Brief Communication

Reduced Weekly Subcutaneous Doses of Bortezomib in Combination with Cyclophosphamide and Dexamethasone for Newly Diagnosed Multiple Myeloma

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Abstract

Objective: A combination of bortezomib, cyclophosphamide, and dexamethasone is highly effective in the treatment of newly diagnosed multiple myeloma. Neuropathy is a dose-limiting adverse effect of this regimen. Subcutaneous and weekly injection instead of biweekly intravenous administration are used to reduce neuropathy. In this study, patients treated with subcutaneous weekly reduced the dose of bortezomib to reduce neuropathy and cost of treatment. **Methods:** This is an interventional study, including 16 patients. Enrolled patients received bortezomib 1 mg/m^2 subcutaneously, cyclophosphamide 300 mg/m^2 intravenously, and dexamethasone 40 mg intravenously days 1, 8, 15, and 22 of a 28 cycle. **Findings:** The overall response rate (≥partial response [PR]) was 93.8%. Thirteen of 16 patients (81.3%) were in an acceptable PR and complete response. Two patients (12.5%) achieving a PR. Meantime to achievement, the best response was 71 (55–87) days. Median progression-free survival was 33 (2–56) months, and autologous stem cell transplantation was performed for 68.8% of patients. Five patients (31.25%) experienced Grade I and one patient (6.25%) Grade III (no Grade 2 or 4) of peripheral neuropathy. Dose reduction and drug discontinuation was required in one patient (6.25%). **Conclusion:** A reduced subcutaneous, weekly dose of bortezomib in combination with cyclophosphamide and dexamethasone is effective with manageable profile toxicity and acceptable cost.

Keywords: *Bortezomib, multiple myeloma, neuropathy*

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Introduction

Multiple myeloma is a plasma cell neoplasia characterized by hypercalcemia, anemia, renal failure, and bony lytic lesions. Over the past two decades, the diagnosis and treatment of disease have improved, and the myeloma has changed from a fatal disease to a treatable but incurable disease. The incidence of disease increased by 126% from 1990 to 2016.[1] Multiple myeloma accounts for 17% of hematologic malignancy in the United States.[2] Newly diagnosed patients should be assessed for autologous bone marrow transplantation. Patients eligible for hematopoietic cell transplantation (HCT) receive induction chemotherapy, followed by high-dose chemotherapy and HCT. Patients ineligible for HCT generally receive induction chemotherapy followed by maintenance therapy until the progression. Various combinations of regimens for induction therapy are used. Corticosteroid, immunomodulatory agents, proteasome inhibitors, and alkylating agents are most common drugs that generally used in a combination regimen.

Bortezomib is a 1st-generation proteasome inhibitor that used for *de novo* and relapsed myeloma.[3,4] The use of bortezomib seems to be a significant evolution

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in the treatment of the disease. The response rate with bortezomib varies by a combination regimen that used. Peripheral neuropathy is a significant side effect of bortezomib, albeit it seemed reversible in a majority of patients, but dose reduction and drug discontinuation are necessary for palliation.[5] Subcutaneous injection and weekly injections can be used to reduce bortezomib induce neuropathy. Subcutaneous infusion of bortezomib compared to intravenous administration had an improved safety profile with noninferior efficacy.[6] Weekly injection compared to twice-weekly dose in relapsed/refractory myeloma had comparable outcomes with lower rate neuropathy.[7]

Irrespective of these side effects, bortezomib is an expensive drug but is likely to be cost effective compared with other combinations such as melphalan, prednisolone, thalidomide, or lenalidomide.[8] Jagannath *et al*. reported that in relapsed or refractory multiple myeloma reduced doses of bortezomib, 1 mg/m^2, compared to standard treatments, had comparable overall response rate and lower toxicity, such as neuropathy.[9]

Bortezomib had used in a various combination regimen. Three drug combinations of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) are the first-line regimen for the initial treatment in newly diagnosed patients with high response rate.[10]

This study designed to evaluate the efficacy of reduced doses of bortezomib in the treatment of newly diagnosed multiple myeloma patients. In this study, we assess the effectiveness and adverse effects of once weekly subcutaneous reduced doses of bortezomib 1 mg/m^2 in the CyBorD regimen.

