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# ESHAP versus IEV Chemotherapy for Relapsed or Refractory Hodgkin's and Non- Hodgkin's Lymphoma

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## ABSTRACT

**Background:** High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard treatment for Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) in cases of relapsed or refractory disease. Various salvage chemotherapy regimens have been introduced with specific response rates, toxicity profiles, costs, and stem cell damage before stem cell harvest. The optimal salvage regimen for these patients is unclear.

**Materials and Methods:** In this retrospective analysis, 276 patients with HL and NHL with relapsed or refractory disease after initial treatment that received ESHAP (etoposide, methylprednisolone, cytosine arabinoside, and platinum) or IEV (ifosfamide, epirubicin, etoposide) as salvage regimen were included. We aimed to compare the efficacy of these two chemotherapy regimens as a life-saving treatment in recurrent or refractory disease.

**Results:** The mean age of patients was 33.96 ± 12.39 years. Hodgkin's lymphoma accounted for 60.1% and non-Hodgkin lymphoma (DLBCL) accounted for 39.9% of patients. The overall response rate (ORR) was 79.8% (50% complete response (CR)) for patients with Hodgkin lymphoma who received the ESHAP and 85.6% (55.1% CR) for the IEV regimen. Patients with non-Hodgkin's lymphoma who received the ESHAP plus rituximab regimen had an ORR of 60.9% (CR 40.3%), and patients who received the IEV + Rituximab chemotherapy regimen had an ORR of 72.4% (CR 42.4%) (P = 0.03). However, the mortality rate was lower in patients who received the IEV chemotherapy regimen.

**Conclusion:** IEV treatment is superior to ESHAP in patients with recurrent or refractory Hodgkin's and non-Hodgkin's lymphoma.

**Keywords:** ESHAP; IEV; Hodgkin's lymphoma and non-Hodgkin’s lymphoma

## INTRODUCTION

Lymphoma, including Hodgkin's lymphoma (HL) and non-Hodgkin's lymphomas (NHL), are considered highly curable malignancies [1]. HL can be treated in 70-80% of patients with standard chemotherapy regimens including ABVD (adriamycin, bleomycin, vinblastine, decarbonize) [2-5]. Diffuse large B cell lymphoma (DLBCL) is the most common subtype of NHL, and treatment with several courses of chemotherapy and immunotherapy, including rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), has shown a 50-60% improvement and long term survival[6,7]. However, 10-30% of patients with HL do not achieve complete remission (CR) and 40-60% of patients will relapse shortly after achieving CR.

Moreover, 20-50% of patients with DLBCL will relapse or develop a resistant disease after the standard chemotherapy regimen[6,8-15]. High-dose chemotherapy with autologous stem cell transplantation (ASCT) has become the standard treatment for resistant and recurrent HL and NHL[11,16]. Various salvage chemotherapy regimens with specific response rates, toxicity profiles, cost, and stem cell damage have been introduced before stem cell harvesting.

Salvage chemotherapy regimens can lead to a CR of 10-60% and an overall response rate (ORR) of 40-80%[11,16]. However, the optimal rescue chemotherapy regimen for these patients is not known and more studies are needed to improve the long-term outcome. The present study aimed to compare the effectiveness of the two-salvage chemotherapy including ESHAP and IEV in the treatment of HL and NHL respectively with resistant or refractory disease.

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed data from 330 patients with recurrent or refractory Hodgkin's or non-Hodgkin's lymphoma (DLBCL) from April 2012 to March 2018. We selected patients treated with etoposide, methylprednisolone, ara-C, and cisplatin (ESHAP) or ifosfamide, etoposide, and epirubicin (IEV). In patients with DLBCL and CD20 positive, rituximab was added to the treatment regimen. In eligible cases, patients underwent autologous ASCT transplants after rescue treatment. This study was performed in Amir Hospital affiliated with Shiraz University of Medical Sciences (SUMS).

We enrolled patients with biopsy-proven lymphoma after reaching the standard chemotherapy protocol (ABVD or EBEACOPP) for Hodgkin and (CHOP ± Rituximab) for non-Hodgkin's lymphoma who were not in complete remission or relapsed after attaining CR to standard chemotherapy. Inclusion criteria were as follows: All patients were 18-80 years of age ranges, adequate organ function as defined by a left ventricular ejection fraction greater than 45%; creatinine clearance ≥ 60 mL/min; total bilirubin < 2 mg/dl; serum transaminase levels < 3× upper limit of normal value and receiving 3 cycles of chemotherapy.

