Original Article

Comparison of Ifosfamide, Carboplatin and Etoposide versus Etoposide, Steroid, and Cytarabine Cisplatin as Salvage Chemotherapy in Patients with Refractory or Relapsed Hodgkin's lymphoma

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Abstract

Background: Refractory or relapsed Hodgkin's disease (HD) occurs in 10-50% of patients. The treatment of choice for these patients is high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT). Response to salvage chemotherapy (SCT) partial remission (PR) is necessary before HDCT with ASCT. However, its applicability is restricted mostly to patients responding to salvage chemotherapy. Optimal salvage regimen for these patients is unclear. In this study, our aim was to compare the efficacy profiles of ifosfamide, carboplatin, and etoposide (ICE) and etoposide-steroid-cytarabine-cisplatin (ESHAP) (cytosine arabinoside, cisplatin, and dexamethasone) regimens in the salvage treatment of relapsed or refractory HD. **Materials and Methods:** In this retrospective analysis, 114 patients with primary refractory or relapsed HD who received ICE or ESHAP salvage regimen were included. **Results:** Of 114 patients, 47 (41.2%) were females and the median age was 31.5 years. Response could be evaluated in 114 patients. Of 114 patients, 38 (33%) achieved complete remission (CR) and 21 (18.4%) achieved PR, leading to an overall response rate (ORR: CR + PR) of 51.4%. In the evaluable ICE group (n = 41), rates of CR, PR, and ORR were 21.9%, 17.1%, and 39% and in the ESHAP group (n = 73), rates of CR, PR, and ORR were 39.7%, 19.2%, and 58.9% (for ORR, P = 0.04), respectively. **Conclusion:** In patients with relapsed or refractory HD, treatment with ESHAP seems to have higher rates of response than ICE regimen does.

Keywords: *Carboplatin, etoposide, etoposide-steroid-cytarabine-cisplatin, Hodgkin's lymphoma, ifosfamide, refractory, relapse*

Introduction

Over 90% of patients with localized Hodgkin's disease (HD) get cured. In patients with good prognostic factors, extended field radiotherapy (RT) had a high cure rate. Increasingly, patients with all stages of HD are treated initially with chemotherapy (CT).[1,2]

The prognosis of Hodgkin's lymphoma patients has improved very much.[2,3] Although new CT regimens plus new RT techniques and immunotherapy result in high complete remission (CR) rates, 10-30% of patients with HD do not achieve a CR. Also 40-60% of patients suffer relapse shortly after achieving CR.[4-12]

The patients with refractory or relapsed HD still have a poor prognosis.[4] Currently, high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is the treatment of choice for such relapsed or refractory patients.[4,13-19]

In addition, superiority of HDCT followed by ASCT compared with conventional salvage chemotherapy (SCT) in relapsed or refractory disease was demonstrated in prospective trials for HD and NHL (Non-Hodgkin's Lymphoma).[4,14,16,17] It was also shown that a maximal reduction of tumor load prior to transplantation is important.[4,13,15,18,20,21]

A number of SC (Salvage Chemotherapy) regimens have been proposed in order to provide maximum cytoreduction before HDCT and improve the outcome of patients with relapsed or refractory lymphoma.

Most commonly used SC regimens including DHAP (Dexamethasone, High

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dose cytozin Arabinozid, Platinium which nowadays its expansion is known as cytosine arabinoside, cisplatin, and dexamethasone), etoposide-steroid-cytarabine-cisplatin (ESHAP which previously was the abbreviation of Etoposide, Steroid, High dose cytozin Arabinosid, Platinium and today stands for the mentioned expansion) (etoposide, methylprednisolone, high-dose cytosine Arabinoside, and Cisplatin), IIVP (Ifosfamide, Idarubicin, and VeP), and ifosfamide, carboplatin, and etoposide (ICE) with or without rituximab(R) can lead to CR of 10-60% and overall response rate (ORR) of 40-80%.[4,21-30] Optimal SC regimen for these patients is unclear and it needs more studies to improve transplant eligibility and long-term outcome.

In our study, the aim was to compare the efficacy of the two salvage regimens, namely ESHAP and ICE, in the treatment of relapsed or refractory Hodgkin's lymphoma, retrospectively.

Materials and Methods

Patients

In this double center retrospective analysis, 114 patients who had complete data, with primary refractory or relapsed HD who received ICE or ESHAP SCT at the Medical Oncology Department of Esfahan and educational hospitals of Shiraz University from April 2002 to April 2012 were included. Inclusion criteria were as follows: Adequate organ function as defined by a left ventricular ejection fraction greater than 45%; creatinine clearance ≥60 mL/min; total bilirubin <2 mg/dL; and serum transaminase levels <3× upper limit of normal value. The patients with incomplete data were exited from our study. There was no age restriction.

