IEV (Ifosfamide, Epirubicin, VP16) Regimen as Salvage Therapy for Early Relapsed/Refractory non-Hodgkin/Hodgkin Lymphoma

Mohammadali Mashhadi,[1] Hossein Rahimi,[2] Behrooz Najafi,[3] Adnan Khosravi[4]

[1]Hematology- Oncology Department, Zahedan University of Medical Sciences, Zahedan, Iran
[2]Hematology- Oncology Department, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Hematology- Oncology Department, Gilan University of Medical Sciences, Gilan, Iran
[4]Hematology- Oncology Department, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondig author: Dr. Mohammadali Mashhadi, MD; Associated professor in Hematology-Oncology, Zahedan University of Medical Sciences, Zahedan, Iran
Phone number: 09153411445
Email: dralimashhadi@yahoo.com

Abstract

Introduction: Management of early relapsed or refractory lymphoma [Hodgkin & non- Hodgkin Lymphoma (HL & NHL)] is a matter of problem, especially when hematopietic stem cell support is not available. The aim of this study was to evaluate effectiveness of IEV Regimen (Ifosfamide, Epirubicin, VP16), in lymphoma patients who are not candidate for stem cell transplantation. Because the majority of our patients are nonadequate for stem cell transplantation (refuse of this modality and economic problem). This reason leads to use of more effective treatment. This trial approved with ethic committee of medical university.

Patients and Methods: Twenty four patients (16 male and 8 female) with early relapsed i.e. before 6 months of primary therapy (N= 21) or refractory lymphoma (N= 3) were entered. Of 24 patients 18 were diagnosed as NHL and 6 as HL. 10 cases were in stage II, 12 cases in stage III and 2 cases in stage IV. In an inpatient setting all of the patients received 3- 4 consecutive cycles of IEV (Ifosfamide, Epirubicin, VP16) and MESNA equal to Ifosfamide for uroprotection. Cycles were repeated every 21 days, for a total of three courses.

Results: The overall response rate was 92% (50% complete response and 42% partial response). Complete response were observed in 8 with NHL and 4 with HL and partial response in 9 with NHL and 1 with HL respectively. There was no response in 8% (1 patient with NHL and another with HL). Toxicities were: grade 1 neutropenia (10%) and 4 (40%), grade 1 thrombocytopenia (20%), grade 2 anemia (40%) nausea (100%), fever in 80%, neutropenic fever in 30%, pneumonia in 20%, of patients, but the majority of patients improved over treatment. One case died from progressive disease and co infection with no response to antibiotic therapy. The major cause of drug toxicity was Ifosfamide (high dose usage and 3 days continuous IV infusion). Tolerance to the regimen was good.

Conclusions: Our results revealed the efficacy of the IEV regimen as salvage therapy in primary refractory and early relapsed NHL & HL without stem cell support.

Key words: IEV, Refractory NHL lymphoma, Salvage therapy, Hodgkin's lymphoma

Introduction

The therapeutic approach of early relapsed and refractory non-Hodgkin's lymphoma (NHL) and Hodgkin lymphoma (HL) is a major challenge in the medicine. Although Hodgkin and Non Hodgkin Lymphoma (HL & NHL) are curable in all stages,(1, 2) but the treatment of refractory and early relapse lymphoma with conventional and standard therapy such as chemotherapy or radiotherapy is not an appropriate and satisfactory treatment.(3, 4) In these situations choice of treatment is high dose chemotherapy and stem cell transplantation.(5,6) In majority of studies the use of IEV regimen was combined with hematopoietic stem cell transplantation.(7, 8, 9) Other salvage regimen in early relapse/refractory NHL/HL were:

DHAP: Dexamethason, Cytozar, Cisplatin with maximum response and prolong duration in 12 % of patients,(10) and ESHAP: Etoposide, Solu-medrol, Cytarabine, Cisplatin with 2 years disease free survival in 15%.(11) Both protocols (DHAP, ESHAP) were associated with lower response rate and durable remission and high treatment related toxicity.(10, 11)

Patients with usage of IEV regimen without stem cell transplantation less likely to experienced long term survival and usage of stem cell support is mandatory to achieved long term survival or cure,(12) but the majority of patients are not suitable for stem cell transplantation (refuse of this modality, high cost and of course availability only in tertiary centers). The aim of this study was to evaluate therapeutic effectiveness of IEV Regimen (Ifosfamide, Epirubicin, VP16), when hematopoietic stem cell transplantation is not possible.