Patients with incomplete data were not included in our study. 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 CR or progression during front-line treatment. Recurrence was histopathologically confirmed in patients with recurrence more than one year after their primary diagnosis, or radiologic evidence of recurrence in any organ other than the primary site. No histopathologic study was done in patients with recurrence in less than one year of diagnosis and radiologic evidence of recurrence in the primary site.

### Treatment plan

ESHAP Chemotherapy regimen consisted of etoposide,60 mg/m$^2$ on days 1-4 given intravenously; Methylprednisolone, 500 mg on days 1-4 given intravenously; Cytosine arabinoside, 2000 mg/m$^2$ on days 5 given intravenously; and Cisplatin, 25 mg/m$^2$ on days 1-4 given intravenously regimen was administered as follows: Ifosfamide (2500 mg/m$^2$, continuous IV infusions on days1-3 with mesa), Etoposide (200 mg/m$^2$ infusion for 2 hours, on days 1-3) and Epirubicine (50 mg/m$^2$ in the first day, infusion over 30 minutes). Rituximab 375 mg/m$^2$ was added to the treatment protocol in NHL patients.

To reduce the risk of cisplatin-induced nephrotoxicity, patients were hospitalized up to 36 hours before chemotherapy and hydrated with normal saline for 12 hours before chemotherapy, which continued until 8 hours after cisplatin. Dexamethasone, granistrone, aprepitant were used as antiemetics. All patients were hospitalized with 2000 mL of intravenous fluid hydration during chemotherapy. Chemotherapy was repeated every 3 weeks for 3 cycles, and the treatment cycle was delayed for several days in the case of granulocytopenia (neutrophils < 1.0 × 109/dL) or thrombocytopenia (platelets < 100 ×109/dl). In the case of neutropenic fever, the dose of chemotherapy is reduced.

**Assessment of response**

All patients were evaluated after each chemotherapy cycle using CBC, ESR, LDH, LFT, history taking, and physical examination. At the end of the third cycle of chemotherapy, a CT scan of the neck, chest, and abdomen was performed to assess the response. Complete response (CR) was considered when the largest tumor diameter decreased by more than 90%, partial response (PR) was defined as a 50–90% decrease in the largest tumor diameter, and patients with a decrease of less than 50% were considered resistant or refractory disease. Patients with CR and PR after salvage chemotherapy are candidates for ASCT. Patients with less than 50% reduction in tumor size after the third cycle of ESHAP or IEV chemotherapy were switched to a cross-regimen.

**Statistical analysis**

Computer-based statistical packages for Windows Social Science, version 21.0 (SPSS 21.0) were used to analyze the data. The differences between the variables were tested using chi-square and independent t-test. A P-value < 0.05 was considered significant.

**Ethics statements**

In this study, all procedures involving human participation were performed following the ethical standards of the institutional and/or National Research Committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences.

**RESULTS**

**Patient Characteristics**

In this study, 330 patients with lymphoma were examined, of which 54 were excluded from the study due to incomplete information, and finally, 276 were examined. Among 276 patients, 178 (64.5%) were male and 98 (35.5%) were female. The mean age of the patients was 33.96 ±12.39 years. Hodgkin's lymphoma comprised 60.1% (166) of patients and non-Hodgkin's lymphoma (DLBCL) comprised 39.9% (110) of patients.

In the analysis of patients based on the type of chemotherapy regimen, 192 patients (69.6%) received ESHAP chemotherapy, of which 115 patients (59.9%) had HL and 77 patients (40.1%) had NHL. Out of 84 patients (30.4%) who received the IEV chemotherapy regimen, 51 patients (60.7%) were in the Hodgkin group and 33 patients (39.3%) were in the non-Hodgkin group.

Table 1 shows the average age and sex of patients based on the type of lymphoma and chemotherapy regimen. According to the data in the table, there was a significant difference between the studied groups in terms of mean age (P = 0.001), so patients with non-Hodgkin's lymphoma had a higher mean age. Also, there was no statistically significant difference in terms of gender distribution (P = 0.28).

**Response**

Hodgkin patients who received ESHAP achieved 50% CR and 29.8% PR. In HL, who received IEV chemotherapy, CR and PR were 55.1% and 30.6%, respectively. Patients with NHL receiving ESHAP chemotherapy achieved 40.3% CR and 26% PR. CR and PR in these patients with IEV chemotherapy were 42.4% and 30.3%, respectively. The highest percentage of CR was observed in Hodgkin's lymphoma treated with IEV and the highest percentage of non-response (NR) was observed in non-Hodgkin's lymphoma treated with ESHAP with 26 cases (33.8%). A comparison of groups showed that the rate of response and remission are significantly different (P = 0.03) (Figure 1).

