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The Evaluation of Generic Bortezomib Molecule in Newly Diagnosed Multiple Myeloma Patients

Sinan Mersin, Ayfer Gedük, Özgür Mehtap, Pınar Tarkun, Serkan Ünal, Merve Gökçen Polat, Kemal Aygün, Emel Merve Yenihayat, Hayrunnisa Albayrak, Abdullah Hacıhanifioğlu

University of Kocaeli, Medical Faculty, Department of Hematology, Kocaeli, Turkey

Sinan Mersin, MD, University of Kocaeli, Medical Faculty, Department of Hematology, Kocaeli, Turkey
sinanmersin86@msn.com
0000-0001-7588-6000

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Abstract

Aim: Constantly increasing health expenditures lead use of generic molecules and generics of bortezomib have been used for a long time. The aim of this study is to retrospectively examine the effectiveness, side effects and reliability of generic bortezomib in newly diagnosed multiple myeloma (MM) patients.

Methods: The data of 95 patients who received four cycles of bortezomib as a first- or second-line therapy in a single center were retrospectively recorded. Treatment responses, side effects and progression free survival (PFS) rates have been calculated and compared.

Results: Of the 95 patients, 42 used the original and 53 used the generic molecule. Epidemiological data, MM types, genetic risk groups, laboratory values at diagnosis and bortezomib treatment lines (as a first line or second) were evaluated, and there was no statistical difference between the two groups. When the response rates were evaluated with International Myeloma Working Group (IMWG) criteria, there were no significant difference (p: 0,42). Partial response (PR) and above response rates were similar (%81 vs %79,2 p:0,836). PFS values were 42.8 months in the original and 37.8 months in the generic molecule group (p: 0,68). Side effects were seen in 44,2% of patients, and the most common side effects were neuropathy, cytopenias and infections. They were similar in both groups (p: 0,67).

Conclusion: Although this retrospective study is limited, it is the first study comparing the original molecule of bortezomib with its generic. There was no statistical difference between the two groups in terms of treatment responses, PFS times and side effects. However, large-scale evaluations can help obtain healthier data on this subject.

Key words: bortezomib, multiple myeloma, equivalent, generic

Introduction

Multiple myeloma is a plasma cell dyscrasia that constitutes 14% of all hematological malignancies and 20% of mortality due to hematological malignancies. It has no cure with current treatment options. In a study examining the global data of 2016, it was shown that the total incidence of MM was 2.1 per 100000 (95% UI, 1.8-2.3) and 1.5 per 100000 (95% UI, 1.3-1.7) total deaths were associated with myeloma [1] and the incidence has increased over the past 30 years [2, 3].

The proteasome is the main extra lysosomal system of cells and inhibition of this system causes cell cycle arrest and apoptosis mainly in neoplastic cells. These proteasome inhibitors mainly used for myeloma and lymphoma and bortezomib was the first one that is used. Although patients became refractory to this treatment after a while, it is still used in the first line of myeloma treatment [4-6]. In recent years, new proteasome inhibitors such as carfilzomib and ixazomib have been developed and they are used in these relapsed/ refractory MM patients and treatment response rates were better [7].

In the optimal treatment approach of newly diagnosed patients, besides good efficiency and reliability, cost balance should also be taken into account. Health expenditures for multiple myeloma continues to increase in total, with the increase in incidence, as well as the costs of new treatments [3]. Because of this increase, it requires the development of generic drugs and patients had to use these molecules because of the price difference. But the use of generic molecules initially creates concerns among physicians in terms of effectiveness and side effects. We planned this study in order to eliminate this uncertainty. For bortezomib, it has more than seventy generics in use and four generics has been used in our country. In our center, Borcade is used as a generic and in this study, we compared this molecule with the original one (Velcade) [4, 8].

