



Original Article

The efficacy of Bortezomib-based regimens on survival state in newly diagnosed multiple myeloma patients

Kawa Muhamedamin Hasan*

Medicine and Clinical Hematology, College of Medicine, Hawler Medical University/ Consultant Physician and Clinical Hematologist, Nanakali Hospital for Blood Diseases and Cancer, Erbil, Kurdistan region- Iraq



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Abstract

The prognosis of patients with multiple myeloma (MM) has significantly improved over the past ten years because of several innovative treatments, including the proteasome inhibitor Bortezomib and immunomodulatory drugs (IMiDs) like Thalidomide and Lenalidomide. The present study aimed to determine the effectiveness of Bortezomib-based regimens on survival state of MM patients. This retrospective study included 204 newly diagnosed MM patients who were registered at Nanakali Hospital for Blood Diseases and Cancer, Erbil- Iraq, between April 2008 and April 2022. The patients were split into two primary groups: those receiving treatment with Bortezomib and those not. Clinical and laboratory data, treatment type, responsiveness to induction therapy, and survival results were examined in the enrolled patients' medical records. The mean patient age was 60 years, males constituted 55.8% of the included patients. At the time of diagnosis, 98 individuals (48%) had stage 3 illness. Except for the LDH, which was noticeably higher in the non-Bortezomib group, the patients laboratory results did not substantially change between the Bortezomib and non-Bortezomib groups ($p = 0.001$). In patients treated with Bortezomib, the complete response (CR) rate following induction was substantially greater (35.2%) than in those treated without Bortezomib (9.1%). Compared to the non-Bortezomib group, the median survival time of the Bortezomib group was considerably greater ($p < 0.001$). Bortezomib has a significant role in inducing a CR before bone marrow (BM) transplantation, and it has a significant role in the survival outcome in MM.

Keywords: Bortezomib, NDMM, Survival outcome

1. Introduction

The clonal plasma cell illness known as MM produces monoclonal immunoglobulin and is associated with symptoms such as anemia, bone pain, renal failure, immunodeficiency, and hypercalcemia [1]. It makes up about 10% of hematological malignancies and 1% of all cancers. It is the second most common hematological malignancy. When diagnosed, most patients are older than 65, with a median age of 70 [2].

For patients who are eligible for transplantation, the current standard course of treatment is an induction regimen lasting four to six cycles, followed by an autologous stem cell transplant (ASCT) and a maintenance phase that lasts until the illness progresses or becomes toxic. The transplant-ineligible patients are typically treated with more than six induction cycles, usually 8 to 12, followed by the maintenance phase, or the induction phase is followed by subsequent 2 to 4 consolidation cycles of the same treatment used in the induction phase, followed by maintenance [3, 4].

The typical treatment of MM is a combination of pharmacological agents and ASCT, taking into consideration patient's status including age, comorbidities, performance

status and eligibility for ASCT. There are different pharmacological classes used for treatment of MM, immunomodulatory drugs (IMiDs) such as Thalidomide, Lenalidomide and Pomalidomide, proteasome inhibitors (PIs) such as Bortezomib, Carfilzomib, Ixazomib, the monoclonal antibodies such as Daratumumab, Elotuzumab; histone-deacetylase inhibitors (HDACi) such as Panobinostat, Ricolinostat) [5–7].

The goal of treating myeloma patients in both transplant-eligible and transplant-ineligible candidates is to have a prolonged survival through the best possible response and have a good quality of life [8]. Thalidomide, Bortezomib, and Lenalidomide have significantly improved the overall survival (OS), the progression-free survival (PFS), and the overall response rates (ORRs) [9].

Despite the approval of more recent medications, the first-generation proteasome inhibitor bortezomib is still a commonly used antimyeloma treatment for both newly diagnosed multiple myeloma (NDMM) and relapsed myeloma patients [6]. When used in conjunction with other medications, Bortezomib is the go-to treatment for MM. In the UK, the National Institute for Health and Care Excellence (NICE) has approved its use to treat NDMM

* Corresponding author.