In the present study, 47 cases (17%) had a change in chemotherapy regimen, which was due to a lack of proper response to chemotherapy. 30 patients (63.8%) were switched from ESHAP to IEV and 17 (36.2%) from IEV to ESHAP. Patients who changed their chemotherapy from ESHAP to IEV had a significantly higher CR than the second group (P = 0.03). Also, the highest amount of GCSF administration (P = 0.61) and the highest rate of bone marrow transplantation (P = 0.04) were observed in HL treated with IEV, which was statistically significant between the groups. Also, the highest rate of pegfilgrastim administration was observed in NHL and IEV patients and the highest mortality rate was observed in NHL treated with

ESHAP chemotherapy (Table 2). In this study, the most common side effects were anemia in 119 cases (43.1%) and neutropenic fever in 34 cases (12.3%). There was no statistically significant difference between the groups.

**Table 1:** Demographic data of lymphoma subtypes

| Lymphoma subtype | Regimen | Mean age ±SD | Gender Number(percent) | |
|---|---|---|---|---|
| | | | Male | Female |
| Hodgkin | ESHAP | 30.1±73.33 | 76(66.1%) | 39(33.9%) |
| | IEV | 31.1±76.34 | 34(66.7%) | 17(33.17%) |
| Non-Hodgkin | ESHAP | 37.14±97.01 | 45(58.4%) | 32(41.6%) |
| | IEV | 39.13±24.84 | 23(69.7%) | 10(30.3%) |
| P | | 0.001 | 0.28 | |

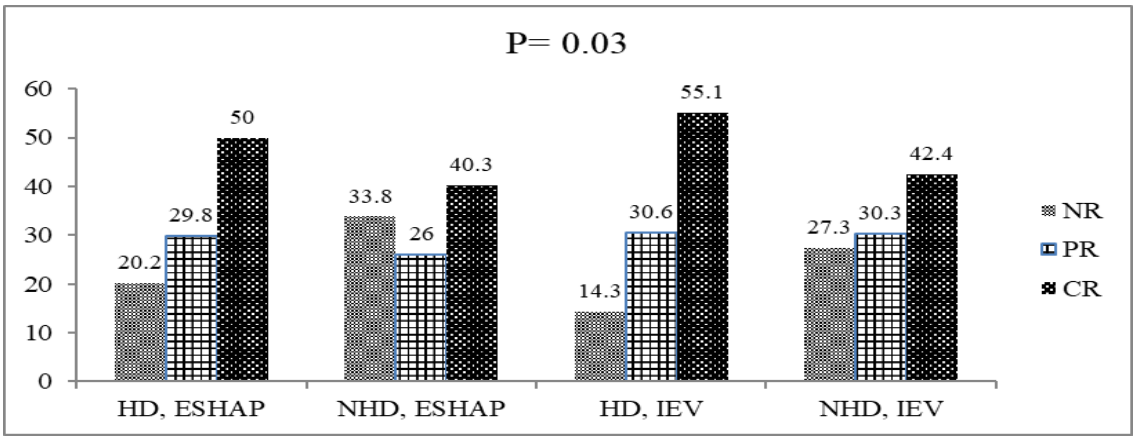


Figure1. Response rate according to regimen and lymphoma subtype (HD: Hodgkin disease, NHD: non-Hodgkin disease)

**Table 2:** Treatment variables and sequela separated lymphoma subtype and chemotherapy regimen

| Lymphoma subtype Regimen | Hodgkin | | Non-Hodgkin | | p |
|---|---|---|---|---|---|
| | ESHAP (n=115) | IEV (n=51) | ESHAP (n=77) | IEV (n=33) | |
| Chemotherapy switch | 19(16.5%) | 10(19.6%) | 11(14.3%) | 7(21.2%) | 0.59 |
| GCSF administration | 37(32.2%) | 25(49%) | 31(40.3%) | 15(45.5%) | 0.61 |
| Mean number of GCSF | 53.62±2 | 79.77±2 | 41.77±2 | 85.66±2 | 0.16 |
| Peg-filgrastim Administration | 11(9.6%) | 16(31.4%) | 4(5.2%) | 14(42.4%) | 0.001 |
| Autologous SCT | 37(32.2%) | 19(37.3%) | 8(10.4%) | 9(27.3%) | 0.04 |
| Mortality | 15(13%) | 5(9.8%) | 25(32.5%) | 6(18.2%) | 0.01 |
| Neutropenic fever | 10(8.7%) | 3(5.9%) | 11(14.3%) | 10(30.3%) | - |
| Diarrhea | 10(8.7%) | - | 2(2.6%) | 2(6.1%) | - |
| Anemia | 43(37.4%) | 28(54.9%) | 36(46.8%) | 12(36.4%) | - |