Materials and methods

The files of 340 patients diagnosed with MM between 2011 and 2019 in a single center were retrospectively scanned. 95 patients received only original (Velcade) or generic (Borcade) bortezomib treatment for at least 4 cycles in the first or second line of therapy with cyclophosphamide and dexamethasone. VCD therapy was selected over VTD (bortezomib, thalidomide and dexamethasone therapy) mainly because of reimbursement rules of the country. Original molecule users used bortezomib between March 2011 to March 2017 while generic molecule users used between May 2015 to February 2019. Of the 95 patients included in the study, 42 used the original molecule and 53 used the generic molecule. Patients who received both original and generic molecule, who received more than one generic molecule, who received bortezomib as a third line of treatment or received bortezomib after autologous stem cell transplantation/relapse excluded from study.

IMWG diagnostic criteria were sought in the diagnosis of patients, ISS criteria were used for staging, and genetic risk factors were also made according to IMWG criteria [9]. Routine laboratory analysis, radiological imaging and PET-CT examinations of the patients were performed in our hospital's central laboratory, radiology department and nuclear medicine units respectively. IMWG response criteria were also used in post-treatment response evaluations. Consent was obtained from the ethics committee of our hospital for the analysis of patient files.

After the demographic characteristics of our patients, M protein levels at diagnosis, MM types, disease stages, genetic risk groups, extramedullary involvement and lytic lesions in their bones, laboratory values at the time of diagnosis and the first treatments they received

before bortezomib-cyclophosphamide-dexamethasone (VCD) therapy, if any, were recorded. After receiving VCD treatment for 4 cycles, patients' response evaluation was performed. Some of the patients who responded to the treatment were transplanted immediately, while some went to the autologous stem cell transplant (ASCT) after continuing the same treatment. This was due to ASCT availability at their treatment time and treatment continued to keep their response rates. Patients who could not achieve ASCT were followed up. A small number of patients with or without ASCT received maintenance of lenalidomide therapy (It was 10mg/day for 21 days in 28-day period as a standard in both groups). The recurrence dates of these patients were recorded in both groups, and progression-free survival times were calculated. Hematological and non-hematological side effects occurring during treatment were rated and recorded according to the latest National Cancer Institute toxicity criteria (CTCAE) [10].

Statistical Analysis

SPSS statistics program was used in the analysis. Student-t test was used in the analysis of numerical data with normal distribution, Mann-Whitney U test was used in the analysis of data that do not fit the normal distribution and more than two categorical data, Chi-square test was used in the analysis of binary categorical data and Kaplan-Meier test used for estimating the survival times. A "p" value of <0.05 was considered statistically significant.

Results

Epidemiological data is given in Table 1. There was no statistical difference in the distribution of patients and the associated p values are also given.

As can be seen in Table 1, the majority of patients in both groups were male and the average age of diagnosis was over 60. The rate of stage 2 patients in the original molecule group was 50%, and a more homogeneous distribution was observed in the generic molecule group. When the disease stages distributed according to the treatment lines, even though it is statistically insignificant and that there were only 11 patients in generic group of second treatment line, the high-risk patient group had a little more percentage in the second treatment line in generic molecule group (p: 0,43 and 0,49). Otherwise, the distributions were similar to the upper groups which they belong to. When evaluated in terms of MM types, the most common myeloma type was IgG Kappa in both groups. The rate of high-risk patients was 21.4% in the original molecule group, 37.7% in the generic molecule group. When this risk groups distributed between treatment lines and high-risk patients evaluated, there were some differences between sub-groups. Original molecule users in first line of treatment and generic molecule users in second line had a higher percentage of high-risk then to the upper groups which they belong to. Number of patients in sub-groups were low and it is statistically insignificant but should be noted when evaluating results in those sub-groups (p:0,34 and 0,49). Also, it should be noted that genetic risk assessment could not be made for the vast majority of patients. To sum it all, there was no significant statistical difference between groups and sub-groups according to the treatment lines. Extramedullary involvement, lytic lesion rates, mean laboratory values at the time of diagnosis were also similar in both groups.

