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ORIGINAL ARTICLE

A multicenter phase II trial of etoposide, methylprednisolone, high-dose cytarabine, and oxaliplatin for patients with primary refractory/relapsed aggressive non-Hodgkin's lymphoma

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Abstract
Purpose We investigated the efficacy and toxicity of the etoposide, methylprednisolone, high-dose cytarabine, and oxaliplatin (ESHAOx), in which oxaliplatin (Ox) was substituted for cisplatin in the ESHAP [etoposide (E), methylprednisolone (S), high-dose cytarabine (HA), and cisplatin (P)] regimen, for patients with refractory/relapsed aggressive non-Hodgkin's lymphoma (NHL).
Materials and methods The ESHAOx consisted of E (40 mg/m^2 on days 1–4), S (500 mg on days 1–5), HA (2 g/m^2 on day 5), and Ox (130 mg/m^2 on day 1) every 3 weeks to a maximum of six cycles. Responses were assessed every three cycles.
Results Twenty-seven patients were enrolled (19 with relapsed and 8 with refractory; 10 with an IPI score of 3–5). The overall response rate was 63% [95% confidence interval (95% CI) 45–81%], including eight complete remissions (CR) and one unconfirmed CR (33%). The median duration of response was 9.9 months (95% CI 5.7–14.2 months). After a median follow-up of 18.6 months, the median progression-free and overall survival was 5.3 months (95% CI 3.9–6.7 months) and 15.1 months (95% CI 9.4–20.9 months), respectively, with a 1-year survival rate of 61.5%. Most common grade 3/4 hematologic toxicities were neutropenia (56%) and thrombocytopenia (35%), whereas no patient experienced grade 3/4 renal or neurotoxicity.
Conclusion The efficacy and toxicity profiles suggested that the ESHAOx can be an alternative option for patients with refractory/relapsed aggressive NHL.

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Introduction

Aggressive non-Hodgkin's lymphoma (NHL) is usually chemotherapy-sensitive and curable disease. However, despite the high degree of responsiveness to CHOP and CHOP-like induction regimen, 40–50% of these patients fail to achieve a complete response (CR) or relapse after front-line therapy [1]. The patients with refractory or relapsed aggressive NHL have poor long-term outcomes. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has been established to treat patients with chemotherapy-sensitive relapse [2]. The primary goal of salvage chemotherapy, therefore, is to achieve a high response rate for subsequent ASCT or, for patients not eligible for ASCT, to achieve durable remission duration with acceptable toxicity.

Platinum-containing regimens, such as DHAP (dexamethasone, cytarabine, and cisplatin), ESHAP, and ICE (ifosfamide, carboplatin, and etoposide), are commonly used for salvage chemotherapy [2–8]. In patients with refractory or relapsed NHL, these regimens have resulted in response rates (RR) of 40–70%, including CR rates of 20–30%, with 3-year survival rates of 15–30%. The renal and neurological toxicities of these regimens, however, preclude further treatment in many patients and reduce the impact of platinum therapy on survival [3–6].

Oxaliplatin, a novel platinum derivative with a 1,2-diaminocyclohexane carrier ligand [9], has a different cytotoxicity profile than cisplatin and carboplatin do; in many cell lines, oxaliplatin shows no or partial cross-resistance with cisplatin [10]. Furthermore, oxaliplatin is active in the treatment of primary refractory or relapsed NHL, either as a single agent or in combination with other agents [11–14]. In contrast to cisplatin, oxaliplatin has minimal renal and auditory toxicities. These findings suggested that oxaliplatin (Ox), in combination with etoposide (E), methylprednisolone (S), and high-dose cytarabine (HA), would be safe and effective in patients with primary refractory or relapsed aggressive NHL.

Materials and methods

This was an open-label, single-arm, multicenter phase II study. The primary endpoint was overall response rate to the etoposide, methylprednisolone, high-dose cytarabine, and oxaliplatin (ESHAOx). The secondary endpoints included safety and survival outcomes, such as duration of response (DR), progression-free survival (PFS), and overall survival (OS). The study was approved by each participating institution's ethics committee, and written informed consent was obtained from each patient.

