Response of Bortezomib Versus Non-Bortezomib Based Regimen in Newly Diagnosed Patients of Multiple Myeloma

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Abstract

Objective: To evaluate the response of Bortezomib based regimen versus non Bortezomib based regimen in treatment of newly diagnosed multiple myeloma patients.

Methods: Equal number of newly diagnosed Multiple Myeloma patients treated with Bortezomib and non-Bortezomib based regimen were included in the study after informed consent. Baseline characteristics were recorded. Response was assessed after 4 cycles of therapy according to International Myeloma Working Group (IWMG). Data was analyzed using SPSS version-23. Initial frequencies and percentages of data were obtained. Descriptive variables were reported as mean & frequencies. Intergroup Analysis was done using Mann Whitney test with $p \leq 0.05$ taken as significant.

Results: In the Bortezomib containing arm, 25.9% patients achieved Complete response (CR) while very good partial response (VGPR), partial response (PR) was seen in 40% and 14.81% patients respectively. Here, 3.7% patients had progressive disease (PD). In non-Bortezomib arm, no one achieved a complete response, while 37.03%, 33.33%, 14.8% and 7.4% patients had VGPR, PR and SD and PD respectively. The difference in response between the two arms was significant as interpreted by Mann Whitney test $p \leq 0.05$.

Conclusion: Bortezomib based regimens are associated with better response rates in newly diagnosed patients of Multiple Myeloma in Pakistani population.

Keywords: multiple myeloma, bortezomib.

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Introduction

Multiple Myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow. Multiple myeloma accounts for about 1.8 % of all cancers and slightly over 17 % of hematological malignancies in the United states.[1] Multiple Myeloma is frequently diagnosed among people aged 65 to 74 years with median age being 69 years. Exposure to radiation, benzene and other organic solvents, herbicides and insecticides may play a role. There is an increased risk of multiple myeloma in first degree relatives.[2] Until recently, MM was defined by the presence of end-organ damage, more frequently causing hypercalcemia, renal failure, anemia, and bone lesions that is attributed to the clonal process. In 2014, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for MM to add three additional biomarkers: clonal bone marrow plasma cells greater than or equal to 60%, serum free light chain (FLC) ratio greater than or equal to 100 provided involved FLC level is 10 mg/L or higher, or more than one focal 5mm lesion on MRI scan. In addition, the definition was revised to allow CT and PET-CT to diagnose MM bone disease. High-risk cytogenetic abnormalities have led to the development of a new staging system in addition to standard laboratory markers of prognosis.[3]

Newly diagnosed Multiple Myeloma is sensitive to a variety of cytotoxic drugs. Although Multiple myeloma is incurable, and periods of remission can be achieved by various therapies, the course of multiple myeloma is characterized by recurring relapses leading to multi-

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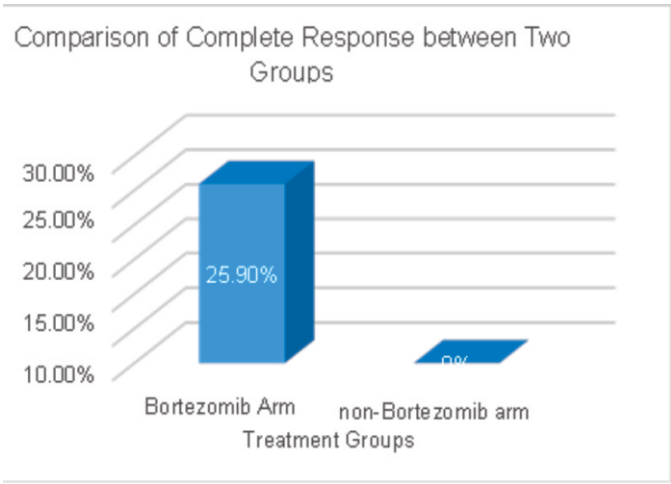
refractory disease and death. Multiple myeloma field remain the subject of intensive research, and new combination regimen are tested in both relapse and newly diagnosed Multiple Myeloma. Most commonly used regimen for the treatment of newly diagnosed multiple myeloma include proteosome inhibitors and Immune modulators like Lenalidomide as a corner-stone of therapies. The standard of care is Induction with Triplet regimen followed by Autologous stem cell transplant (ASCT). Promising emerging data with combination of Lenalidomide, Bortezomib and dexamethasone have produced better results. A clinical trial has shown benefit of overall response rate 85%.[5]