Bortezomib was used in combination with cyclophosphamide and dexamethasone. Bortezomib dosage was 1,3 mg/m^2 and it is reduced to 1,1 mg/m^2 in patients with side effects like neuropathy. Bortezomib was given subcutaneously to all patients. Cyclophosphamide dosage was 500 mg. Dexamethasone dosage was 40 mg to patients below 60 years old and 20 mg to patients above 60 years old. The response rates of the patients to the treatment containing bortezomib they received in the first or second line are given in Table 2.

The patients' responses are evaluated after 4 cycles of treatment and another evaluation was made for patients who got more than 4 cycles in pre-transplantation period. Those rates were in the same group according to IMWG criteria for each patient. When the patients' responses are evaluated there are some minor differences between the two molecule groups but this

difference is not statistically significant (p: 0,42). When responses rates are divided into two as above MR or below PR, the results were similar in both groups (81% vs 79,2% p: 0,83). In our country reimbursement rules did not allow the use of bortezomib as a first line of treatment for a period of time. Patients were able to use bortezomib after at least two cycles of a combination treatment that did not contain bortezomib like vincristine, doxorubicin and dexamethasone (VAD). After the reimbursement rules were arranged, patients were able to use bortezomib treatment in the first line of treatment. For this reason, 27 of the patients received bortezomib containing regimens as a second line of therapy after 2 cycles of VAD combination therapy. 11 of 27 patients were in the generic molecule group, 16 of them were in the original molecule group (p: 0,63). Treatment results also analyzed according to these sub-groups: The rate of PR and above was higher in those using the generic molecule in the group that received the bortezomib treatment as first line (%81 vs %76,9) and in those using the original molecule in the group that received bortezomib treatment as second line (%87,5 vs %72,7). These results may be because of the higher percentage of high-risk patients in those sub-groups but again it was not statistically significant (p:0,76 and p:0,33 respectively). Before the progression-free survival times of the patients were calculated, whether the patients had extra VCD treatment cycles, whether the patients went into ASCT and whether they received a maintenance lenalidomide treatment were compared in both groups. Some of the patients in both groups received extra cycles of VCD treatments due to ASCT availability at their treatment time. The maximum number of treatment cycles were 8 in both groups and means of the treatment cycle numbers were 5,2 in original and 5,7 in generic molecule group (p:0,89).23 (%54,8) of the patients using the original molecule and 25 (%47,2) of the patients using the generic molecule were transplanted. In both molecule groups, high-dose cyclophosphamide therapies were used for mobilization. All mobilizations had succeeded with enough stem cell collection and there was no difference between molecule groups regarding mobilization and transplantation toxicities. After transplantation, all patients in both molecule groups got engrafted successfully and no serious complications were seen in both groups after transplantation. 12 (30.8%) of the patients using the original molecule and 13 (24.5%) of the patients using the generic molecule used maintenance lenalidomide treatment. Lenalidomide dosage was 10mg/day for 21 days in 28-day period as a standard in all patients. There was no significant difference between the groups in these respects (p: 0.537 p:0.637 respectively). The median follow-up time was higher in original molecule group mainly because of treatment dates (30 months vs 20 months). Considering all these differences, it should be kept in mind that the statistical data on PFS values are very weak. However, PFS values were calculated for the two groups to give an idea. PFS values were 42,8 (±SD 4,8) months in original arm and 38,3 (±SD 5,89) months in generic arm but there was no statistically significant difference (p: 0,68).