Eligibility criteria

All patients had pathologically confirmed, measurable, refractory or recurrent NHL, according to the World Health Organization (WHO) classification [15]; were previously treated with CHOP or CHOP-based chemotherapy; had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3; had adequate bone marrow function, defined as absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L; had adequate liver function, defined as total bilirubin level $\leq$2 times the institutional upper limit of normal (ULN), and levels of serum transaminases $\leq$3 times the institutional ULN; and were negative for human immunodeficiency virus. Patients with symptomatic central nervous system involvement and pregnant or breastfeeding women were excluded. Patients with grade 2 or more peripheral neuropathy at the time of study entry were also excluded.

Pretreatment assessments

At screening, every patient underwent a full medical history and physical examination, including evaluation of ECOG PS and vital signs. Laboratory studies included a complete blood count with differential and serum chemistry profile [including levels of creatinine, lactate dehydrogenase (LDH), and β_2 microglobulin]. Patients with previously documented bone marrow infiltration and those clinically suspected of bone marrow involvement with current relapse underwent bone marrow aspiration and biopsy. Radiologic examination, including a chest radiograph and CT scans of the chest, abdomen, pelvis, and other involved disease sites, were required within 3 weeks of starting treatment.

Treatment

The ESHAOx consisted of E [40 mg/m^2 intravenously (i.v.) over 2 h on days 1–4], S (500 mg i.v. over 15 min on days 1–5), HA (2.0 g/m^2 i.v. over 2 h on day 5), and Ox (130 mg/m^2 i.v. over 2 h on day 1) every 3 weeks for a maximum of six cycles. No pre- or post-chemotherapy hydration was required for oxaliplatin administration. Patients received standard antiemetic treatment as per the practice of each institution. Treatment was halted for documented disease progression, unacceptable adverse events, or patient withdrawal. At the investigator's discretion, candidates for ASCT could be removed from the study and proceed to stem cell mobilization.

The subsequent cycle was delayed if ANC was $<1.5 \times 10^9$/L or platelet count was $<75 \times 10^9$/L on the first day of infusion. Nonhematologic toxicities, excluding alopecia, nausea, and vomiting, should be resolved to grade 1 or less prior to the initiation of each cycle. If an event did not resolve within 3 weeks following the time of planned treatment, the patient was withdrawn from the study.

Doses of etoposide, cytarabine, and oxaliplatin were reduced by 20% in subsequent cycles in patients with grade 4 neutropenia for more than 7 days; febrile neutropenia; grade 4 thrombocytopenia; grade 3 or 4 nonhematologic toxicities. Prophylactic G-CSF was permitted at the physician's discretion.

Efficacy and safety assessments

Responses were evaluated by the International workshop Criteria [16] after the third cycle and after 1 month from the end of the entire protocol. Adverse events were graded according to the NCI CTCAE v.3.0.

Statistical analysis

The primary end point was overall response rate (ORR). Simon's two-stage optimal design was used to determine the sample size and decision criteria for this phase II study. With a target activity level of 60% and the lowest RR of interest set at 30%, 24 patients would be required with a 90% power to accept the hypothesis and a 5% significance level to reject the hypothesis. The study was designed to be halted if four or fewer of the first eight patients responded; and, if 10 or fewer responses were observed by the end of the study, no further investigation of the drug would be warranted. Allowing for a loss to follow-up rate of 10%, a total of 27 patients was required. Demographic, safety, and laboratory data were analyzed using descriptive statistics, while survival analysis methods based on Kaplan–Meier estimates were used to analyze survival outcomes, including DR, PFS, and OS. DR was calculated from onset of an objective response to subsequent disease progression, death, or last contact, whichever was earliest. For all patients, PFS was measured from the initiation of chemotherapy to disease progression, last contact, or death, whichever was earliest. OS was measured from the initiation of chemotherapy to death or last contact, whichever was earliest.

Results

Patient characteristics

A total of 27 patients from eight institutions were enrolled between April and December 2006. Patient characteristics are summarized in Table 1. Eleven patients (41%) were above the age of 60 years, 17 (63%) had elevated LDH, and 20 (74%) had stage III or IV disease on entry into the study. Eight patients (30%) had failed to achieve CR following their induction regimen and six (22%) did not respond to their last treatment regimens. Of note, six patients (22%) were previously treated with a platinum-containing regimen (ESHAP, DHAP, or ICE). Nineteen patients (70%) were previously treated with rituximab combined with CHOP or CHOP-like regimens. One patient had received prior high-dose chemotherapy and ASCT. The most frequent histologic subtype was diffuse large B cell lymphoma (74%); in two patients, it had been transformed from indolent lymphoma.

