IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

Assessment of Effectiveness and Adverse Effect of New Combination Chemotherapy (irinotecan, cisplatin, and dexamethasone) in Relapse and Refractory Hodgkin Lymphoma

Mahdi Tabarraee[1], Atefeh Rezaee[2], Sara Abolghasemi[3], Mojtaba Ghadiany[1], MariaTavakoli Ardakani[4], Mahshid Mahdizadeh[4], Neda Hamidi[1], Katayoon Ghasemi[5]

[1]Department of Hematology-Oncology, Shahid Beheshti University of Medical Sciences, Taleghani Hospital, Tehran, Iran
[2]Department of Hematology-Oncology, Ahvaz Jondishapur University of Medical Sciences, Shahid Baghaei Hospital, Ahvaz, Iran
[3]Department of Infection, Taleghani Hospital, Tehran, Iran
[4]Department of Bone Marrow Transplant, Shahid Beheshti University of Medical Sciences, Taleghani Hospital, Tehran, Iran
[5]Department of Hematology-Oncology, Hormozgan University of Medical Sciences, Shahid Mohammadi Hospital, Bandar Abbas, Iran

Corresponding Author: Atefeh Rezaee, Department of Hematology-Oncology, Ahvaz Jondishapur University of Medical Sciences, Shahid Baghaei Hospital, Ahvaz, Iran
E-mail: atefehrezaee1981@gmail.com

Received: 31, Oct, 2020
Accepted: 01, May, 2021

ABSTRACT

Background: Chemotherapy with Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD regimen) cannot cure all patients with Hodgkin lymphoma. In this study, we evaluated the efficacy and adverse effect of a new regimen consist Irinotecan, Cisplatin, and Dexamethasone (ICD) in relapsed and refractory Hodgkin lymphoma as the second to fifth line of treatment.

Materials and Methods: We performed a retrospective study in 26 relapsed or refractory patients with Hodgkin lymphoma receiving at least the first-line chemotherapy regimen (ABVD) and (ICD) as salvage therapy in Thaleghany Hospital from 2012 to 2018. This regimen consisted of Irinotecan 65mg/m2 D1, D8, Cisplatin 30mg/m2 D1, D8, and dexamethasone 40mg D1, 2, 8, and 9 was administered every 3 weeks for 6 cycles. Treatment was discontinued in cases of disease progression or severe toxicity. Response to treatment was evaluated after two cycles. Patients with complete and partial remission were candidates for high-dose chemotherapy and autologous stem cell transplantation. Twenty-four patients were enrolled in the study. The mean age of 22 patients was 31.5 (19-67) years. Seven patients (29.1%) were in the first recurrence, and 17 (70.8%) were in the second or subsequent recurrence.

Results: According to this study, three patients (12.5%) had complete response, 13 (45%) had partial response, four (16.6%) had stable disease, and four (16.6%) had progressive disease. Nine patients (37.5%) received high-dose chemotherapy and autologous stem cell support after ICD regimen. None of the cycles of chemotherapy were delayed due to treatment-related adverse event. Overall survival after six months in all patients was 91%, and mortality rate was 8.3% at the end of the study.

Conclusion: The goal of salvage chemotherapy in relapsed or refractory Hodgkin Lymphoma is achieving CR or PR preparation patients for stabilization with BMT. Thus, we recommend ICD as one of the most effective protocols with overall response rate of 66% in this population.

Keywords: Relapse; Refractory; Hodgkin lymphoma; Irinotecan; Cisplatin; Salvage chemotherapy

INTRODUCTION

Relapse after initial treatment will occur in approximately 10 to 15 percent of patients with early-stage disease and up to 40 percent of patients with advanced-stage disease at diagnosis[1-3]. At present, in relapsed or refractory lymphoma patients, high-dose chemotherapy with autologous stem cell transplantation is the treatment of choice. However, its use is more limited to patients responding to life-saving chemotherapy, so these patients need salvage treatment[4]. Sometimes disease is refractory to the first salvage treatment, and other salvage treatment is needed. Some regimens have had good results, such as IEV Regimen (Ifosfamide, Epirubicin, VP16)[5], but the best salvage treatments are not clear, specially some of them are expensive and unavailable. In adjuvant MOPP trials, survival after salvage therapy was 78% at 5 years for nodular disease compared with 20% for recurrence with bone marrow involvement[6]. Junji Suzumiya evaluated Irinotecan hydrochloride (CPT-11), Carboplatin, and dexamethasone in relapsed and refractory lymphoma patients with the overall response rate of 36% but concluded that the duration of response is too short[7]. In Kuruvilla et al. study, GDP (Gemcitabine, Dexamethasone, and Cisplatin) as second-line therapy in patients with R/R HL showed a 62% response rate[8]. In two studies by Ghadiany et al. [9] and Kang et al. [10], ICD (Irinotecan, Cisplatin, Dexamethasone) was evaluated in refractory non-Hodgkin lymphoma patients previously treated with R-CHOP or CHOP or as first salvage treatment. Overall, all patients achieved a 71% to 75% response rate, but surprisingly patients treated as first-line salvage achieved an overall response rate of 90% [9, 10]. However, in the Kang study, the high prevalence of neutropenia was a limiting factor. In numerous studies in similar populations, Gemcitabine and Vinorelbine combination showed ORR of 72% and CR of 35% [11], Ifosfamide, Vinorelbine, and Prednisolone (IGEV) % and Vinorelbine and Pegylated liposomal doxorubicin (GVD) with ORR of 81.3%, and 70%, respectively [12, 13]. Bendamustine at the dose of 120 mg/m2 resulted in the intent-to-treat ORR of 53%, with CRs of 33%[14]. We evaluated the modified ICD by combining G-CSF with Irinotecan and Cisplatin in reduced doses among relapsed or refractory patients with Hodgkin lymphoma receiving at least the first-line chemotherapy regimen (ABVD), and the feasibility and effectiveness of this regimen were also evaluated.