Primary refractory disease was defined as failure to achieve CR with a front-line regimen or CR duration of <3 months after the completion of CT or progression during front-line treatment. Early relapse was defined as a CR lasting for ≥3 months but <12 months and late relapse as ≥12 months.[3-5,8,31,32]

All patients had biopsy-proven Hodgkin's lymphoma. Details of patient characteristics and disease status prior to SCT were obtained. Patient's first-line CT regimen was ABVD (Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine). Current stage was evaluated.[33] For staging purposes; the patients' files which included their physical examination results, chest X-ray and computed tomography scans, bone marrow aspirate and biopsy, and gallium scans, were reviewed.

Salvage therapy

Seventy-three patients were given ESHAP and 41 patients were given ICE. After completion of the treatment, patients were followed up. The ESHAP regimen typically was administered for every 3-4 weeks: Etoposide, 40 mg/m^2 on days 1-4 given intravenously; methylprednisolone, 500 mg on days 1-4 given intravenously; cytarabine, 2000 mg/m^2 on day 5 given intravenously; and Cisplatin, 25 mg/m^2 on days 1-4 given intravenously.[28,34,35]

The ICE regiment was administered as follows: Ifosfamide, 1670 mg/m^2 with an equal dose of MESNA (2-Mercapto Ethane SulfuNAte), IV on days 1, 2, and 3; carboplatin (area under the curve = 5, Calvert's formula to a maximum dose of 800 mg) IV on day 2; etoposide, 100 mg/m^2/d IV on days 1, 2, and 3; and G-CSF (Granulocyte Colony Stimulating Factor) administered at 5 μg/kg on days 5-12 subcutaneously.[4,15,26,31,36]

Assessment of response

Response to therapy was decided on the basis of comparison of case records assessed by physical examination of all palpable lymph node regions (before each course) and computed tomography scans of the involved sites performed before and after the 2nd or 3rd courses of SC according to the standard response definition criteria by the International Working Group.[4,37] A CR was defined as the disappearance of all clinical and radiographic evidence of disease for at least 1 month. Partial remission (PR) was defined as a greater than 50% reduction in the product of the largest diameter and its perpendicular to measurable disease lasting more than 1 month. Any response less than PR were considered failure of treatment.[4]

Statistical analysis

For data analysis, computer-based statistical package for social sciences for windows, version 19.0 (SPSS 19.0) was used. Differences between dichotomous variables were tested by Chi-square test. Unless otherwise stated, all the *P* values were two-sided with a *P* value of 0.05 was considered statistically significant.

Results

Patient characteristics

Median age of patients was 31.5 years (range: 15-69 years). Of 114 relapsed or refractory patients, 67 (58.8%) were male and 78 patients (78.9%) were younger than 45 years. Patients' clinicopathological characteristics are summarized in Table 1.

Efficacy

Response could be evaluated in all patients (100%). Of them, 38 (33%) patients achieved CR and 21 (18.4%) achieved PR, leading to an ORR of 51.4%. In the ESHAP group, rates of CR, PR, and ORR were 39.7%, 19.2%, and 58.9%, respectively. In the ICE group, rates of CR, PR, and ORR were 21.9%, 17.1%, and 39%, respectively. The response rates for ESHAP regimen seem to be higher than those for ICE that was statistically significant ($P = 0.04$) [Table 2].

Table 1: Clinical and pathological characteristics of patients

	ESHAP (73) (%)	ICE (41) (%)
Sex		
Male	43 (58.9)	24 (58.5)
Female	30 (41.1)	17 (41.5)
Age		
≥45	15 (20.5)	9 (22)
<45	58 (79.5)	32 (78)
Stages		
1 and 2	45 (61.6)	21 (51.2)
3 and 4	28 (38.4)	20 (48.8)
Disease status at SCT		
Refractory	19 (26.0)	4 (9.7)
Early relapse	18 (24.6)	12 (29.2)
Late relapse	36 (49.4)	25 (61.1)
HB		
≥10	48 (65.8)	27 (65.9)
<10	25 (34.2)	14 (34.1)
LDH		
<480	51 (69.8)	28 (68.2)
≥480	22 (30.2)	13 (31.8)
BM involvement		
No	57 (78.1)	31 (75.6)
Yes	16 (21.9)	10 (24.4)