When the side effects related to molecules are evaluated, side effects were seen in 44.7% of patients using Bortezomib. The most common side effects were seen as neuropathy, anemia, thrombocytopenia, neutropenia and infections. Side effects were observed in 20 patients (47,6%) receiving the original molecule, and 22 patients (41,5%) receiving the generic molecule (p: 0,67). When the side effect grades were evaluated according to CTCAE, grade 3-4 side effects were observed as neuropathy in 4 patients (2 patients in the original molecule, 2 patients in the generic molecule group), all remaining side effects were observed as grade 1-2. Vincristine therapy (which included in VAD regimen) can also cause permanent neuropathy so to better separate this from bortezomib side effect that been investigated, neuropathy is evaluated in both first line and second line sub-groups. In the first line treatment sub-group neuropathy risk was higher in original molecule group and in the second line group it was vice versa. But these differences were statistically insignificant (%23 vs %7,1 p:0,08 and %18,8 vs %27,3 p:0,66 respectively). (The side effects seen in both groups and the associated

p value comparing groups are given in Table-3.

Discussion

Nowadays, it is known that the treatment results of patients are improved with new drugs. However, the increase in health spending related to these drugs leads health authorities to some alternatives. One of the first examples of this condition is generic imatinib therapy. It was reported that the responses of chronic myeloid leukemia patients with original imatinib were protected by generic products and annual cost was reduced by 96% [11]. In two real-life studies, generic imatinib has been reported to be effective and safe in first line treatment [11, 12] . Also, there are studies about economics of generic drugs on country scale or about factors for choosing generic products [13, 14]. Other than imatinib, there are only few studies comparing generic molecules with their original counterparts. Those studies include comparison of low molecular heparin and psychoactive drugs with their generic counterparts[15, 16]. Apart from those and as far as we know, our study is the first one comparing original bortezomib with its generic molecule.

Bortezomib has been licensed by FDA in 2003 in patients with multiple myeloma, it had been used as a combination therapy with cyclophosphamide and dexamethasone since 2007 [17-19]. In our country, original molecule is used as a combination therapy since 2010. Generic bortezomib was launched by obtaining a license in 2012. In accordance with the reimbursement policy of the health authority, it has started to be used in patients due to the price difference. The generic bortezomib caused some concerns among physicians at first because of its effectiveness or side effect profile.

In our study where the data of patients were examined; the distribution of epidemiological features, stages, disease types and other risk factors among the groups was not statistically different. When the response rates to treatment were evaluated, there was no statistically difference between the two groups in both the first-line treatment and the second-line treatment. There were some statistically insignificant differences have been observed between sub-groups and that can be due to percentage of high-risk patients. Treatment response rates in both groups are similar to those studies in which the original bortezomib molecule was combined with cyclophosphamide and dexamethasone. In these studies, any response rate (PR and above) was 80% and similar data were obtained in both groups in our study [17, 19-21]. The results showed us that the responses of patients using the generic bortezomib molecule are similar to those of the original molecule (%81 original arm, %79,2 generic arm). Even though the data is statistically weak there was also no significant difference between progression-free survival times, and these values were similar to other studies on the VCD protocol [22, 23]. When the side effects were evaluated, no significant difference was found between the two groups. The most common side effects were evaluated as neuropathy, cytopenias and infections similar to other studies, and in our study diarrhea side effect was observed less than other bortezomib studies [17, 19, 20, 22-24].

Multiple myeloma is a disease in which response rates are increased with new treatments and total survival is prolonged but there is no cure chance. It is a fact that such diseases bring additional costs to health expenditures of countries. Generic medicines can be an alternative both to provide access to new medicines and to reduce the burden on health expenditures. Although this retrospective study includes a limited number of patients, it is the first study with the generic bortezomib that came into use in our country. Our data show that the drug's post-cure responses are similar to the original molecule, and the side effects are similar to the original molecule and manageable. Randomized, prospective studies with a greater number of patients and follow-up time are needed to understand whether the use of generic bortezomib in multiple myeloma treatment affects long-term survival.