Table 1 Baseline characteristics ($n = 27$)

Characteristics	Number	Percentage
Male:female	17:10	63:47
Age > 60 years	11	41
ECOG PS 0-1:2	24:3	89:11
Extra-lymphatic involvement	14	52
Elevated serum LDH (>250 IU/L)	17	63
Ann Arbor stage III or IV	20	74
International prognostic index		
Low/low-intermediate	17	63
High-intermediate/high	10	37
Histology		
Diffuse large B cell[a]	20	74
Peripheral T cell	3	11
NK/T cell	2	7
Follicular Gr3	1	4
Anaplastic large cell	1	4
Number of previous treatments		
1	16	59
2	6	22
≥3	5	19
Prior regimen		
Rituximab plus CHOP or CHOP-like regimen	19	70
Platinum-containing regimen	6	22
Disease status		
Primary refractory	8	30
First relapse	14	52
Second or subsequent relapse	5	18
Response to the last treatment before the ESHAOx		
Nonresponder	6	22
Responder[b]	21	78

Median age (range): 54 years (35–71 years); time from last treatment, median (range): 8.1 months (0.8–51.1 months)

[a] Two patients were transformed from indolent lymphoma

[b] Patients who achieved at least partial response to their last treatment regimens

Efficacy and survival results

Twenty-five patients completed at least three cycles of therapy. One patient was lost to follow-up after receiving one cycle and another one died of treatment-related causes after two cycles. These two patients are included in the response and survival analysis based on the intent-to-treat analysis. An ORR after three cycles of the ESHAOx was 63% (95% CI 45–81%), including five CRs (19%) and 12 PRs (44%). At the end of completion of the study, three patients with a PR had achieved a CR and one with a PR achieved an unconfirmed CR (CRu), resulting in a CR/CRu rate of 33%. Of the 21 patients having experienced at least a PR to their last treatment, seven achieved a CR, one achieved a CRu, and eight achieved a PR, resulting in an RR of 76%, while among the six patients having not responded to their last treatment, only one achieved a CR, resulting in an RR of 17% ($P = 0.015$). Of the six patients treated previously with platinum-containing regimens, one achieved a CR and three achieved a PR, resulting in an RR of 67%. Responses to the ESHAOx are presented in Table 2. The median RD in the 17 responding patients was 9.9 months (95% CI 5.7–14.2 months). After a median follow-up of 18.6 months, the median PFS and OS were 5.3 months (95% CI 3.9–6.7 months) and 15.1 months (95% CI 9.4–20.9 months), respectively, with a 1-year survival rate of 61.5% (Fig. 1).

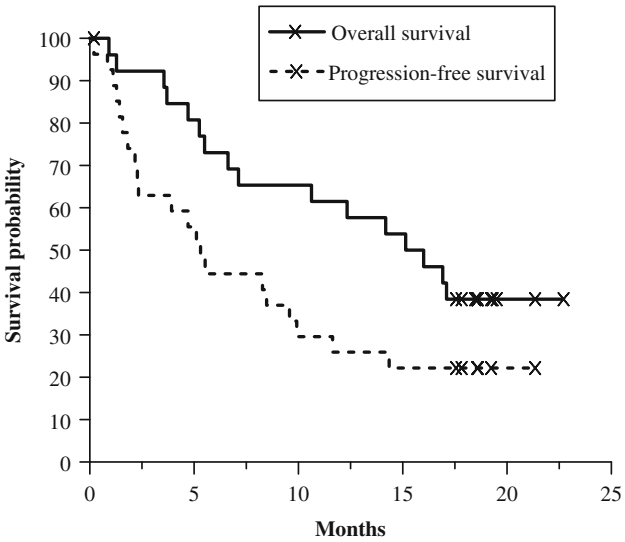

Fig. 1 Overall and progression-free survival for all patients

Treatment-related toxicities

The 27 patients received a total of 103 cycles of the ESHAOx treatment, with a median number of four cycles per patient. Except one who was lost to follow-up after one cycle, 26 patients were assessable for toxicity. The reasons for cessation were planned decision ($n = 8$), high-dose

