Modified Irinotecan Plus Cisplatin and Dexamethasone (ICD) Combination Chemotherapy as Salvage Chemotherapy for Patients with Relapsed/Refractory Diffuse Large Cell Lymphoma

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Abstract About 50 % of patients with diffuse large cell lymphoma are candidate for salvage chemotherapy followed by bone marrow transplantation in the selected patients. In the current study we evaluated modified ICD (Irinotecan, Cisplatin, and Dexamethasone with G-CSF support) as salvage chemotherapy in the patients previously treated with R-CHOP or CHOP. In a retrospective study we evaluated 16 patients treated with modified ICD: irinotecan 65 mg/m² (max 100 mg)/day plus cisplatin 30 mg/m² (max 50 mg)/day and dexamethasone 40 mg/day on days 1 and 8. Prednisolone 200 mg divided in 2 doses was given orally on days 2 and 9. G-CSF (PDgrastim) was administered at 300 µg/day subcutaneously on days 4–6 and 11–13. pre- and post-hydration was given according to our hospital protocol. Overall response rate was 75 % for all of the patients and 90 % for the patients treated as first line salvage. The median overall survival was 23 ± 12 months. There was no grade 3/4 of neutropenia and no cycles of chemotherapy were delayed due to leucopenia. Modified ICD might be an

effective salvage regimen for refractory/relapsed lymphoma patients. Unlike original ICD, leucopenia does not seem to be a limiting factor. So we conclude that modified ICD shall be considered as a safe and effective regimen for salvage chemotherapy in refractory/relapsed patients.

Keywords Diffuse large cell lymphoma · Irinotecan · Cisplatin · Salvage chemotherapy

Introduction

Aggressive non-Hodgkin lymphoma (NHL) even in advanced stage is a curable disease but about 50 % of the patients experiences relapse or do not respond to first line initial chemotherapy [1]. This group of the patients needs to be treated with salvage chemotherapy plus autologous stem cell transplantation but optimal salvage regimen is already unclear [2, 3]. Kang et al. [4] evaluated ICD (irinotecan, cisplatin and dexamethasone) regimen as salvage chemotherapy on 15 patients with relapsed or refractory lymphoma. This protocol was effective with 71 % overall response rate, but the incidence of neutropenia with delay of subsequent cycles was a limiting factor [4]. We evaluated the modified ICD by adding G-CSF and varying the dose of irinotecan and cisplatin. The feasibility and efficacy of modified ICD were evaluated in our study.

Patients and Methods

Patients

Between August 2008 and February 2009, modified ICD protocol was used as salvage chemotherapy for relapsed or

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refractory lymphoma in our hospital. The details of modified ICD protocol are illustrated in next paragraph. In a retrospective study we evaluated and reported the outcome of patients with relapsed/refractory lymphoma who were treated with modified ICD in our hospital. The patients were accepted for evaluation if they had the following inclusion criteria: Age between 18 and 70 years, an Eastern Cooperative Oncology Group (ECOG) performance status of less than two, acceptable bone marrow function (defined as platelet count more than 100,000/ μ L and absolute neutrophil count (ANC) more than 1,500/ μ L), appropriate renal and hepatic function, diagnosed with relapsed or refractory diffuse large cell lymphoma (DLCL) B or T cell type and were treated with CHOP or R-CHOP as first line chemotherapy. The patients who have been treated with modified ICD as first or second salvage chemotherapy were included in the study. The current study was designed and conducted according to the latest Declaration of Helsinki.

Modified ICD Chemotherapy Regimen

Modified ICD chemotherapy consisted of 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) was administered 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 in 2 doses was given orally on days 2 and 9. G-CSF (PDgrastim) was administered at 300 μ g/day subcutaneously on days 4–6 and 11–13. This protocol was planned to repeat every 3 weeks.

All chemotherapy drugs were given in the outpatient department. This schedule was planned to be continued until disease progression, severe toxicity or stem cell transplantation or up to 6 cycles.

Response Criteria

Response to treatment was evaluated by computed tomography (CT) scan that have been done during treatment or after the last cycle of chemotherapy. The best response was used as the response for analysis. The response to chemotherapy was evaluated according to Response Criteria for NHL Used NCI of Canada Clinical Trials Group [5]. The overall survival (OS) was measured from the start day of modified ICD until death or the last follow up. The progression free survival (PFS) was measured from the start day of modified ICD until lymphoma progression or death. The event-free survival (EFS) was measured from the start day of modified ICD until manifestation of any treatment failure sign. Treatment failure was defined as discontinuation of treatment for reasons

such as disease progression, toxicity, patient preference, initiation of new treatment due to lack of observable progression or death. Adverse reactions were assessed by the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Results

We found out 16 patients with aggressive NHL and 2 patients with Hodgkin lymphoma (HL) were treated with modified ICD in our hospital from August 2008 to February 2009. Medical files of these patients were evaluated in this retrospective study. The patients' characteristics are presented in Table 1. The median age was 48 $\pm$ 19 (range 18–78) years. Male to female ratio was 11/5 and 63 % of the patients had B cell lymphoma. All the patients had acceptable bone marrow, renal and hepatic function. R-CHOP and CHOP protocols have been used as first line chemotherapy in 60 and 40 % of patients with B-cell lymphoma. Modified ICD regimen was used as first salvage treatment in 69 % of the patients and as second salvage chemotherapy in 31 % of them. Total 58 cycles of modified ICD chemotherapy was administered to the patients, with mean number 3.6 (range 2–6) per patient. Response evaluation was done in all of the patients with CT scan during or after the last cycle of ICD. If the patients had 2 or more times CT scans, that one reporting a better response was considered for analysis.