Patients and methods

24 patients (16 male and 8 female) with early relapsed or refractory NHL/HL entered in this prospective study. All patients received standard regimen for HL and NHL in early treatment protocol: (CHOP for NHL cytoxan 600 mg/m^2, Adriamycin 45mg/m^2, prednisolone 100 mg/day 1-→5, Vincristin 1.4mg/m^2/cycle for 6 cycles) and ABVD for HL: (Adrimycin 25mg/m^2, Vinblastin 6 mg/m^2, Dacarbazine 375mg/m^2, Bleomycin 10 mg/m^2/cycle for 12 cycles). Complete physical examination was done and all of slides reviewed to confirm initial diagnosis. The patients with Karnofsky status >70 were entered of them 18 cases were NHL and 6 cases HL. 10 cases were stage II, 12 cases were stage III and 2 were stage IV. The age distribution was: 22-64 and mean age was 38 years.

Restaging was done according to Ann Arbor staging system. Chest X- Ray, abdominal and pelvic CT scan, bone marrow aspiration and biopsy were requested. Laboratory profile requested including Liver function tests, Kidney function test (every rising in BUN/Creatinine or electrolyte imbalance due to renal dysfunction), any Cardiac abnormality determined with ECG, Echocardiography and cardiac consultation.

All patients admitted in Hematology Oncolgy ward and in isolated room. Patients received 3- 4 consecutive cycles of IEV (epirubicine 100 mg/m^2/day, only day 1, Ifosfamide 2,000 mg/m^2/d continuous IV infusion for 3 days, and etoposide 150 mg/m^2/day for 3 days, days 1- 3 each cycle) and equal dose of Ifosfamide, all patients received MESNA 2,000 mg/m^2/day continuous IV infusion for 3 days for uroprotection. Courses were repeated every 21 days, with a target total of three courses.

At the end of treatment, toxicities were evaluated by physical examination and appropriate laboratory tests and recorded. If the patients had Neutropenia <500, the GCSF was begin and continued until the rising of Neutrophil to more than 1000.

All of the patients evaluated with physical examination and appropriate laboratory investigation prior to every cycles of treatment and during follow up.

Definition of response:

Complete response (CR): No evidence of disease (clinical and paraclinic).

Partial response (PR): ≥50% decreased in primary disease.

No response (NR): Not evidence of response to this protocol.

Results

In this single center study (south east of Iran), the 24 patients with NHL/HL were entered and received this protocol. The male to female ratio was 2:1. The stage of disease was in 10 cases stage II and in 12 cases stage III and in 2 cases was stage IV. The median duration of follow up was 23 months (6-48). The overall response rate was 92% (CR+PR) with 52% complete response (8 cases were NHL and 4 cases HL) and 40% partial response (8 cases NHL and 1 case HL). Only 8% showed no response (1 case NHL and other case was HL).

18 cases NHL and 6 cases were HL, 2 cases received autologous stem cell transplantation but others received salvage chemotherapy alone. 21 patients had early relapse and 3 had primarily refractory disease. 2 cases of these refractory diseases candidate for stem cell transplantation. One case was 28 years male with refractory HL and received first stem cell transplantation after the second relapse due to standard therapy. And 1 year later to stem cell cell transplantation, the primary disease recure and candidate for IEV regimen. He had 18 months remission and then, experienced relapse and candidate for second stem cell transplantation but rejected for this modality with stem cell center. This patient retreated with IEV regimen and remains in remission up to 28 months. The other patient that received autologous stem cell transplantation with partial remission, was refractory NHL and died after 6 months of stem cell

Table- 1. Characteristic of patients and response to treatment.