E-mail address: mah_kawa@yahoo.com (K. M. Hasan).

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in transplant-eligible patients when it is combined with dexamethasone (Vd) (IFM trial) or with thalidomide (VTD) (PETHEMA trial) [10]. Bortezomib has also been approved by NICE for treatment of NDMM in transplant non-eligible patients in combination with melphalan and a prednisolone (VMP) (VISTA trial) [11]. Bortezomib is NICE-approved as well for relapsed MM, in combination with dexamethasone (Vd) (APEX trial) [12].

The current study's objective was to assess the effectiveness of Bortezomib by contrasting the frequencies of induction phase response and survival outcomes between MM patients receiving Bortezomib and those not.

2. Materials and Methods

This retrospective study included 204 patients, they were NDMM patients. The study took place from April 2008 to April 2022 at Nanakali Hospital for Blood Diseases and Cancer in Erbil, Northern Iraq. The patients were divided into two main groups based on whether the induction phase of the treatment involved Bortezomib (the Bortezomib treated group) or not (the non-Bortezomib treated group). The Bortezomib group included 105 (51.5%) patients while the non-Bortezomib group included 99 (48.5%) patients. Individuals without complete dates were not included in this study.

The medical records of all patients were checked for clinical findings and laboratory data. Patients' characteristics including age, gender, date of diagnosis, and evidence of bone involvement like pain or fracture were scrutinized. Laboratory findings included complete blood count, blood film, renal function tests (RFT), serum lactic dehydrogenase (LDH), serum calcium, serum and urine protein electrophoresis, serum and urine immunofixation, BM aspiration and biopsy, imaging including plain X-ray, CT scan or MRI.

The type of treatment modalities was checked, Bortezomib group (105 patients) included VRD (Velcade= Bortezomib, Revlimid= Lenalidomide, Dexamethasone) 52%, VTD (Velcade, Thalidomide, Dexamethasone) 33%, VCD (Velcade, Cyclophosphamide, Dexamethasone) 18%, MVP (Melphalan, Velcade, Prednisolone) 2%, while non-Bortezomib group (99 patients) included CTD (Cyclophosphamide, Thalidomide, Dexamethasone) 54%, VAD (Vincristine, Adriamycin= Doxorubicin, Dexamethasone) 26%, TD (Thalidomide, Dexamethasone), RD (Revlimid, Dexamethasone), RCD (Revlimid, Cyclophosphamide, Dexamethasone) (TD, RD and RCD 8%), MTD (Melphalan, Thalidomide, Dexamethasone), MTP (Melphalan, Thalidomide, Prednisolone) and MP (Melphalan, Prednisolone) (MTD, MTP and MP 11%). Only 42 patients (20%) had ASCT, of them 36 (34%) patients were of the Bortezomib group and 6 patients (6%) were of the non-Bortezomib group. The type of response to induction treatment was determined as complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD) and progressive disease (PD). The kind of therapy and the disease's clinical stage were then connected with the survival rates.

2.1. Ethical consideration

This study was performed as per the Helsinki Declaration. Data were fully anonymized before being accessed. The ethical committee of Hawler Medical University's College of Medicine gave its approval to the study.

2.2. Statistical analysis

Data analysis was done with SPSS version 26. The proportions of the two study groups were compared using the Chi-square test of association. When the predicted frequency (value) of more than 20% of the table's cells was less than 5, Fisher's exact test was utilized. The means of the two study groups were compared using the unpaired t-test. The log-rank test was used to compare the survival times of the curve's categories after Kaplan-Meier survival curves were plotted. When a p-value was less than 0.05, it was deemed statistically significant.