Methods

This was an interventional study conducted on patients with multiple myeloma from 2014 to 2017. Sixteen newly diagnosed patients (age range: 44–64-year-old) based on the International Myeloma Working Group updated the criteria included in the study,[11] who referred to Omid Hospital, Isfahan, Iran. Before starting treatment benefits and side effects of treatment clearly explained to the patients, and then, all of them read and signed the consent form. Patients with concurrent disease that induced neuropathy, severe heart and pulmonary disease, signs of amyloid light-chain amyloidosis, and recurrent or refractory myeloma excluded from the study. Patients treated with bortezomib 1 mg/m^2 subcutaneously, cyclophosphamide 300 mg/m^2 intravenously, and dexamethasone 40 mg intravenously days 1, 8, 15, and 22 of a 28 days cycle. All medications were administered weekly for 4 consecutive weeks. At the end of each cycle, laboratory findings were evaluated, and patients categorized as complete, acceptable partial, and partial response (PR) based on the International Myeloma Working Group consensus criteria.[12] Patients with at least PRs, who were eligible for HCT, referred for transplantation, and for patients with stable disease after two cycles and patients with progressive disease alternative treatment were used. Neurologic examination was performed for all patients at baseline and beginning of each period. Bortezomib induces peripheral neuropathy graded per National Cancer Institute common toxicity criteria for adverse events.[13]

Results

Sixteen patients with newly diagnosed multiple myeloma were evaluated. The mean age was 54 (44–64) years. Sixty-two percent were men, and 38% were women. 37.5%, 50%, and 12.5% of patients were in International Staging System, Stage I, II, and III, respectively. Fifteen patients had symptomatic disease (Durie–Salmon Stage II or III). Other baseline disease characteristics are summarized in Table 1.

The overall response rate (≥PR) was 93.8% (15/16). Thirteen of 16 patients (81.3%) were in very good PR and complete response. Two patients (12.5%) achieving a PR. One patient (6.2%) had progressive disease after two cycle chemotherapy. Meantime to achievement, the best response was 71 (55–87) days. After a median follow-up of 36 (20–57) months from the time of diagnosis, four of 16 patients died. Median progression-free survival was 33 (2–56) months, and HCT was performed for 68.8% (11 patients) of patients. Ten of 11 patients referred for HCT were able to mobilize peripheral blood stem cells with granulocyte colony-stimulating factor (G-CSF) alone and the other with G-CSF and plerixafor [Table 2].

All patients were assessed for peripheral neuropathy. Fourteen patients completed all four cycle chemotherapy.

Table 1: Baseline patient demographics and disease characteristics (mean, *n*=16)

Myeloma characteristic	Normal value
Hemoglobin (gr/dL)	11.03
Serum creatinine (mg/dL)	1.50
Serum calcium (mg/dL)	10.36
Bone lesion (%)	75
Serum ß2 microglobulin (mg/L)	3.8
Serum albumin (g/dL)	3.8
Myeloma subtype (%)	
IgG-κ	50
IgG-λ	25
IgA-κ	12.5
Kappa light chain	12.5

Table 2: Case-by-case description of the toxicity and efficacy of the regimen

Patient number	Sex	Age	Response	Neuropathy
1	Female	49	CR	Grade I
2	Male	51	CR	Grade III
3	Male	52	APR	Grade I
4	Female	59	CR	No neuropathy
5	Female	52	CR	No neuropathy
6	Male	64	APR	No neuropathy
7	Female	60	CR	Grade I
8	Male	44	APR	No neuropathy
9	Male	51	APR	Grade I
10	Female	51	APR	Grade I
11	Female	53	PR	Grade I
12	Male	51	CR	Grade I
13	Male	57	CR	Grade I
14	Male	53	PR	No neuropathy
15	Male	59	No response	No neuropathy
16	Male	59	CR	No neuropathy