Material & Methods

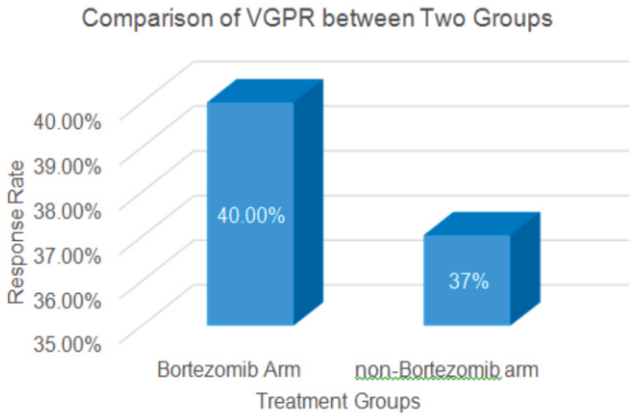
This study was designed to assess response of Bortezomib based regimen versus non Bortezomib based regimen in the treatment of newly diagnosed multiple myeloma patients in Pakistan. After determining the baseline characteristics, an equal number of newly diagnosed patients were assigned different treatment arms. Arm A included patients treated with Bortezomib based therapy, Bortezomib, Lenalidomide, Dexamethasone (VRD) & Bortezomib, Dexamethasone (VD) whereas patients in Arm B were given Non Bortezomib based regimen Melphalan, Prednisone, Thalidomide (MPT), Prednisone, Thalidomide (PT) & Lenalidomide & Prednisone (RD). Response to each cycle was assessed after 4 cycles of therapy according to International Myeloma Working Group (IWMG). Data was analyzed using SPSS version 23. Initial frequencies and percentages of data were obtained and descriptive variables were reported as mean and frequencies. Mann-Whitney test was applied setting 95% confidence interval and p value of <0.05 to be taken as significant. We went through the records of patients who qualified after meeting our inclusion criteria. Inclusion criteria involved patients aged from 30 to 80 years of age and newly diagnosed patients of Multiple Myeloma according to latest International Myeloma Working Group (IMWG) diagnostic criteria.

Results

Demographic details of patients **(Table 1)** in both the arms are tabulated. In Arm A, Bortezomib based regimen, 85.1% of the patients received VD and the remaining 14.81% received VRD. Out of these a complete response (CR) was observed in 25.9% of the patients, very good partial response (VGPR) and Partial response (PR) was seen in 40% and 4% respectively. Here, 3.7% patients had a progressive disease (PD). In Arm B, Non Bortezomib based regimen, 55.55% of the patients received MPT, whereas 29.63% and 14.81% got PT and RD respectively. In this arm, no one achieved CR, while 37.03%, 33.33%, 14.8% and 7.4% patients had VGPR, PR, SD and PD A Mann-Whitney test was applied as our data was non parametric and it indicated that Induction response was greater for Valcade based therapy (Mdn=2) than for the Non Valcade Based Therapy (Median=3), U = 241.000, p = 0.026.