Variable	status	Response to treatment					
		No response		Partial response		Complete respons	
		No	%	No	%	No	%
Sex	Female	1	4.15 5	3	12.5 %	4	16.6 %
	Male	0	0 %	8	33.3 %	8	33.3 %
Age	≤60	0	0 %	7	29 %	8	33.3 %
	>60	1	4.15 %	5	20.8 %	3	12.5 %
B symtoms	+	1	4.15 %	7	29 %	6	25 %
	-	0	0 %	7	29 %	3	12.5 %
LDH	>Normal	1	4.15 %	12	50 %	8	33.3 %
	≤Normal	0	0 %	0	0 %	3	12.5 %
Karnofsky p.	<90	1	4.15 %	3	12.5 %	5	20.8 %
	≥90	0	0 %	9	37.5 %	6	25 %
Bulky D.	+	1	4.15 %	0	0 %	3	12.5 %
	-	0	0 %	12	50 %	8	33.3 %
Extranodal	+	1	4.15 %	0	0 %	2	8.8 %
	-	0	0 %	12	50 %	9	37.5 %
Dis. state	Refractory	1	4.15 %	2	8.3 %	0	0 %
	Relapse	0	0 %	11	45.8 %	10	41.25 %
Stage before	Stage II	0	0 %	6	25 %	4	16.6 %
	Stage III	0	0 %	8	33.3 %	4	16.6 %
	Stage IV	1	4.15 %	0	0 %	1	4.15 %

transplantation in feature of progressive disease.(Table- 1)

The most common treatment related toxicity was transient fever that observed in 18 cases. The major cause of drug toxicity was Ifosfamide (high dose usage and 3 days continuous IV infusion) which reported in separated papers.(13, 14) Other toxicities were:

grade 1 neutropenia (10%) and 4 (40%), grade 1 thrombocytopenia (20%), grade 1 anemia (40%), nausea (100%), fever in 80%, neutropenic fever in 30%, pneumonia in 2 cases, but the majority of patients improved with appropriate treatment. One case died from progressive disease and co infection with no response to antibiotic therapy. Tolerance to the regimen was good. The probabilities of overall survival, and the disease-free survival at the end of study were 80%, with median duration 23 months Patients with grade 4 neutropenia need administration of G-CSF. Decrease in Platelet count was 15-17%.

Decrease in level of hemoglobin was observed in 40% of cases, but majority was grade I and didn't need to erythrocyte transfusion. Three cases had urinary tract infection that resolved with antibiotic therapy. Pneumonia was observed in 2 cases that treated with conventional therapy.

The pulmonary (except for infection), renal, cardiac and hepatic dysfunction due to the treatment were not observed. Renal and neuropsychiatric manifestation of drug toxicity (Ifosfamide) were reported separately.(13, 14)

In these studies the treatment related toxicities with IEV regimen were minimal and predictable.

Discussion

The salvage chemotherapeutic agents were more effective than standard regimen (CHOP/ABVD) in the treatment of early relapsed NHL/HL. One of the most effective regimen was usage of Ifosfamide and Etoposide. The response rate with these regimen was 35-75% and this parameter in CHOP regimen in early relapsed and refractory Lymphoma (NHL/HL) was less than 10%.(12)

The evaluation of IEV regimen in early relapsed and refractory Lymphoma reported in 2001 year in UK. The response rate in this study was 45 %.(12) Although, when we evaluated all literature about the efficacy of IEV regimen without stem cell support in patients with early relapsed/refractory lymphoma near to all of them were with stem cell support. One study with IEV regimen without stem cell support (in 17 cases of 65) revealed the minimal duration and maximum response duration was 14 months (2- 14) but in our study the result was very vary to this report.(7, 8, 9)

2 of these studies reported in 2007 with Mark J. Bishton and his workers,(17) and in 2008 with C.P. Fox and his workers,(12) that used stem cell support after the usage of IEV regimen. In these studies, the over all response rate were 80.4% and 83%respectively.

In other study with Pier Luigi Zinzani in 2002: All patients treated with IEV regimen and then received stem cell transplantation (Except 17 cases that non-

suitable for stem cell transplantation, but the maximum duration time of response was very little 14 months (2- 14). In the end of treatment the over all response rate was 77% and 32% had complete response. This study revealed the efficacy and cost and toxicity of IEV regimen were acceptable and very limited.(8, 9)

These studies (above) revealed that the IEV regimen was more effective than others regimen. The response rate was 77 % and complete response and partial response was 32% and 45% respectively, and in the study of Choi,(11) all of patient had benefit of this treatment and 1/3 of patients had complete response.

