Open Access

Original Article

Response Of Bortezomib, Cyclophosphamide And Dexamethasone Induction Chemotherapy In Multiple Myeloma Patients Presenting To Combined Military Hospital Rawalpindi

Atiq-ur-Rehman, Riaz Ahmad, Amjad khan, Romana Razzaq*

Department of Oncology Combined Military Hospital /National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Department of Obstetrics and Gynaecology, Combined Military Hospital /National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the response rate and tolerability of Bortezomib, Cyclophosphamide and Dexamethasone (VCD) induction therapy in multiple myeloma patients.

Study Design: Prospective longitudinal study

Place and Duration of Study: Department of Oncology, Combined Military Hospital, Rawalpindi Pakistan, from Mar to Sep 2020.

Methodology: Patients of either gender aged >20-65 years, newly diagnosed cases of multiple myeloma, Durie-Salmon stage II/III, were included. Patients were given Bortezomib, Cyclophosphamide and Dexamethasone induction therapy for a 21-day cycle. Response rate and tolerability were measured.

Results: A total of 147 patients were included in the study. There were 75(51%) male and 72(49%) female.The overall response rate was seen in 93(63.3%) patients, complete response was seen in 30(20.4%), and partial response was seen in 63(42.9%) patients. The overall response rate was significantly associated with age, myeloma type, and Karnofsky's performance status (*p*-value<0.001).

Conclusion: The novel sequential 3-drug combination of Bortezomib, Cyclophosphamide and Dexamethasone is safe and well tolerated for multiple myeloma patients. The results of the current study increase evidence of a moderately high response rate with Bortezomib, Cyclophosphamide and Dexamethasone induction therapy.

Keywords: Bortezomib, Cyclophosphamide, Dexamethasone, Karnofsky performance status, Neutropenia, Febrile neutropenia, Chemotherapy-induced febrile neutropenia.

How to Cite This Article: *Rehman AU, Ahmad R, khan A, Razzaq R. Response Of Bortezomib, Cyclophosphamide And Dexamethasone Induction Chemotherapy In Multiple Myeloma Patients Presenting To Combined Military Hospital Rawalpindi. Pak Armed Forces Med J 2024; 74(1): 133-136. DOI: https://doi.org/10.51253/pafmj.v74i1.5777*

INTRODUCTION

Multiple myeloma (malignant disorder) is associated with uncontrolled clonal plasma cell proliferation, leading towards several complications, organ dysfunction and mortality. An estimated 10% of haematological malignancies are due to multiple myeloma.[1] A pre-malignant condition MGUS (monoclonal gammopathy of undetermined significance) is responsible for the evolution of multiple myeloma.[2] According to the literature, MGUS (3%) is found in individuals aged>50 years and leads to myeloma in 1% per year. However, smouldering and asymptomatic myeloma transform among 10%/year in the initial five years, followed by 3%/year in the next five years and 1% in subsequent ten years.[3,4]

Diagnostic criteria of multiple myeloma are expressed by unexplained end-organ damage, including i) hypocalcaemia, ii) Renal insufficiency, iii) Anemia, and iv) bony lesions (CRAB) among clonal plasma and light chain patients.[5] The burden of diseases and survival rate is usually predicted by the staging system (international staging system and Durie-Salmon staging system).[6]

Management of multiple myeloma is dependent upon the patient's age and eligibility for transplant. In past decades, initial therapy of multiple myeloma has changed due to the introduction of new drugs like proteasome inhibitors and immunomodulatory drugs (Bortezomib and thalidomide, respectively).[7] Literature reported that a combination of Bortezomib with Dexamethasone has a high response duration and improved response rate compared to previous approaches (vincristine/Dexamethasone/doxorubicin regimens).[8] Several phase II and III trials studied the efficacy of these drugs with 3-4 combinations.[9,10] Pakistan is a developing country with limited research opportunities in the chemotherapy field. The present study helps to understand the efficacy of VCD treatment in multiple myeloma patients. The present study was planned to determine the response rate and

Correspondence: Dr Atiq-ur-Rehman, Department of Oncology, Combined Military Hospital Rawalpindi Pakistan.