MTERIALS AND METHODS

Patients

In a retrospective study between August 2012 and February 2018, we evaluated the modified ICD protocol in 26 patients aged between 18 and 70 years with relapsed or refractory Hodgkin lymphoma. These patients had an Eastern Cooperative Oncology Group (ECOG) performance status of less than two and appropriate renal and hepatic function. They received a first-line chemotherapy regimen (ABVD), a subsequent regimen (Table 1), and then ICD as salvage therapy. They had acceptable bone marrow function (defined as platelet count more than 100.000/µL and absolute neutrophil count (ANC) more than 1.500/µL). The definition of primary refractory HL included no response to the first-line therapy or progression within three months after the end of the treatment, and relapsed HL is defined as a reappearance of disease at a later time. This study was a retrospective study, and the data were collected from patients receiving this regimen. This project was approved by Ethics Committee of Shahid Beheshti University of Medical Sciences with morality ID: IR.SBMU.MSP.REC.1399.744. Patients' privacy was fully protected during the research.

Modified ICD Chemotherapy Regimen

In this protocol, we administered Irinotecan 65 mg/m2 (max 100 mg) by intravenous infusion over 90 min on days 1 and 8, Cisplatin 30 mg/m2 (max 50 mg) on days 1 and 8, pre-and post-hydration was given according to hospital protocol. Dexamethasone was given 40 mg by IV infusion on days 1 and 8. Prednisolone 200 mg divided into two doses was given orally on days 2 and 9. G-CSF (PD-Grastim) was administered at 300 µg/day subcutaneously on days 4–6 and 11–13. This protocol was repeated every three weeks. We planned this schedule to be continued until disease

progression, severe toxicity or stem cell transplantation, or up to 6 cycles.

Response criteria

Response to treatment was evaluated using computed tomography (CT) scan during treatment or after the last cycle of treatment. To assess response to chemotherapy, the Lugano Classification from the American Society of Clinical Oncology was used as Revised Criteria for Response Assessment of Hodgkin and Non-Hodgkin Lymphoma[15]. The definition of overall survival (OS) was the time of onset of modified ICD until death or last follow-up. The definition of progression-free survival (PFS) was the time of onset of modified ICD until lymphoma progression or death. The definition of event-free survival (EFS) was the time of onset of modified ICD until manifestations of any sign of treatment failure. Treatment failure was defined as the discontinuation of treatment for reasons such as disease progression, toxicity, patient preference or death.

RESULTS

From August 2012 to February 2016, 26 relapsed or refractory patients with Hodgkin lymphoma who received the first-line chemotherapy regimen (ABVD) and then received (ICD) as salvage therapy were entered into this study. The patients' characteristics are presented in (Table 1). Severe diarrhea and seizure prevented the continuation of chemotherapy in two patients. We did not find the reason for the seizure, so these two patients were excluded from the study. The median age of the 24 patients was 35 ± 10 (range 19–67) years, and 50% (11/11) of patients were men. All patients had a good performance status (ECOG score of 0 or 1), and bone marrow, kidney, and liver function were acceptable. Seven patients (29.1%) were in the first recurrence, and 17 (70.8%) were in the second or subsequent recurrence. We lost two patients (one male and one female) at the end of the study. Response to treatment was assessed by CT scan in all patients during or after the last cycle of ICD. Out of 24 patients, three (12.5%) patients achieved complete response (CR), 13(45%) partial response (PR), four (16.6%) stable disease (SD), and four (16.6%) progressive disease (PD), respectively. 66% of patients achieved the overall response rate (CR + PR). Nine patients (37.5%) received high-dose chemotherapy and autologous stem cell support, four of whom after 3 and 5 cycles of ICD and others three months after the end of the ICD regimen, and two patients died at the end of treatment. Median disease-free survival (95% CI) after combination salvage chemotherapy in three patients with CR was 431 days (345-517) (Figure 1). Median progressive-free survival (95% CI) after salvage chemotherapy in total patients was 450 days (359-517) (Figure 2). Overall survival after six months was 91%, and the mortality rate was 8.3%.