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Figure 1. PFS Evaluation

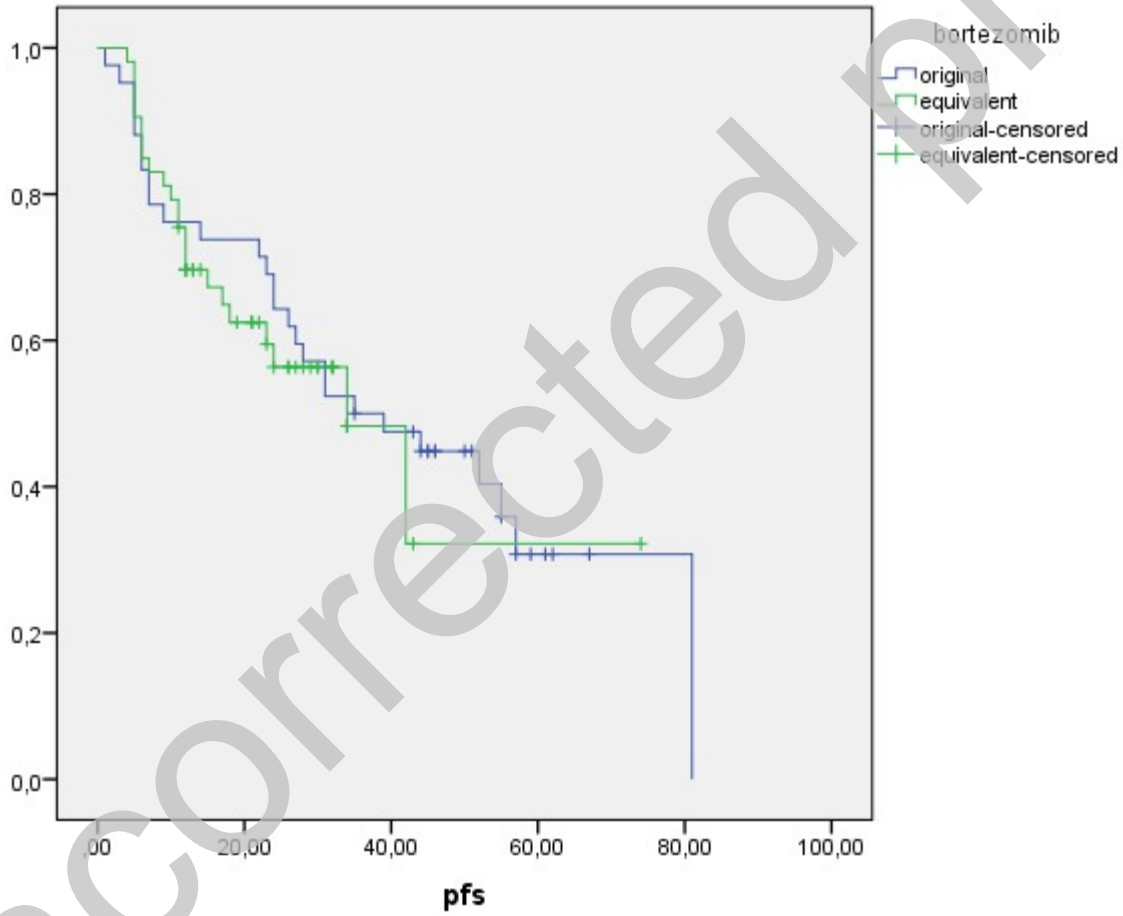

Table 1. Characteristics of Patients			
	Original Molecule Number (%)	**Equivalent Molecule Number (%)**	**p value**
Total number of patients	42	53	
Average age (Min-	64 (36-87)	62 (32-85)	0,37