Graph 1: *Comparison of Complete Response between groups.*



Graph 2: *Comparison of VGPR between groups.*

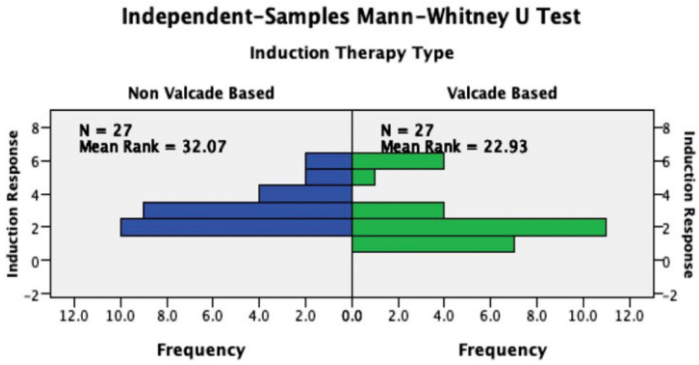


Figure 1: *Mann-Whitney U Test:*

Table 1: *Demographics of Patients Included in Study*

Demographics	Bortezomib Arm	Non Bortezomib Arm	P value
Age (Years)	69.11±9.54		
Gender, n (%)			
Male	14 (51.85)	10 (37.03)	>0.05
Female	13 (48.16)	17 (67.97)	
ISS Stage, n (%)			
Unknown	09 (33.33)	09 (33.33)	
I	05 (18.52)	07 (25.93)	>0.05
II	05 (18.52)	06 (22.22)	
III	08 (29.62)	05 (18.52)	
Serum Immunoglobulin, n (%) IgG	21 (77.78)	20 (74.10)	>0.05
IgA	06 (22.22)	07 (25.93)	
Free light chain, n (%) Kappa	20 (74.10)	19 (70.37)	>0.05
Lambda	07 (25.93)	08 (29.63)	
Bone lesion at presentation, n (%)			>0.05
Yes	24 (88.89)	20 (74.10)	
No	03 (11.11)	07 (25.93)	
Hemoglobin (g/dl)	9.9±1.89		
Creatinine Clearance	68.50±36.89		

Discussion

After the introduction of Melphalan-Prednisone in 1960s, a 30-year stationary period followed where multiple chemotherapy combinations were tried and tested but didn't improve the survival of patients significantly. Initially, a doublet therapy of Melphalan-Prednisone was considered suitable for elderly patients where as a high dose Melphalan followed by Stem cell transplant was standard of care for young patients.[8] However, the development of new drugs with novel mechanisms of action such as Thalidomide, Lenalidomide and Bortezomib has changed the initial therapy outline of Multiple Myeloma. Availability of Bortezomib (V) has significantly improved the response rate leading to an improved survival. In the year 2010, six additional agents were approved for the treatment of Multiple Myeloma: Pomalidomide, Carfilzomib, Panobionostat, Daratumumab, Elotuzumab and Ixazomib.[4] But unfortunately due to high cost it becomes unaffordable for most of our population.

Induction with triplet regimen e.g., VRD/VCD/VTD in recent times have shown significantly higher response rates. Various trials have been done on international level that compared Bortezomib versus non Bortezomib chemotherapy based regimens6. In a Phase 2 study done by Richardson et al, VDR combination was studied in untreated Multiple Myeloma patients. All the patients achieved at least a partial response after a median of 10 cycles. 37% showed a complete response and 74% of the patients had a ≥ VGPR5. In contrast, The VGPR and CR rates appear lower in current study; 25.9% and 40% respectively, than the study by Richardson et al. A smaller sample size and the number of induction cycles may be reasons for the difference. Furthermore, a Randomized phase III trial of Bortezomib, Melphalan and Prednisolone vs Melphalan and Prednisolone alone, San Miguel et al. demonstrated a similar result where a combination of three drugs indicated higher response and survival benefit.[7] Another study, IFM randomized phase III study was conducted where Bortezomib plus Dexamethasone showed greater post-induction CR and at least VGPR when compared with VAD (Vincristine, Adriamycin, Dexamethasone).[9] It is important to note that our study was done on a smaller scale and in a limited setting where there was a difficulty to follow up patients as some patients didn't show up for their follow up appointments. The cytogenetics also play an important role in determining the overall res-ponse rates and thus limits the use of standard drug doses when considering tolerability of our patients. Therefore, it becomes quite difficult to compare our study with various trails done at international level.

Conclusion

Adding Bortezomib to our therapy has proven to be an additional benefit for our patients but the results are still not as good as those of international studies. Therefore, further studies on a larger scale are required to draw an analogy with results at an international level.

Conflict of Interest

None

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Authors Contribution

ZA: Conceptualization of Project
SW: Data Collection
DMM: Literature Search
YS: Statistical Analysis
NKAZ: Drafting, Revision
KAM: Writing of Manuscript