3. Results

The study's participants comprised 204 MM patients, with a mean age of 59.81±11.68 years. Of them, 114 patients were male, accounting for 55.8% of the total. Table 1 illustrates the patient characteristics of the two studied groups. The Eastern Cooperative Oncology Group (ECOG) performance status was 2 in 118/204 patients. Bone involvement was encountered in 194 (95.1%) patients. Stage 3 MM according to the International Staging System (ISS) was encountered in 98 (48%) of the patients. The clinical parameters did not show significant variations between the Bortezomib and the non-Bortezomib treated groups.

Table 2 compares the laboratory data of the Bortezomib and the non-Bortezomib treated groups at time of diagnosis. The mean serum LDH level in the non-Bortezomib group was significantly higher than in the Bortezomib group (295.02 versus 242.35 IU/L, p=0.001). Between the two groups under study, there were no discernible variations in the other laboratory data, which included Hb, WBCs, Plt count, serum levels of creatinine, calcium, and beta2 microglobulin. The immunoglobulin isotypes and the plasma cell count in the BM aspirates and biopsies did not vary between the two groups.

The number of induction therapy cycles did not significantly differ between the two groups. (p=0.354). The Bortezomib treated group achieved significantly higher CR rates before BMT than the non-Bortezomib treated group (35.3% versus 9.1, p<0.001) (Table 3).

Table 4 and Figure 1 show the mean and median survivals of the Bortezomib and the non-Bortezomib treated groups. The estimated mean and median survivals of the Bortezomib group were significantly higher than the non-Bortezomib group (72.8 and 62 versus 39.2 and 23 months, p<0.001, respectively).

Table 5 and Figure 2 reveal the association between the stage of the disease and mean and median survival times. The advanced disease stage correlated negatively with the mean and median survival times.

4. Discussion

While a large body of research has addressed the function of Bortezomib in MM, to date, no studies from the Kurdistan Region of Iraq have evaluated the impact of Bortezomib for newly diagnosed MM. Currently, more new agents such as Carfilzomib (next-generation PIs) and Pomalidomide (IMiDs) have been approved by the FDA, [13, 14] but they are not available in our hospitals and markets. For this reason, MM patients in Iraq are still typically treated with chemotherapy regimens that include Bortezomib.

In the present study, 105 patients with MM received treatment using regimens based on Bortezomib, while 99 individuals had treatment using alternative therapeutic

Table 1. Patients characteristics.

	Bortezomib	non-Bortezomib	Total	P-Value
	No. (%)	No. (%)	No. (%)	
Age (years)				
<50	18 (17.1)	19 (19.1)	37 (18.1)	
50-59	38 (36.1)	31 (31.3)	69 (33.8)	
60-69	26 (24.7)	23 (23.2)	49 (24.0)	
≥70	23 (21.9)	26 (26.2)	49 (24.0)	0.818*
Mean (SD)	59.55 (11.15)	60.09 (12.27)		0.743†
Gender				
Female	43 (40.9)	47 (47.4)	90 (44.1)	
Male	62 (59.0)	52 (52.5)	114 (55.8)	0.348*
ECOG score				
1	17 (16.1)	14 (14.1)	31 (15.1)	
2	60 (57.1)	58 (58.5)	118 (57.8)	
3	27 (25.7)	26 (26.2)	53 (25.9)	
4	1 (0.9)	1 (1.0)	2 (0.9)	0.971**
Bone disease				
Involved	99 (94.2)	95 (95.9)	194 (95.1)	
Not involved	6 (5.7)	4 (4.1)	10 (4.9)	0.749**
Stage (ISS)				
Stage 1	22 (20.9)	16 (16.1)	38 (18.6)	
Stage 2	32 (30.4)	36 (36.3)	68 (33.3)	
Stage 3	51 (48.5)	47 (47.4)	98 (48.0)	0.557*
Total	105 (100.0)	99 (100.0)	204 (100.0)	

By Chi-square test. **By Fisher's exact test. †By unpaired t-test.

Table 2. Laboratory data of the Bortezomib and the non-Bortezomib treated groups at presentation.