Table 2 Responses to the ESHAOx combination

Characteristic	No.	After third cycle		At the end of treatment	
		ORR	CR/CRu	ORR	CR/CRu
		No. (%)	No. (%)	No. (%)	No. (%)
All patients	27	17 (63)	5 (19)	17 (63)	9 (33)
IPI					
Low/low-intermediate	17	12 (71)	4 (24)	12 (71)	7 (58)
High/high-intermediate	10	5 (50)	1 (10)	5 (50)	2 (20)
Prior treatment regimen					
Rituximab plus CHOP or CHOP-like	19	12 (63)	4 (21)	12 (63)	7 (37)
Platinum-containing	6	4 (67)	0	4 (67)	2 (33)
Disease status					
Primary refractory	8	4 (50)	0	4 (50)	2 (25)
First relapse	14	8 (57)	4 (29)	8 (57)	5 (36)
Multiple relapse	5	5 (100)	1 (20)	5 (100)	2 (40)
Response to the last treatment before the ESHAOx[a]					
Nonresponder	6	1 (17)	0	1 (17)	1 (17)
Responder[a]	21	16 (76)	5 (19)	16 (76)	8 (38)
Duration of last remission					
≤1 year	12	8 (67)	3 (25)	8 (67)	4 (33)
>1 year	9	8 (89)	2 (22)	8 (89)	4 (44)

ESHAOx etoposide, methylprednisolone, high-dose cytarabine, and oxaliplatin; *ORR* overall response rate; *CR* complete remission; *CRu* unconfirmed CR

[a] Patients who achieved at least partial response to their last treatment regimen

Table 3 Adverse events during the ESHAOx treatment ($n = 26$)

	Worst toxicity grade by patient (%)			
	1	2	3	4
Leukopenia	4 (15)	5 (19)	4 (15)	6 (23)
Neutropenia	3 (12)	3 (12)	2 (8)	13 (50)
Anemia	9 (35)	9 (35)	4 (15)	1 (4)
Thrombocytopenia	4 (15)	3 (12)	3 (12)	6 (23)
Febrile neutropenia[a]	–	–	3 (12)	1 (4)
Sensory neuropathy	16 (62)	2 (8)	0	0
Motor neuropathy	3 (12)	0	0	0
Nausea	12 (46)	1 (4)	0	0
Vomiting	5 (19)	0	0	0
Diarrhea	3 (12)	1 (4)	1 (4)	0
Hepatic toxicity	5 (19)	0	1 (4)	0
Stomatitis	2 (8)	0	0	0
Asthenia	5 (19)	1 (4)	0	0
Alopecia	8 (31)	1 (4)	0	0
Myalgia	5 (19)	0	0	0

One patient was lost to follow-up after cycle

ESHAOx etoposide, methylprednisolone, high-dose cytarabine, and oxaliplatin

[a] One patient died after febrile neutropenia or grade 5 (4%)

chemotherapy with ASCT ($n = 7$), treatment failure ($n = 8$), patient refusal ($n = 1$), and toxicity ($n = 3$). The latter three patients stopped treatment because of treatment-related death following neutropenic fever, reactivation of preexisting viral hepatitis, and prolonged grade 3 neutropenia for more than 3 weeks, respectively. The adverse events are listed in Table 3. Grade 3/4 neutropenia occurred in 15 patients (58%), of whom five developed febrile neutropenia. Only two patients received prophylactic growth factor support at the subsequent cycle. Grade 3/4 thrombocytopenia developed in nine patients (35%), but none experienced significant hemorrhage. The most common nonhematologic toxicity was sensory neuropathy in 18 (70%) patients, but it was limited to grade 1 or 2. No pharyngolaryngeal dysesthesia, a well-known adverse effect of oxaliplatin, was observed in the current study as well as grade 1 or more renal toxicity.

Stem cell mobilization and ASCT after the ESHAOx

Out of 17 patients under the age of 65 years, who might be eligible for ASCT before starting the ESHAOx, 10 (59%) achieved at least a PR after 3 cycles. Except two patients, one who experience progression of the disease in bone marrow after five cycles, and the other who experience progression in cervical lymph node after six cycles, the remaining eight patients underwent stem cell mobilization with the ESHAOx plus G-CSF, with a median number of CD34-positive cells collected of 6.4×10^6/kg (range 2.8–11.6×10^6/kg), obtained from one to three times of leukapheresis. Seven patients received high-dose chemotherapy and ASCT, whereas one declined it. The median time to neutrophil recovery (>0.5×10^9/L) was 10 days (range 9–17 days), and the median time to platelet recovery (>20×10^9/L) was 12 days (range 9–18 days).