Max):			
Gender (Female-Male):	13/29 (31/69)	14/39 (26,4/73,6)	0,65
Stage (ISS):			0,25
I	8 (19)	16 (30,2)	
II	21 (50)	18 (34)	
III	13 (31)	19 (35,8)	
Stage as in treatment lines	First - Second	First - Second	First - Second
I	5 (19,2) – 3 (18,8)	13 (31) – 3 (27,3)	0,43 – 0,49
II	13 (50) – 8 (50)	15 (35,7) – 3(27,3)	
III	8 (30,8) – 5 (31,5)	14 (33,3) – 5(45,5)	
Myeloma type:			
IgG kappa	16 (38,1)	12 (22,6)	0,1
IgG lambda	3 (7,1)	12 (22,6)	
IgA kappa	7 (16,7)	10 (18,9)	
IgA lambda	2 (4,8)	2 (3,8)	
Lambda light chain	6 (14,3)	11 (20,8)	
Kappa light chain	6 (14,3)	1 (1,9)	
Non-secretory	2 (4,8)	4 (7,5)	
Genetic risk group:			0,13
Standard risk	9 (21,4)	20 (37,7)	
High risk	3 (7,1)	6 (11,3)	
Unknown	30 (71,4)	27 (50,9)	
Genetic risk groups as in treatment lines	First - Second	First - Second	First - Second
Standard risk	5 (19,2) – 4 (25)	15 (35,7) – 5 (45,5)	0,34 – 0,07
High risk	3 (11,5) – 0	4 (9,5) – 2 (18,2)	
Unknown	18 (69,2) – 12 (75)	23 (54,8) – 4 (36,4)	
During the diagnosis;			
Extramedullary involvement	8 (19)	8 (15,1)	0,74
Lytic lesions	28 (66,7)	41 (77,4)	0,28
Laboratory results	Mean (± SD)	Mean (± SD)	
Hemoglobulin (gr/dl)	10,53 (1,87)	10,38 (1,92)	0,779
Leukocyte ($x10^9$/l)	6254 (2517)	6546 (2568)	0,451
Platelets ($x10^9$/l)	238045 (124255)	204602 (83510)	0,29
Creatinine (mg/dl)	1,2 (1,12)	1,31 (1,11)	0,62
Calcium (mg/dl)	9,44 (0,9)	9,58 (1,21)	0,712
ISS: International Staging System; SD: standard deviation.			

Table 2. Response to treatments			
	Original Molecule Number (%)	**Equivalent Molecule Number (%)**	**p value**
Total response rates			0,42
Progression	3 (7,1)	3 (5,7)	
SD	0	3 (5,7)	
MR	5 (11,9)	5 (9,4)	
PR	11 (26,2)	21 (39,6)	
VGPR	13 (31,0)	11 (20,8)	
CR	10 (23,8)	10 (18,9)	
Total response rates			0,83
PR and above	34 (81)	42 (79,2)	
MR and below	8 (19)	11 (20,8)	
Response rates as first line			0,21
Progression	2 (7,6)	2 (4,7)	
SD	0	1 (2,3)	
MR	4 (15,3)	5 (11,9)	
PR	4 (15,3)	18 (42,8)	
VGPR	9 (34,6)	7 (16,6)	
CR	7 (26,9)	9 (21,4)	
Response rates as first line			0,76
PR and above	20 (76,9)	34 (81)	
MR and below	6 (23,1)	8 (19)	
Response rates as second line			0,44
Progression	1 (6,2)	1 (9)	
SD	0	2 (18,2)	
MR	1 (6,2)	0	
PR	7 (43,8)	3 (27,3)	
VGPR	4 (25)	4 (36,4)	
CR	3 (18,8)	1 (9)	
Response rates as second line			0,33
PR and above	14 (87,5)	8 (72,7)	
MR and below	2 (12,5)	3 (27,3)	
PR: Partial response; VGPR: very good partial response; CR: full response; SD: stable disease; MR: minimal response			

Table 3. Side effects			
	Original Molecule Number (%)	**Equivalent Molecule Number (%)**	**p value**
Any side effect	20 (47,6)	22 (41,5)	0,67
Neuropathy	9 (21,4)	6 (11,3)	0,26
Anemia	4 (9,5)	8 (15,1)	0,54
Neutropenia	2 (4,8)	4 (7,5)	0,69
Thrombocytopenia	3 (7,1)	2 (3,8)	0,65
Respiratory tract infections	4 (9,5)	4 (7,5)	0,72
Diarrhea	4 (9,5)	3 (5,7)	0,69