Received: 01 Dec 2020; revision received: 11 Feb 2021; accepted: 01 Mar 2021

tolerability of Bortezomib, Cyclophosphamide and Dexamethasone (VCD) induction therapy in multiple myeloma patients.

METHODOLOGY

The prospective longitudinal study was conducted at the Department of Oncology, CMH Rawalpindi, Pakistan from March to September 2020, after approval from the Hospital Ethical Committee (123/11). The sample size was calculated with an overall recovery response rate of 75%, using the WHO calculator.11 Patients with multiple myeloma were selected using non-probability consecutive sampling.

Inclusion Criteria: Patients of either gender, aged >20 to 65 years, newly diagnosed cases of multiple myeloma, Durie-Salmon stage II/III, creatinine clearance greater than 30 ml/min, aspartate aminotransferase or alanine aminotransferase <2·5 times the upper limit of normal (ULN), patients following at least one of CRAB criteria [hypercalcaemia, impaired renal function, anaemia and bone alteration (serum level >0·25 mmol/l, serum creatinine >173 µmol/l, haemoglobin 20 g/l, lytic lesions or osteoporosis with compression bone fractures respectively)], Karnofsky performance greater than or equal to 60% and normal haematological functioning (i) neutrophils ≥3·0 × 109/l, (ii) leucocytes ≥3·0 × 109/l were included.

Exclusion Criteria: Patients with congenital anomalies, myocardial infarction in the last six months, uncontrolled angina, developmentally disabled patients, patients with grade ≥2 peripheral neuropathy, or other serious concomitant diseases were excluded .

Consent forms were signed by all participating multiple myeloma patients. A 21-day cycle of VCD was given to patients Bortezomib 1·3 mg/m2 intravenously (at 1,4, 8 and 11 days), Cyclophosphamide 900 mg/m2 intravenously (at day 1) and Dexamethasone 40 mg orally (at 1, 2,4, 5, 8, 9, 11, 12 days). The response rate was measured using the European Society for Blood and Marrow Transplantation (EBMT) criteria of overall response rate (complete and partial response). In contrast, tolerability was measured in terms of adverse events.

Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value of ≤0.05 was considered statistically significant.

RESULT

A total of 147 patients were included in the study. There were 75(51.0%) male and 72(49.0%) female. The mean age of patients was 41.7±8.8 years. Myeloma type was IgG in 91(61.9%), IgA in 32(21.78%), light chain 19(12.9%) and others 5(3.4%) patients. According to Durie-Salmon staging, 98(66.7%) were in Stage II, while 49(33.3%) were in Stage III.Karnofsky performance status was 60-70% in 25(17.0%), 71-80% in 21(14.3%), 81-90% in 35(23.8%) and 91-100% in 66(44.9%) patients as shown in Table-I. The overall response rate was seen in 93(63.3%) patients, complete response was seen in 30(20.4%), and partial response was seen in 63(42.9%) patients.

Table-I: Demographic and Clinical charachteristics of the Study Participants (n=147)

	Frequency
Gender	
Male	**75(51.0%)**
Female	**72(49.0%)**
Age in Years	
20-40 years	**64(43.5%)**
41-65 years	**83 (56.5%)**
Myeloma Type	
IgG	**91(61.9%)**
IgA	**32(21.7%)**
Light chain	**19(12.9%)**
Others	**5(3.4%)**
Durie Salmon Staging	
II	98(66.7%)
III	49(33.3%)
Karnofsky Performance Status	
60-70%	25(17.0%)
71-80%	21(14.3%)
81-90%	35(23.8%)
91-100%	66(44.9%)

Patients with IgG myeloma type had more overall response than those with IgA, Light chain and other myeloma types (p<0.001). Karnofsky's performance status also showed statistical significance with an overall response rate (p<0.001), Most females showed complete response compared to partial response (73.0% vs 34.9%, p=0.004). Patients aged 41-65 years showed more complete responses than those aged 20-40 (p=0.014). Patients in Kranofsky performance status 71-80% showed complete response compared to others (p-value <0.001) as shown in Table-II.