ESHAP: Etoposide–steroid–cytarabine–cisplatin, LDH: Lactate dehydrogenase, HB: Hemoglobin, BM: Bone marrow, SCT: Salvage chemotherapy, 1-It seems lesser number of patients in stage 3 and 4 was due to their mortality, ICE: Ifosfamide, carboplatin and etoposide

Table 2: Response of relapsed or refractory Hodgkin's disease patients to salvage chemotherapy

Response (%)	ESHAP *n*=73 (100%)	ICE *n*=41 (100%)
CR	29 (39.7)	9 (21.9)
PR	14 (19.2)	7 (17.1)
ORR=CR+PR	43 (58.9)	16 (39.0)
Failure	30 (41.1)	25 (69.0)

CR: Complete response, PR: Partial response, ORR: Overall response rate, ESHAP: Etoposide–steroid–cytarabine–cisplatin, ICE: Ifosfamide, carboplatin and etoposide, HD: Hodgkin's disease

Comparisons

Our study showed that there were no significant statistical differences in below items:

- Female patients (P = 0.404)
- Patients younger than 45 years (P = 0.395)
- Refractory patients (P = 0.275)
- Patients with early relapse (P = 0.053)
- Patients with late relapse (P = 0.761)
- Patients in stages 1 and 2 (P = 0.075)
- Patients in stages 3 and 4 (P = 0.521)[1]
- Patients with hemoglobin equivalent and more than 10 mg/dL (P = 0.273)
- Patients with hemoglobin less than 10 mg/dl (P = 0.340)
- Patients with Bone Marrow involvement (P = 0.146)
- Patients without BM involvement (P = 0.60)
- Those who had lactate dehydrogenase (LDH) more than 480 (P = 0.124)
- Those who had LDH less than 480 (P = 0.155).

But in male patients (P = 0.046) and patients older than 45 years (P = 0.025), statistical differences were significant.

Response to treatment according to clinical and pathological characteristic is summarized in Table 3 for ESHAP group and Table 4 for ICE group.

Discussion

Results of this study show that ORR in ICE group was 39% and that in ESHAP group was 58.9%. In similar studies, ORR of SCT regimens has been reported from 10-80%. For example, Imataki *et al*. reported response rate of 68% with salvage ESHAP regimen versus salvage ACES regimen.[16] Abali *et al*., by comparing ICE and DHAP regimens, reported response rate of 68% with ICE group versus 48% for DHAP regimen.[4]

The treatment outcomes of conventional dose SCT regimens are still not satisfactory especially for primary refractory or relapsed patients.[3-11] Nevertheless, they can achieve long-term disease-free survival after HDCT and ASCT. The role of HDCT and ASCT in the treatment of relapsed or refractory lymphoma was demonstrated in three randomized trials, including BNLI, PARMA, and HD-R1.[4,14,16,17,38] Also, it was shown that the most important factors affecting outcome in HDCT studies are chemo sensitivity to SCT, tumor load, and remission status before HDCT.[4,13,15,18,20,21] Thus, it is clinically important to have an effective and well-tolerated SCT regimen. Numerous regimens have been used for cytoreduction prior to ASCT including DHAP, ICE, ESHAP, and IIVP with or without R. Response rates to these commonly used second-line regimens for patients with relapsed or refractory lymphoma vary between 40% and 80%.[4,21-29] Although these regimens had been found to be effective, they had different toxicity profiles, and unfortunately prospective randomized studies comparing these regimens are lacking. In this study of ICE versus ESHAP, rates of ORR for the entire cohort were 39% and 58.9%, respectively. For example, Moskowitz *et al*. reported response rates of 66% with salvage ICE regimen.[30] Nordic Lymphoma Group reported 59% ORR and the ratio of patients with refractory disease was 27.5%.[4,23] In our series, we demonstrated that the ESHAP regimen could achieve an ORR of 58.9% in patients with relapsed or refractory Hodgkin's lymphoma.

For response to SCT, age, interval time between primary treatment and relapse, hemoglobin, BM involvement, White Blood Cell count, and serum albumin level are the prognostic factors.[39-41] It seems that the other factors such as tumor sensitivity to CT, immunohistochemical characteristics, primary pathology, and sensitivity are undetermined terms.