	Bortezomib		Non-Bortezomib		p
	Mean	(SD)	Mean	(SD)	
Hb (g/dL)	9.48	(2.23)	9.56	(2.24)	0.811†
WBC (x10 ⁶ /L)	6.92	(3.68)	7.90	(3.67)	0.061†
Platelets (x10 ⁶ /L)	204.70	(94.87)	217.15	(99.64)	0.361†
Creatinine (mg/dL)	2.03	(2.08)	2.20	(2.03)	0.561†
Calcium (mg/dL)	9.50	(1.33)	9.47	(1.37)	0.845†
B2MG (mg/L)	7.39	(7.79)	7.62	(7.76)	0.832†
LDH (IU/L)	242.35	(111.78)	295.02	(117.57)	0.001†
BMA-PC%	39.47	(25.26)	37.70	(24.86)	0.615†
BMB-PC%	49.27	(21.56)	47.64	(19.52)	0.573†
Ig isotypes	No.	(%)	No.	(%)	
IgA K	9	(8.5)	8	(8.0)	
IgA L	14	(13.3)	9	(9.0)	
IgG K	45	(42.8)	51	(51.5)	
IgG L	8	(7.6)	3	(3.0)	
KLC	16	(15.2)	23	(23.2)	
LLC	12	(11.4)	5	(5.0)	
Non-secretory myeloma	1	(0.9)	0	(0.0)	0.187*
Total	105	(100.0)	99	(100.0)	

†By unpaired t-test. *By Chi-square test. BMA: bone marrow aspiration, PC: plasma cell, BMB: bone marrow biopsy, K: Kappa, L: Lambda, LC: Light chain.

Table 3. Treatment and outcome.

	Bortezomib	Non-bortezomib	Total	p
	No. (%)	No. (%)	No. (%)	
No. of treatment cycles				
≤ 6	41 (39.0)	45 (45.5)	86 (42.2)	0.354*
> 6	64 (61.0)	54 (54.5)	118 (57.8)	
Type of response before bone marrow transplantation (BMT)				
Complete remission (CR)	37 (35.2)	9 (9.1)	46 (22.5)	
Very good partial response (VGPR)	53 (50.5)	53 (53.5)	106 (52.0)	
Partial response (PR)	5 (4.8)	25 (25.3)	30 (14.7)	
Stable disease (SD)	0 (0.0)	1 (1.0)	1 (0.5)	
Progressive disease (PD)	10 (9.5)	11 (11.1)	21 (10.3)	< 0.001*
Total	105 (100.0)	99 (100.0)	204 (100.0)	

*By Chi-square test.

Table 4. The survival time in the groups.

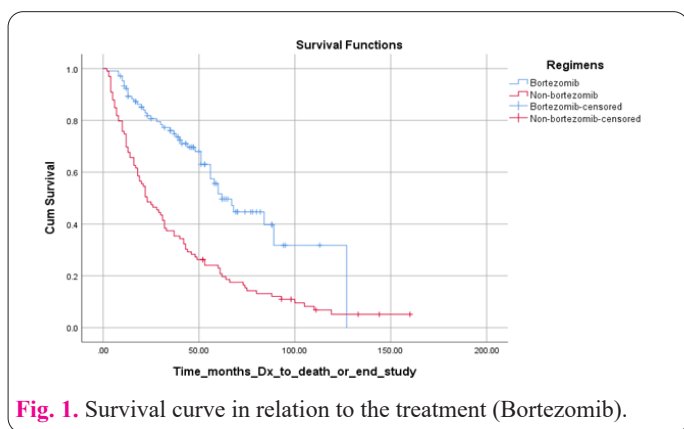
Regimens	Estimate (months)	SE*	Mean		Median			
			95% CI		Estimate (months)	SE	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Bortezomib	72.897	5.804	61.521	84.273	62.000	5.677	50.874	73.126
non-Bortezomib	39.220	4.108	31.167	47.272	23.000	4.069	15.026	30.974
Overall	56.265	3.994	48.437	64.093	43.000	4.722	33.746	52.254

P < 0.001 By Log Rank (Mantel-Cox). SE= Standard of Error, 95% CI= 95% Confidence Interval.