CR=Complete response, APR=Acceptable partial response, PR=Partial response

Of the two patients who did not complete treatment, one patient had progressive disease, and another had Grade III peripheral neuropathy that had not resolved by drug discontinuation. Five patients experienced Grade I peripheral neuropathy and one patient Grade III (no Grade 2 or 4). Only one patient (6.25%) required doses reduction and drug discontinuation.

Discussion

The availability of new drugs with different mechanisms has revolutionized the treatment of multiple myeloma. One of the regimens used is CyBorD, which has been associated with a high response rate in various studies. Data from three phase II studies in newly diagnosed multiple myeloma have shown high response rates with CyBorD.[14-16] Reeder *et al*. reported an overall response rate of 89%, with 62% of them had good PR.[14] Analysis of Deutsche Studiengruppe Multiples Myelom (DSMM) Xia trial indicated overall response rate and complete response rate of 84% and 10%, respectively.[15] In EVOLUTION trial, CyBorD in newly diagnosed myeloma patients led to overall response rate of 75%.[16] In all three studies, bortezomib was administrated at the doses of 1.3 mg/m^2 intravenously 1, 4, 8, and 11 of 21 days cycle.[14-16]

The overall response rate in our study was 93.5% that was comparable with three previous studies although no head-to-head comparison was made between this study and prior studies. One of the most critical complications of this combination is neuropathy, with an estimated up to 39%.[15] In this study, to reduce this complication, bortezomib was administered subcutaneously at weekly doses of 1 mg/m^2 in combination with cyclophosphamide and dexamethasone.

In the DSMM Xia trial, 39% of patients had polyneuropathy, but only 3% had Grade 3 polyneuropathy.[15] Reeder *et al*. reported 46%, 13%, and 7% Grade I, II, and III neuropathy, respectively, in which study 27% of patients required drug discontinuation.[14] Due to high rate adverse events such as neuropathy in twice weekly bortezomib, Reeder *et al*. modified their regimen to a once-weekly protocol. In their study, overall response rate was similar to the biweekly schedule, but Grade 3/4 adverse effects such as neuropathy were less, besides fewer doses reduction required.[17] In our study, five patients (30.6%) experienced Grade I peripheral neuropathy and one patient (6.25%) Class III (no Grade 2 or 4). Only one patient (6.25%) required doses reduction and drug discontinuation. Compared with the previous studies, incidence of neuropathy, especially Grade 3/4 are less, and fewer patients require doses reduction and drug discontinuation. However, because of the small number of samples in our study, the conclusions should be cautious.

Bortezomib is an expensive drug. Hill *et al*. reported that target prices for bortezomib in 2016 were £411 per cycle in the United Kingdom.[18] If the cost of the drug is reduced, but its effectiveness has not changed, not only more patients can use this drug but also patients experience fewer adverse effects. In our study, the reduced doses of bortezomib do not appear to affect its efficacy, and the cost of drug has also decreased significantly. The most important limitations of this study are its small sample size.

The most important limitations of this study are its small sample size. Due to the small sample size, we cannot generalize the results of this study to all patients. On the one hand, the small sample size makes it impossible to head compare the results of this study with other studies. Of course, this study can be used as a pilot study to design a study with appropriate sample size.

Reduced subcutaneous, weekly doses of bortezomib in combination with cyclophosphamide and dexamethasone seems to be effective with manageable profile toxicity and acceptable cost.

Authors' Contribution

Farzaneh Ashraf and Azadeh Moghadass performed literature search, prepared, edited, discussed and contributed to the final manuscript. Ali Darakhshandeh devise the project, designed and contributed to the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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