In the study that was done in 2000 year the response rate to IEV regimen was 100% (complete response 30% and partial response 70%) respectively.(18) In this study stem cell support used.

But in our study: The usage of IEV regimen was effective and over all response rate (complete & partial response) was very good with long time duration and was more than other studies especially in non hematopoitic stem cell support situation. Treatment related toxicities and drug toxicities were acceptable and only one case had significant toxicity with major problem.

Conclusion

This study revealed, the usage of IEV regimen was effective therapeutic approach without stem cell support and we could use in a setting of early relapse/refractory lymphoma that we didn't have stem cell support.

Refferences

1. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992; 327: 1478- 1484.

2. Fisher RI, Gaynor ER, Dahlberg S et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328: 1002-1006.

3. Longo DL, Duffey PL, Young RC et al. Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. J Clin Oncol 1992; 10: 210-218.

4. Salles G, Shipp MA, Coiffier B. Chemotherapy of non-Hodgkin's aggressive lymphomas. Semin Hematol 1994; 31: 46- 69.

5. Philip T, Guglielmi C, Hagenbeek A et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333: 1540–1545.

6. Schmitz N, Sextro M, Pfistner B et al. High-dose therapy followed by hematopoietic stem cell transplantation for relapsed chemosensitive Hodgkin's disease: final results of a randomized GHSG and EBMT trial (HD-R1). Proc Am Soc Clin Oncol 1999; 18: 2a (Abstr 5).

7. Zinzani PL, Barbieri E, Visani G et al. Ifosfamide, epirubicin and etoposide (IEV) therapy in relapsed and refractory high-grade non-Hodgkin's lymphoma and Hodgkin's disease: Haematologica 1994; 79: 508-512.

8. Zinzani PL, Tani M, Molinari AL et al. Ifosfamide, epirubicin and etoposide regimen as salvage and mobilizing therapy for relapsed/refractory lymphoma patients. Haematologica 2002; 87: 816-821.

9. P. L. Zinzani.,* Ifosfamide, epirubicin and etoposide (IEV) in non-Hodgkin's lymphoma and Hodgkin's disease: the Italian experience. Annals of Oncology 14 (Supplement 1): i43–i45, 2003.

10. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1002.

11. Choi C W, Paek Ch W, Seo J H, Kim B S, Shin S W, Kim Y H, Kim J S. ESHAP Salvage Therapy for Relapsed or Refractory Non-Hodgkin's Lymphoma J Korean Med Sci. 2002; 17: 621-4.

12. C.P.Fox, A.K.MCMillan, M.J. Bishton, A.P. Haynes and H. Russell. IVE (Ifosfamide, epirubicin and etoposide) is more effective stem cell mobilization regimen than ICE (Ifosfamide, carboplatin, etoposide) in the context of salvage therapy for lymphoma. British journal of Hematology. 2008; 141, 244- 248.

13. Mashhadi M A, Khosravi A R. Neuropsychiatric Toxicity of Ifosfamide in Patients Admitted for Chemotherapy International Journal of Hematology Oncology and Stem Cell Research (IJHOSCR), Jan., 2010.

14. Mashhadi M A. Renal side effect of Ifosfamide in patients admitted for chemotherapy. Journal of research in medical science 2008; 13: 5 240- 243.

16. Longo DL, Duffey PL, Young RC et al. Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low

probability for cure. J Clin Oncol 1992; 10: 210-218.
17. Mark J. Bishton, Richard J. Lush, Jenny L. Byrne, Nigel H. Russell, Bronwen E. Shaw and Andrew P. Haynes. Ifosfamide, Etoposide and Epirubicin is an effective combined salvage and peripheral blood stem cell mobilization regimen for transplant- eligible patients with Non-Hodgkin Lymphoma and Hodgkin disease. British journal of hematology; 2007: 136, 7520761.
18. Holowiecki J, Wojciechowska M, Giebel S, Krawczyk-Kulis M. Ifosfamide, Etoposide, Epirubicin, and G-CSF: an effective mobilization regimen for PBSCT in heavily pretreated patients. Transplant Proc. 2000 Sep; 32 (6): 1412- 5.