Table 5. The mean and the median survival time in relation to the disease stage.

ISS stage	Estimate	SE	Mean		Median			
			95% CI		Estimate	SE	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Stage I	78.423	9.745	59.322	97.524	73.000	13.253	47.023	98.977
Stage II	58.967	5.623	47.946	69.988	51.000	7.598	36.108	65.892
Stage III	42.618	4.812	33.187	52.048	28.000	4.437	19.304	36.696
Overall	56.265	3.994	48.437	64.093	43.000	4.722	33.746	52.254

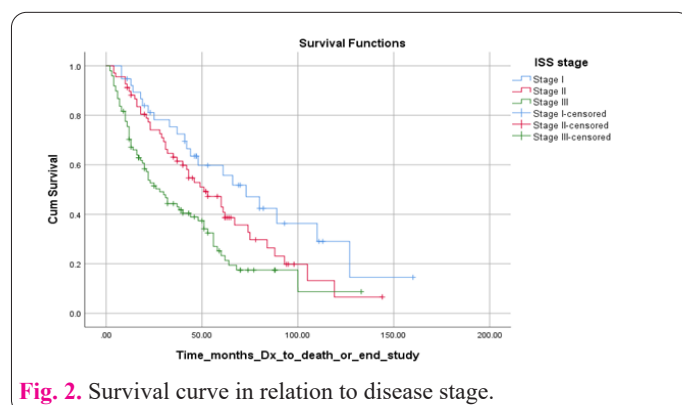
P = 0.001 By Log Rank (Mantel-Cox). SE: Standard of Error, 95% CI= 95% Confidence Interval.



agents prior to the advent of Bortezomib. The recruited MM patients had a mean age of around 60 years, which is comparable to previous research [15–17]. Among the patients, 64% were under 65 years of age (131 patients); our figure is much higher than a study done by Kazandjian² but very close to He et al.[15] Male patients constituted 55% of the patients, approximate figures were reported in pre-

vious studies [9, 17, 18]. The study found no statistically significant variations in the fundamental demographic and clinical features of age, gender, performance level, illness stage, and bone involvement between the two groups under investigation.

Approximately three-quarters of the patients (73%) had a good performance status, the ECOG score was 1 or 2. The



performance score of our patients was somewhat different from a previous study by Rajab et al [19] who reported an ECOG score of 0 to 2 in 41% of their patients but was comparable to the Afram et al study [20]. Almost 95% of our MM patients had bone involvement at time of diagnosis, nearly similar results were reported in other studies [21–23]. However, a Swedish report by Bilmark et al found a lower rate of bone involvement [8]. According to the ISS, 48% of our patients were stage 3 at time of presentation; many previous studies reported lower clinical stages of their patients [8, 9, 16, 17], this discrepancy is probably because of misdiagnosis or late medical consultation of our patients. The vast majority of our cases (99.6%) had secretory myeloma and the frequency of immunoglobulin isotypes were: IgG Kappa in 52.4%, IgA in 19.6%, and light chain myeloma in 27%. The proportion of light chain myeloma was slightly above than the standard level of 15–20% [24].

According to the patient's laboratory results, the non-Bortezomib group had a considerably higher serum LDH level. A high serum LDH level in myeloma is related to disease burden and a higher chance for relapse, and it is a marker of poor prognosis [25]. All other hematological and biochemical test values, including the beta 2 microglobulin, did not significantly vary between the two studied groups. The mean plasma cell count in BM aspirates and biopsies did not vary either within the study groups.