Table 3: Rate of response in etoposide–steroid–cytarabine–cisplatin group according to clinical and pathological characteristics

	CR (29)	PR (14)	ORR (43)	Failure (30)
Gender (%)				
Male	18 (41.8)	6 (13.9)	24 (55.7)	19 (44.3)
Female	11 (36.7)	8 (26.7)	19 (63.4)	11 36.6)
Age (%)				
≥45	8 (53.3)	1 (6.6)	9 (59.9)	6 (40.1)
<45	21 (36.2)	13 (22.4)	34 (58.6)	24 (41.4)
Disease state at SCT (%)				
Refractory	7 (36.8)	5 (26.3)	12 (63.1)	7 (36.9)
Early relapsed	11 (61.1)	1 (5.5)	12 (66.6)	6 (33.4)
Late relapsed	11 (30.5)	8 (22.2)	19 (52.7)	17 (47.3)
Stage (%)				
I, II	19 (42.2)	7 (15.5)	26 (57.7)	19 (42.3)
III, IV	10 (35.7)	7 (25.0)	17 (60.7)	11 (39.3)
Hb (%)				
≥10	18 (37.5)	12 (25.0)	30 (62.5)	18 (37.5)
<10	11 (44.0)	2 (8.0)	13 (52.0)	12 (48.0)
BM involvement (%)				
Yes	5 (31.2)	3 (18.7)	8 (49.9)	8 (51.1)
No	24 (42.1)	11 (19.3)	35 (61.4)	22 (38.6)
LDH (%)				
≥480	11 (47.8)	3 (13.0)	14 (60.8)	9 (39.2)
<480	18 (36.0)	11 (22.0)	29 (58.0)	21 (42.0)

CR: Complete response, PR: Partial response, ORR: Overall response rate, LDH: Lactate dehydrogenase, HB: Hemoglobin, BM: Bone marrow, SCT: Salvage chemotherapy

Our analysis had several limitations: First, it is a retrospective analysis and the fact that the small number of sample size limits its statistical power is the second limitation. However, to the best of our knowledge, there is no prospective randomized trial comparing salvage ESHAP versus ICE regimens. Third, the initially unmatched treatment groups revealed significant differences in patient's clinicopathological characteristics. Finally, long-term survival such as mortality, morbidity, and outcome of ASCT (if to be done) were not evaluated.

We suggest more similar prospective randomized trial study to be done with more variable salvage regimen and evaluation of more factors, such as primary pathology of tumor, cytogenetic differences, immunohistochemical studies, and patient's long-term survival to determine optimal SCT regimen for these patients.

Despite its limitations, our study gives an idea on the efficacy and tolerability of both regimens in the treatment of patients with relapsed or refractory Hodgkin's lymphoma. In Iran, our evaluation was the first study for comparison of SCT regiments in HD. In similar studies, patients were included in both HL and NHL, but in our study there were only HD patients.

Table 4: Rate of response in ifosfamide-carboplatin–etoposide group according to clinical and pathological characteristics

	CR (9)	PR (7)	ORR (16)	Failure (25)
Gender (%)				
Male	3 (12.5)	5 (20.8)	8 (33.3)	16 (66.7)
Female	6 (35.2)	2 (11.7)	8 (46.9)	9 (53.1)
Age (%)				
≥45	0 (00.0)	2 (22.2)	2 (22.2)	7 (77.8)
<45	9 (28.1)	5 (15.6)	14 (43.7)	18 (56.3)
Disease state at SCT (%)				
Refractory	0 (00.0)	1 (25.0)	1 (25.0)	3 (75.0)
Early relapsed	2 (16.6)	2 (16.6)	4 (33.2)	8 (66.8)
Late relapsed	7 (28.0)	4 (16.0)	11 (44.0)	14 (56.0)
Stage (%)				
I, II	3 (14.3)	4 (19.1)	7 (33.4)	14 (66.6)
III, IV	6 (30.0)	3 (15.0)	9 (45.0)	11 (55.0)
Hb (%)				
≥10	6 (22.2)	6 (22.2)	12 (44.4)	15 (55.6)
<10	3 (21.4)	1 (7.1)	4 (28.5)	10 (71.5)
BM involvement (%)				
Yes	2 (20.0)	1 (10.0)	3 (30.0)	7 (70.0)
No	7 (22.6)	6 (19.3)	13 (41.9)	18 (58.1)
LDH (%)				
≥480	2 (15.3)	4 (30.6)	6 (45.9)	7 (54.1)
<480	7 (25.0)	3 (10.7)	10 (35.7)	18 (64.3)

CR: Complete response, PR: Partial response, ORR: Overall response rate, LDH: Lactate dehydrogenase, HB: Hemoglobin, BM: Bone marrow, SCT: Salvage chemotherapy

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Conflicts of interest

There are no conflicts of interest.

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