After a median follow-up of 18.7 months for survivor from the first day of the ESHAOx treatment, the median PFS of the seven patients undergoing ASCT was 14.4 months (95% CI 7.4–21.3 months) and the median OS was not yet reached.

Discussion

We have demonstrated that the ESHAOx showed promising activity in patients with primary refractory or relapsed aggressive NHL. The ORR of 63% and the CR/CRu rate of 33% were comparable to those of other salvage regimens, which showed ORRs of 40–70%, including CR/CRu rates of 20–30% [2–8, 13]. Notably, these responses to the ESHAOx were observed in heavily pretreated patients with several poor prognostic features, including primary refractory disease [17], relapse within 1 year [18], and high-intermediate/high IPI score at relapse [19]. The responsiveness to the ESHAOx seemed to be related to prior response to the last treatment. However, there was no difference in response rates between those having prior history of platinum-based chemotherapy or those having not, suggesting that there might be non- or incomplete cross resistance between oxaliplatin and cisplatin [20, 21]. These findings suggest that the ESHAOx may be a good alternative option for patients who have failed or could not tolerate other platinum-based chemotherapy, such as DHAP and ESHAP, considering that, although platinum-based regimens are

frequently adopted as salvage regimens for patients with refractory or relapsed NHL [2–6], these have substantial treatment-related toxicities, such as renal impairment, and even treatment-related mortalities in more than 5% [3, 4, 6]. Substitution of oxaliplatin for cisplatin in the DHAP regimen resulted in more favorable nonhematologic toxicity profiles, but the DHAOx were also associated with frequent grade 3/4 hematologic toxicity of 66–75% and grade 3/4 thrombocytopenia of 76–86% [13, 14]. In the current study, the most common and significant toxicity of the ESHAOx was also hematologic toxicity with frequencies of grade 3/4 neutropenia of 58% and grade 3/4 thrombocytopenia of 35%, yet more favorable than the DHAP or DHAOx [13, 14]. We also observed favorable nonhematologic toxicity. Notably, considering that no hydration was required and no renal toxicity was observed, this ESHAOx regimen may be advantageous in elderly or frail patients with multiple comorbidities or in patients with decreased left ventricular ejection fraction or overt congestive heart failure due to prior treatment with doxorubicin. Some concerns peripheral neuropathy, the most common nonhematologic toxicity of oxaliplatin, but in the current study, 70% of the patients experienced mild and reversible neuropathy only, which was limited to grade 1 or 2. It might be in part due to low cumulative dose of oxaliplatin with a median cumulative dose of oxaliplatin of 520 mg m^{-2} (range 130–780 mg m^{-2}), considering that the risk of functional impairment was estimated at 10% in patients receiving a cumulative oxaliplatin dose of 780 mg/m^2 [22].

On the other hand, although not an initially planned end point, even in heavily treated patients, adequate numbers of CD34-positive cells could be collected during mobilization and hematopoietic engraftment could occur within the expected time. The Parma trial clearly demonstrated that high-dose chemotherapy with ASCT increases survival outcomes in younger patients with relapsed NHL [2]. Response to salvage chemotherapy is correlated with post-transplant survival [23]. However, not all patients can undergo high-dose chemotherapy with ASCT, because of unsuccessful mobilization, preexisting nonhematologic toxicity, or comorbidity. Therefore, effective salvage therapy prior to high-dose chemotherapy with ASCT should have significant cytoreductive activity, little extrahematologic toxicity, and sufficient mobilizing capacity to allow the collection of adequate numbers of peripheral stem cells. Therefore, the ESHAOx might be a good alternative therapeutic option for candidates for high-dose chemotherapy with ASCT and further studies will be required.

In conclusion, the ESHAOx showed promising activity with an acceptable toxicity profile in patients with primary refractory or relapsed aggressive NHL, and this treatment could be a good alternative option. In addition, the ESHAOx was not likely to affect subsequent high-dose chemotherapy with ASCT, warranting further studies in this clinical setting.

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