Complications

The treatment-related AEs of ICD were well tolerated and included nausea in 20 (83.3%), vomiting in four (16.6%), diarrhea in three (12.5%), fever in four (16.6%), and neutropenia in nine (37.5%) patients. Treatment delay has not been reported in any patients (Table 2).

Figure1. Disease-free survival curve

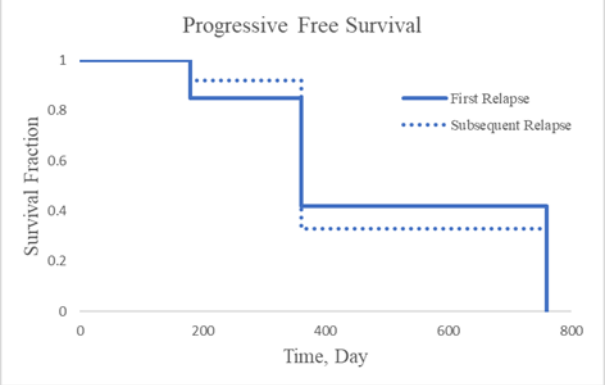

Figure 2. Progressive-free survival curve

Table 1: Patients' characteristic

Character	Number	%
No. of patients	24	
Mean Age, Year	31.5 (19-67)	
Sex, Number (%)		
Male	12	50
Female	12	50
Stage, Number (%)		
I or II	18	75
III or IV	6	25
Histology, (%)		
Nodular Sclerosis	21	87.5
Mixed Cellularity	3	12.5
Type of Chemotherapy		
ABVD	6	25
ABVD + ICE	4	16.6
ABVD + Gemzar / Navelbin	9	37.5
ABVD + Gemzar / Navelbin + ICE	5	20.8
Resistance to ABVD		
First Relapse	7	29.1
Subsequent Relapse	17	70.8
Past RT, Yes (%)	10	41.6
B Symptom, Yes (%)	24	100
HSCT, Yes (%)	9	37.5
ICD cycle (mean)	6(1-10)	

Table 2. Patients' complication

	Grade I / II		Grade III/ IV	
Complication	Number	Percentage (%)	Number	Percentage (%)
Nausea	20	83.3	1	4.1
Vomiting	4	16.6	0	0
Diarrhea	3	12.5	2	8.3
Fever	4	16.6	0	0
Neutropenia	9	37.5	0	0
Infection	1	41.6	0	0

DISCUSSION

Despite significant advances in the management of HL patients, recurrence and refractory disease is challenging. High-dose chemotherapy followed by auto HCT is the treatment of choice in the first relapse or primary refractory disease. However, in the era of new agents such as Brentuximab vedotin (BV) or immune checkpoint inhibitors, the standard salvage treatment before HSCT cannot be easily selected[16]. Clinical activity of Irinotecan has been identified in a wide range of malignancies, including non-small cell lung, colorectal, gastric, ovarian, cervical, and pancreatic cancer, as well as no Hodgkin lymphoma and T-cell leukemia/lymphoma [17]. In 2002, a case report on the efficacy of Irinotecan in relapsed Hodgkin lymphoma demonstrated that Irinotecan has a therapeutic effect in patients with relapsed Hodgkin's lymphoma [18]. Moreover, Ghadiany et al. evaluated the efficacy of Irinotecan in relapsed or refractory non-Hodgkin lymphoma[9,10] and Niitsu et al. evaluated the efficacy of Irinotecan in relapsed or refractory peripheral T-cell lymphoma with good results[19]. Therefore, we evaluated the effect of Irinotecan in combination with cisplatin and dexamethasone on Hodgkin lymphoma patients with promising results and low toxicity.