## DISCUSSION

Salvage chemotherapy followed by autologous stem cell transplantation is the standard treatment for patients with relapsed lymphoma[17-19]. The strongest prognostic factor for outcome after ASCT is complete remission on salvage chemotherapy. Patients with CR have significantly better survival and progression-free survival (PFS) than patients without CR [20-23.]

The various life-saving chemotherapies offered to these patients have been studied from different perspectives, such as response to treatment, side effects, etc., and are sometimes different or similar. However, the best salvage chemotherapy for the treatment of relapsed or refractory HL and NHL is still debated. ESHAP and IEV are two of the most common salvage chemotherapy regimens for this purpose. Finding a chemotherapy regimen with high efficacy and low side effects is very important, so this study was conducted to evaluate and compare IEV and ESHAP regimens as salvage therapy in patients with recurrent and refractory lymphoma.

In the present study, the highest rate of CR was observed in the HL, IEV group at 55.1%, followed by the HL, ESHAP group at 50%, NHL and IEV treatment at 42.4%, and finally NHL, ESHAP at 40.3% complete response. This comparison shows that IEV has a better CR than ESHAP and patients with Hodgkin's lymphoma responded better to treatment than non-Hodgkin's lymphoma.

However, it should be borne in mind that the lower response rate in patients with non-Hodgkin's disease may be due to increasing age or the nature of the disease in this group. However, the use of rituximab in CD20-positive patients is unavoidable. The overall response rate (ORR) in the HL and IEV groups was 85.6%, which was higher than the other groups. Subsequently, the ORR in the HL and ESHAP group was 79.8%, NHL and IEV 72.7%, and the NHL and ESHAP group 66.3%.

In the study by Labrador et al. The ORR rate in patients with relapsed or refractory HL with the ESHAP protocol was 67% (50% CR), where the CR was equal to our study, but the ORR was lower than in our study (67% vs. 79.8%) (24). In another study by Mehrzad et al. in recurrent and resistant HL, compared to ICE and ESHAP chemotherapy regimens, ESHAP was superior to ICE due to higher CR (39.7%) and ORR (58.9%)[11]. In Mashhadi et al.'s study, the ORR of the IEV regimen in patients with relapsed/refractory HL and NHL was 92% (50% CR and 42% PR), which is higher than our study. Also, in this study, CR was higher in NHL patients than in HL patients, which may be due to the small sample size, unlike our study[24].

In a 2015 study by Ramzi et al., in patients with relapsed or refractory HL, the ESHAP regimen resulted in 29.5% CR, 24% PR, and 45.5% no response. The ORR was lower than in our study, but the sample size was also small[8]. Park et al. used ESHAP regimens as salvage therapy in patients with recurrent/refractory non-Hodgkin's lymphoma. CR was 27.3%, PR was 36.4%, and the ORR was equal to our study[15]. Biston et al. evaluated the IEV regimen as a salvage therapy in 143 relapsing/resistant HL and NHL patients. The major response (complete/partial response) to IVE was (80.4%). Subgroup analysis showed an overall response rate of 93.1 for HL, while the NHL showed a response rate of 78.0%. The results of this study are consistent with our study and the response rate was lower in patients with NHL[25].

In our study, the most common side effects of both chemotherapy regimens were anemia and neutropenic fever without statistically significant differences. Interestingly, patients who changed their chemotherapy regimen from ESHAP to IEV had a significantly higher CR than the other group (P = 0.03). Given the higher mortality in the ESHAP regimen group, the higher CR in HL with the IEV protocol, and the acceptable toxicity profile of the IEV regimen, IEV appears to be safer than the ESHAP regimen with higher efficacy.

## CONCLUSION

Finally, this study showed that the IEV regimen had a better response rate than the ESHAP chemotherapy in HL and NHL. Moreover, due to the lower mortality rate in the IEV group and acceptable toxicity profile, using this chemotherapy protocol is recommended as a salvage regimen in recurrent or refractory HL and NHL.

**CONFLICT OF INTEREST**

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest, in the subject matter or materials discussed in this manuscript.

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