Table-II: Association between Overall Response Rate and Partial Response with Study Parameters (n=93)

	Partial response (n=63)	Complete (n=30)	*p*-value
Gender			
Male	41(65.1%)	8 (26.7%)	0.004
Female	22(34.9%)	22(73.3%)	
Age in Years			
20-40 years	57 (90.5%)	7(23.3%)	0.014
41-65 years	6 (9.5%)	23(76.7%)	
Myeloma Type			
IgG	27(42.8%)	15(50.0%)	< 0.001
IgA	22(34.9%)	8(26.7%)	
Light chain	12(19.1%)	4(13.3%)	
Others	2(3.2%)	3(10.0%)	
Durie Salmon Staging			
II	45(71.4%)	9(30.0%)	< 0.001
III	18(28.6%)	21 (70.0%)	
Karnofsky Performance Status			
60-70%	15(23.8%)	0(0%)	< 0.001
71-80%	5(7.9%)	12(40.0%)	
81-90%	7(11.1%)	8(26.7%)	
91-100%	36(57.2%)	10(33.3%)	

DISCUSSION

The latest drugs with novel mechanisms of action have evolved the multiple myeloma treatment landscape and improved the survival rate of patients.10 Several trials were done to see the combined effects of Bortezomib and Dexamethasone with lenalidomide or Cyclophosphamide.[11] Current research in multiple myeloma is conducted to identify the best approach to combining these drugs and the long-term effects in the long run.

The overall response rate in present study was 63.3% after VCD induction. Kumar et al. reported an overall response rate of 85.4% with four cycles of VCD induction.12 Comparable results were reported with other Bortezomib-containing induction drugs like Bortezomib thalidomide Dexamethasone, Bortezomib lenalidomide Dexamethasone and Bortezomib-Dexamethasone with overall response rate ranging from 69-100%.[13] Moreau et al. reported that VCD response depth improvement is also associated with post-high dose therapy/ autologous stem cell transplantation (overall response rate 95% and very good partial response 47%).[14]

In our study, complete response was seen in 20.4% of patients and partial response in 42.9%. Leiba *et al*. reported that 6% complete and 27% partial responses were observed with VCD.[15] However, Kumar *et al*. reported in the phase II trial that 42% partial and 22% complete responses were observed in VCD compared to other combinations.[16]

In the present study, Neutropenia 11.6% was the most frequent haematological adverse event, while nausea and diarrhoea were the most common non-haematological adverse events. Bensinger and colleagues reported that toxicities were predictable and manageable after three cycles of VCS with 11% neuropathy.[17] Orlowski et al. reported that thrombocytopenia, neuropathy and neutropenia toxic profiles were comparable between VCD and VDR.[18]

CONCLUSION

The novel sequential 3-drug combination of Bortezomib, Cyclophosphamide and Dexamethasone is safe and well tolerated for multiple myeloma patients. The results of the current study increase evidence of a moderately high response rate with Bortezomib, Cyclophosphamide and Dexamethasone induction therapy. Early diagnosis and management of multiple myeloma lead to better disease prognosis and patient outcomes.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

AUR & RA: Conception, study design, drafting the manuscript, approval of the final version to be published.

AK & RR: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Kouroukis TC, Baldassarre FG, Haynes AE, Imrie K, Reece DE, Cheung MC. Bortezomib in multiple myeloma: systematic review and clinical considerations. Curr Oncol 2014; 21(4): e573-603. https://doi.org/10.3747/co.21.1798
2. Goldschmidit H, Duerig J, Bertsch U, Kunz C, Hielscher T, Haenel M, et al; German-speaking Myeloma Multicenter Group (GMMG). Response-adapted lenalidomide maintenance in newly diagnosed myeloma: results from the phase III GMMG-MM5 trial. Leukemia 2020; 34(7): 1853-1865. https://doi.org/10.1038/s41375-020-0724-1
3. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 2002; 346(8): 564-569. https://doi.org/10.1056/NEJMoa01133202
4. Lynch HT, Ferrara K, Barlogie B, Coleman EA, Lynch JF, Weisenburger D, et al. Familial myeloma. N Engl J Med 2008; 359(2): 152-157. https://doi.org/10.1056/NEJMoa0708704
5. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al.Monoclonal gammopathy of undetermined

significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood 2009; 113(22): 5412-5417. https://doi.org/10.1182/blood-2008-12-194241
6. Fonseca R, Bergsagel PL, Drach J, Shaughnessy J, Gutierrez N, Stewart AK, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia 2009; 23(12): 2210-2221. https://doi.org/10.1038/leu.2009.174
7. Bladé J, Fernández de Larrea C, Rosiñol L, Cibeira MT, Jiménez R, Powles R. Soft-tissue plasmacytomas in multiple myeloma: incidence, mechanisms of extramedullary spread, and treatment approach. J Clin Oncol 2011; 29(28): 3805-3812. https://doi.org/10.1200/JCO.2011.34.9290
8. Einsele H , Engelhardt M , Tapprich C , Müller J , Liebisch P , Langer C, et al. Phase II study of bortezomib, cyclophosphamide and dexamethasone as induction therapy in multiple myeloma: DSMM XI trial. Br J Haematol 2017; 179(4): 586-597. https://doi.org/10.1111/bjh.14920
9. Davies FE, Wu P, Jenner M, Srikanth M, Saso R, Morgan GJ. The combination of cyclophosphamide, velcade and dexamethasone induces high response rates with comparable toxicity to velcade alone and velcade plus dexamethasone. Haematologica 2007; 92(8): 1149-1150. https://doi.org/10.3324/haematol.11228
10. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, et al; Eastern Cooperative Oncology Group. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010; 11(1): 29-37. https://doi.org/10.1016/S1470-2045(09)70284-0 Erratum in: Lancet Oncol 2010;11(1):14.
11. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 2012; 119(19): 4375-4382. https://doi.org 10.1182/blood-2011-11-395749
12. Kumar SK, Flinn I, Noga SJ, Hari P, Rifkin R, Callander N, et al. Bortezomib, dexamethasone, cyclophosphamide and lenalidomide combination for newly diagnosed multiple myeloma: phase 1 results from the multicenter EVOLUTION study. Leukemia 2010; 24(7): 1350-1356.https://doi.org 10.1038/leu.2010.116
13. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood 2008; 111(5): 2521-2526.https://doi.org 10.1182/blood-2007-08-104984
14. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol 2011;12(5):431-440.https://doi.org 10.1016/S1470-2045(11)70081-X Erratum in: Lancet Oncol 2011; 12(6): 522.
15. Leiba M , Kedmi M, Duek A, Freidman T, Weiss M, Leiba R, et al. Bortezomib-cyclophosphamide-dexamethasone (VCD) Versus Bortezomib-Thalidomide-Dexamethasone (VTD) -Based Regimens as Induction Therapies in Newly Diagnosed Transplant Eligible Patients With Multiple Myeloma: A Meta-Analysis. Br J Haematol 2016; 166(5): 702-710.
16. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 2012; 119(19): 4375-4382. https://doi.org 10.1182/blood-2011-11-395749
17. Bensinger IW, Jagannath S, Vescio R, Camacho E, Wolf J, Irwin D, et al. Phase 2 study of two sequential three-drug combinations containing bortezomib, cyclophosphamide and dexamethasone, followed by bortezomib, thalidomide and dexamethasone as frontline therapy for multiple myeloma. Br J Haematol 2010; 148(4): 562-568. https://doi.org 10.1111/j.1365-2141.2009.07981.x
18. Orlowski RZ, Nagler A, Sonneveld P, Bladé J, Hajek R, Spencer A, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol 2007; 25(25): 3892-901. https://doi.org 10.1200/JCO.2006.10.5460