Complete response (CR) and partial response (PR) were achieved in 19 and 62 % of patients, respectively. Stable

Table 1 Patients' characteristics

Character	Number (%)
No. of patients	16
Sex (male/female)	11/5
Mean age, 56 years (20–67 years) stage	
I or II	4 (25 %)
III or IV	12 (75 %)
Type of lymphoma	
B-cell	10 (63 %)
T-cell	5 (31 %)
Un known	1 (6 %)
B symptom	6 (60 %)
First salvage or second salvage	
First salvage	11 (69 %)
Second salvage	5 (31 %)
Response to CHOP(R-CHOP)	
Complete remission	5 (31 %)
Partial remission	6 (38 %)
Refractory	5 (31 %)

Fig. 1 Overall survival curve

Table 2 Major side effects per 58 cycles

	Grade 1 or 2 (%)	Grade 3 or 4 (%)
Anemia	10	3
Thrombocytopenia	9	5
Neutropenia	10	0
Increased ALT	2	0
Increased AST	2	0
Increased total bilirubin	2	0
Nausea	50	0
Vomiting	40 %	0
Diarrhea	10	5
Increased creatinin	2	2

disease (SD) was seen in 19 % of the patients but no patient experienced a progressive disease (PD) during chemotherapy with modified ICD. The overall response rate (CR + PR) was achieved in 81 % [13/16; 95 % confidence interval (CI), 72–100 %]. Overall response rate was 9 of 10 (90 %) in the patients treated after CHOP(R-CHOP) as first salvage and 4 of 6 (67 %) in the patients were treated as second salvage chemotherapy. Overall response rate was the same between the patients with B-cell and T-cell lymphoma.

Six patients received less than 4 cycles of ICD. Of these 6 patients 1 underwent autologous bone marrow transplantation (BMT) after 3 cycles, 2 did not tolerated the adverse effects (one patient developed irreversible renal failure with creatinine more than 3 mg/dl, another patient experienced severe diarrhea) while we did not find the reasons in other 3 patients.

The median of estimated OS for all patients was 23 ± 15 months and event-free survival was 12 ± 9 months. Autologous BMT was done in 4 patients. The median OS for patients consolidated with BMT and those did not was 29 ± 19 and 21 ± 12 months, respectively (Fig. 1).

Complications

Modified ICD was tolerable with low incidence of complications (Table 2). Nausea (grad 1 or 2) was the most common complication, occurring in 50 % of the subjects. Creatinine was increased in 2 patients and as mentioned before that resulted in the discontinuation of modified ICD in one of them. The neutropenic fever and delayed treatment due to leucopenia were not reported in any of the patients.

Conclusion

Irinotecan is a topoisomerase-I inhibitor and it is effective in many kind of solid tumors including colon, small cell lung, stomach and other organs malignancies. The effectiveness of irinotecan as monotherapy in relapsed or refractory lymphoma is approved with response rate of 11–39 % [4]. The combination of irinotecan plus dexamethasone and mitoxeantron, for treatment of elderly patients with relapsed or refractory lymphoma was evaluated by Niitsu et al. [6] and 11 (37 %) and 7 (23 %) of 30 elderly patients achieved complete and partial remission, respectively. Overall response rate in this study was 60 % that was comparable with findings of other studies.

Kang et al. evaluated the efficacy and safety of irinotecan in combination with dexamethasone and cisplatin in 15 patients with relapsed or refractory lymphoma as first-salvage after R-CHOP chemotherapy. In this study OR was 71 % and the most limiting side effect was neutropenia leading to delay treatment [4].

In our study G-CSF was administrated as primary prophylaxis and subsequently neutropenia was prevented and no course of chemotherapy was delayed because of this adverse effect. This finding parallel with the literature suggest that in patients with relapsed/refractory lymphoma candidate for treatment with irinotecan-based chemotherapy, primary prophylaxis with G-CSF is effective and we strongly recommend it. Overall response rate in our study for all the patients was 81 % but it was 90 % for the subgroup of patients treated as first salvage chemotherapy. Overall response rate of 90 % is acceptable and it is comparable with the results reported for ICE or DHAP protocols [2, 7–9]. This overall response rate is higher than original ICD (70 %) and this may be due to use of G-CSF that allowed us to administrate the planed dose of chemotherapy and complete the treatment protocol. The better response rate presented here also might be attributable to the fact that in our study only 40 % of the patients were treated with RCHOP and 60 % of our patients were not treated with rituximab in first line chemotherapy, therefore they were more sensitive to salvage chemotherapy. While

in Kang study all patients have been treated with rituximab in first line, so perhaps they had been less sensitive to the salvage chemotherapy. The overall response rate in our patients who were treated with R-CHOP in the first line protocol was 75 %, a rate similar to the original ICD's response rate [4].

At the time of study, access to BMT was limited in our country and only 4 of 16 patients were consolidated with BMT. BMT has significant effect on overall survival therefore we can not compare overall survival of our cases with other studies with more patients consolidated with BMT.

The aim of salvage chemotherapy in relapsed or refractory lymphoma is achieving complete or PR to prepare the patients for consolidation with BMT. So we recommend the modified ICD as one of the most effective protocols with overall response rate of 90 % in the patients with relapse or refractory to CHOP and 75 % in the patients with relapse or refractory R-CHOP chemotherapy regimen.

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