Treatment of NDMM includes induction phase, usually 4–6 cycles, ASCT, then maintenance in the transplant-eligible patients, while the transplant-ineligible patients are treated with induction phase, usually 8–12 cycles, and maintenance [4, 26]. The goal of the induction phase is to attain the highest achievable response rate, meanwhile to avoid significant toxicity, and impairment of stem cell collection for transplant illegible patients. In the current study more than half of the MM patients in two treatment arms (Bortezomib and non-Bortezomib groups) had received more than 6 induction cycles, this is probably due to the higher number of patients that were not transplanted, either because they were not eligible or because they did not have a chance of transplantation. In the northern Kurdistan region of Iraq, only one BM transplantation facility is available with a relatively long waiting list; moreover, many patients are financially unable to afford BM transplantation outside Iraq.

In our patient population, the group receiving Bortezomib had a considerably higher response rate to induction phase therapy than the group not receiving the medication. Less than two-thirds (62.6%) of patients in the non-Bortezomib group had \geq VGPR, whereas the majority of patients (85.7%) in the Bortezomib treated group had full response or very excellent partial response (CR+ VGPR). Furthermore, about 35% of patients in the Bortezomib group had CR compared to only 9% in the non-Bortezomib group; this difference was statistically significant. Our results are very similar to a Chinese study by He J et al. [15] and the Spanish PETHEMA trial [27] in which 35% CR was obtained from 6 induction cycles of VTD. Approximate results were published by the phase II Intergroupe Francophone du Myelome study which reported 29% CR rate when VRD was evaluated [28]. It is worth noting that the rate of VGPR in two arms was nearly the same or even a bit higher in the non-Bortezomib group (53.5% versus 50.5% respectively). This indicates that non-Bortezomib agents

like IMiDs (lenalidomide and thalidomide) and alkylating agents (cyclophosphamide and melphalan) that were used prior to the Bortezomib have a good role in myeloma treatment. In addition, it emphasizes the role of Bortezomib in achieving a deeper and better response rate which was very obvious when we compared the CR in both groups. The role of Bortezomib in achieving a higher CR was agreed upon in many previous studies [27–30].

The most crucial phase of myeloma treatment is the induction regimen, which has a direct bearing on long-term results [31]. On the other hand, SCT plays a major part in raising the rate of minimum residual disease (MRD), enhancing patient response rates, and enhancing overall and PFS [32–35]. The median OS of MM patients in this study was 43 months; our survival results are superior to a Jordanian study by Qasem et al [36], which reported median OS of 38 months; though majority of their patients were treated with the non-Bortezomib agents. An OS of 5.2 years was reported by Kumar et al at the Mayo Clinic [37]. In the Bortezomib group, the median survival time was 62 months, while in the non-Bortezomib group, it was 23 months ($P < 0.001$). This notable distinction between the two groups most likely illustrates how the use of Bortezomib medication affects survival rates. Indeed the role of Bortezomib in improving the survival outcomes was approved in previous studies [37–40]. It is important to mention that only 42 (20%) patients in the current study have had ASCT (34% of Bortezomib group versus 6% non-Bortezomib group), this small sample of transplanted patients cannot accurately signify the role of SCT on survival outcomes. The substantial association between the survival time and the illness clinical stage, as determined by IPSS, was another noteworthy discovery in this study. The median survivals in stages I, II, and III were 73, 51 and 28 months respectively. As mentioned earlier, about half (48%) of our patients were in stage III at time of diagnosis and this perhaps had a clear negative effect on the OS time which was 43 months. The correlation between the disease stage and survival outcome was well documented before [8, 26].

5. Conclusion

Bortezomib has a significant role in inducing a CR before BM transplantation, and it has a significant role in the survival outcome in MM.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

After reading it, the author gave the final text the go-ahead to publish.

Ethics approval and consent to participate

Data were fully anonymized before being accessed. The ethical committee of Hawler Medical University's College of Medicine gave its approval to the study.

Informed Consent

The authors declare not to use any patients in this research.

Availability of data and material

The study's supporting data, according to the author, are

included in the article.

Authors' contributions

The author designed research methods, collected the data, analyzed data, and drafted the manuscript.

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