refractory group was poor.

As a new strategy for salvage treatment of lymphoma, high-dose chemotherapy with autologous bone marrow transplantation (ABMT) is currently used. A successful ABMT was first reported by Appelbaum et al. (14), and a favorable impact on survival in patients with relapsed NHL was reported by others (15, 16). For primary refractory cases, a recent study by Kewalramani et al. (4) revealed that there were no survival differences between the partial responders to induction and the induction failure group. They concluded that patients with primary refractory aggressive NHL should receive second-line chemotherapy, with the intent of administering high-dose chemotherapy with ABMT to those with a chemosensitive disease. To discriminate patients more likely to benefit from a subsequent transplant, the ESHAP regimen could be a useful second-line chemotherapy (17). In our series, six patients have undergone ABMT after ESHAP chemotherapy until now (data not shown). We may confirm the effectiveness of the ESHAP regimen to predict a response to ABMT in a subsequent study.

In conclusion, ESHAP chemotherapy was effective and feasible for patients with relapsed NHL. However, in consideration of the short progression-free survival and poor response in the refractory group, a more effective salvage regimen must be sought, and the role of ESHAP chemotherapy to discriminate patients who are more likely to benefit from a subsequent transplant should be evaluated in the future.

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