CONCLUSION

Irinotecan is a topoisomerase-I inhibitor and is used in many tumors. Ghadiany et al. and Kang et al. evaluated the efficacy of Irinotecan in relapsed or refractory non-Hodgkin lymphoma with an ORR of 81% and 71%, respectively[9,10]. Niitsu administered Irinotecan in combination with Mitoxantrone and dexamethasone in relapsed or refractory peripheral T-cell lymphoma with an ORR of 60%[19]. In Kang's study, the most limiting side effect was neutropenia which was a limiting factor, and Ghadiany et al. evaluated this regimen by reducing the dose of drugs and support of GCSF with good results. There are few studies on the efficacy of Irinotecan in Hodgkin lymphoma, so we prescribed this regimen to 24 relapsed or refractory Hodgkin lymphoma patients.
Based on the fact that neutropenia was a limiting factor in Kang's study, we followed the Ghadiany protocol and prescribed the regimen with GCSF support. Delay in drug administration was prevented by GCSF administration. In our study, ORR was 66%, and we were able to refer 37.5% of our patients to transplantation. Regarding our patients' survival after bone marrow transplantation, no information is available. The goal of the salvage chemotherapy in relapsed or refractory Hodgkin Lymphoma is achieving CR or PR preparation patients for stabilization with BMT. Thus, we recommend ICD as one of the most effective protocols with overall response rate of 66% in this population.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. De González AB, Mahesh M, Kim KP, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. Arch Intern Med. 2009;169(22):2071-7.
2. Hasenclever D, Diehl V, Armitage JO, et al. A prognostic score for advanced Hodgkin's disease. N Engl J Med. 1998;339(21):1506-14
3. Oza A, Ganesan T, Leahy M, et al. Patterns of survival in patients with Hodgkin's disease: long follow up in a single centre. Ann Oncol. 1993;4(5):385-92.
4. Abalı H, Ürün Y, Öksüzoğlu B, et al. Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer Invest. 2008;26(4):401-6.
5. Mohammad ali M, Hossein R, Behrooz N, et al. IEV (Ifosfamide, Epirubicin, VP16) Regimen as Salvage Therapy for Early Relapsed/Refractory non-Hodgkin/Hodgkin Lymphoma. Int J Hematol-Oncol. Stem Cell Res. 2011;5(3):11-15.
6. Portlock CS, Rosenberg SA, Glatstein E, et al. Impact of Salvage Treatment on Initial Relapses in Patients With Hodgkin Disease, Stages I–III. Blood. 1978;51(5):825-33.
7. Suzumiya J, Suzushima H, Maeda K, et al. Phase I study of the combination of irinotecan hydrochloride, carboplatin, and dexamethasone for the treatment of relapsed or refractory malignant lymphoma. Int J Hematol. 2004;79(3):266-70.
8. Kuruvilla J, Nagy T, Pintilie M, et al. Similar response rates and superior early progression-free survival with gemcitabine, dexamethasone, and cisplatin salvage therapy compared with carmustine, etoposide, cytarabine, and melphalan salvage therapy prior to autologous stem cell transplantation for recurrent or refractory Hodgkin lymphoma. Cancer. 2006;106(2):353-60.

9. Ghadiany M, Foratyazdi M, Rahimi H, et al. Modified irinotecan plus cisplatin and dexamethasone (icd) combination chemotherapy as salvage chemotherapy for patients with relapsed/refractory diffuse large cell lymphoma. Indian J Hematol Blood Transfus. 2014;30(4):265-8.
10. Kang HJ, Kim WS, Suh C, et al. Irinotecan plus cisplatin and dexamethasone (ICD) combination chemotherapy for patients with diffuse large B-cell lymphoma previously treated with Rituximab plus CHOP. Cancer Chemother Pharmacol. 2008;62(2):299-304.
11. Suyanı E, Sucak GT, Akı ŞZ, et al. Gemcitabine and vinorelbine combination is effective in both as a salvage and mobilization regimen in relapsed or refractory Hodgkin lymphoma prior to ASCT. Ann Hematol. 2011;90(6):685-91.
12. Bartlett NL, Niedzwiecki D, Johnson J, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol. 2007;18(6):1071-9.
13. Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica. 2007;92(1):35-41.
14. Moskowitz AJ, Hamlin Jr PA, Perales MA, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2013;31(4):456-60.
15. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.
16. Knopińska-Posłuszny W, Kulikowski W, Paszkiewicz-Kozik E, et al. Zastosowanie bendamustyny z gemcytabiną i deksametazonem w leczeniu pierwotnie opornej i nawrotowej postaci chłoniaka Hodgkina–wieloośrodkowe badanie obserwacyjne Polskiej Grupy Badawczej Chłoniaków (PLRG). Acta Haematol Pol. 2015;46:58-9.
17. Wagener DT, Verdonk H, Dirix L, et al. Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study. Ann Oncol. 1995;6(2):129-32.
18. Urushihata K, Koizumi T, Kaneki T, et al. Successful salvage therapy of irinotecan for relapsed Hodgkin's lymphoma. Internl Med. 2002;41(8):648-50.
19. Niitsu N, Kohori M, Higashihara M, et al. Phase II study of the irinotecan (CPT-11), mitoxantrone and dexamethasone regimen in elderly patients with relapsed or refractory peripheral T-cell lymphoma. Cancer Sci. 2007;98(1):109-12.