

Response assessment to First Line Chemotherapy with VCD Versus VDR in Diagnosed Cases of Multiple Myeloma at CMH Rawalpindi

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ABSTRACT

Objective: To compare response to first line chemotherapy Bortezomib, Lenalidomide and Dexamethasone (VDR) and Bortezomib, Cyclophosphamide and Dexamethasone (VCD) in diagnosed cases of multiple myeloma at CMH Rawalpindi.

Study Design: Prospective comparative study.

Place and Duration of Study: Medical Oncology Department, Combined Military Hospital Rawalpindi, Pakistan Aug 2023 to Feb 2024.

Methodology: This study was carried out on a cohort of 100 multiple myeloma patients classified as high-risk candidates based on the International Scoring System (ISS) with a score of III. Upon diagnosis, the patients were stratified into two Groups. Group-I received a combination of Bortezomib, Lenalidomide and Dexamethasone, (VDR), whereas Group-II received Bortezomib, Cyclophosphamide and Dexamethasone (VCD). The efficacy of treatment response and the occurrence of treatment-related adverse effects were evaluated and compared between the two Groups after minimum of four-month treatment period.

Results: The final analysis included 100 multiple myeloma patients, with a median age of 37.50 and range 41 years. Among these patients, 63 (63%) were male, and 37 (37%) were female. Number of patients in Group I, which underwent VDR was 51(51%, while in Group II 49 (49%) received VCD treatment. Statistically significant difference was observed in the treatment response, with a notably superior response in VDR treatment compared to those receiving VCD treatment (p -value<0.001).

Conclusion: Patients receiving treatment with Bortezomib, Dexamethasone, and Lenalidomide (VDR) exhibited superior treatment response as compared to Bortezomib, Cyclophosphamide and Dexamethasone(VCD). However, adverse effects did not show a significant difference between the two treatment Groups.

Keywords: Bortezomib, Lenalidomide, Dexamethasone, VCD regimen, VDR regimen, Multiple Myeloma; Response assessment.

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INTRODUCTION

In recent decades, there has been a significant increase in the diagnosis of neoplastic conditions affecting the hematovascular system, leading to alarming mortality and morbidity rates.¹ As the bone marrow serves as precursor of blood cell lines, its malignant involvement results in alterations in various blood parameters, often accompanied by severe systemic consequences.² Recent studies have shown trend towards better prognosis with currently available treatment options in patients with who have been managed appropriately at tertiary care cancer units.³ While complete eradication of multiple myeloma may not always be achievable, attaining partial remission can still improve the treatment outcome and quality of life.⁴ Treatment of multiple myeloma involves multidisciplinary approach, with

chemotherapy serving as a cornerstone.⁵ Various chemotherapeutic regimens have been explored in the management of multiple myeloma. The commonly used drugs for Multiple Myeloma include Proteasome inhibitors (Bortezomib), immune modulators (Lenalidomide), Alkylating agents (Cyclophosphamide) and high dose steroids (Dexamethasone).⁶

In 2022, Bazarbachi *et al.* provided an updated analysis of various combinations such as Bortezomib, Dexamethasone, and Lenalidomide (VDR), as well as Thalidomide-Vd (VTd) or cyclophosphamide (VCD) as induction treatment in newly diagnosed Multiple Myeloma patients.⁷ Gaballa *et al.*, in 2022, examined the real-world outcomes of long-term multiple myeloma patients treated with VDR. Their findings revealed that a significant number of patients achieved complete or partial responses, indicating the effectiveness of this regimen in managing the disease.⁸ Afrough *et al.* (2022) conducted a compared VCD and

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VDR treatments in multiple myeloma patients following autologous stem cell transplantation. Their study concluded that while patients treated with VDR exhibited lower rates of complete response there was no statistically significant difference in progression-free survival between the two Groups.⁹ The overall response rate was 99.7% after autologous hematopoietic cell transplant, with a significantly lower complete remission rate as the final response in the VCD compared to the VDR Group (34% versus 53%; $p=.001$). At 5 years, the progression free survival (PFS) was 38.1% and 40 %for the VCD Group vs VDR Group respectively. A recent study conducted at the Armed Forces Bone Marrow Transplant Centre concluded that the efficacy of VCD was comparable to that of VDR, yet patients receiving VCD experienced a more favorable side effect profile.¹⁰

As multiple therapeutic options have become available with the passage of time with comparable efficacy and overlapping adverse effects, question arises about choice of appropriate treatment regimen. Various studies have tested the efficacy of these regimens individually and in head to head comparison but given the limited local data available, healthcare providers often rely on European or American guidelines for guidance. Hence, we undertook this study with the aim of comparing the response to first-line chemotherapy, namely Bortezomib, Lenalidomide, Dexamethasone (VDR), and Bortezomib, cyclophosphamide, Dexamethasone (VCD), in diagnosed cases of multiple myeloma at the Medical Oncology Department of Combined Military Hospital Rawalpindi.

METHODOLOGY

This prospective comparative study was conducted at the Medical Oncology department of Combined Military hospital Rawalpindi Pakistan from August 2023 to February 2024. Sample was gathered by using the non-probability consecutive sampling technique. Sample size was calculated by using the WHO sample size calculator by using two Groups. Group I with VRD as 51%and Group-II with VCD as 49%.¹¹

Inclusion Criteria: All patients between the age of 18 and 65 years who were suffering from international scoring system (ISS) risk III multiple myelomas and were candidates of transplant were recruited.

Exclusion Criteria: Patients who declined chemotherapy treatment were not enrolled. Patients with known allergies to any of the drugs utilized in

the study or who experienced severe side effects from these medications were excluded from participation. Those who lost to follow up or could not complete the chemotherapy cycle for four months were also excluded from the final analysis.

Ethical approval (via letter number 538) was taken from the ethical review board committee of Combined Military Hospital Rawalpindi. All study participants after diagnosis of ISS risk 3 multiple myeloma were recruited in this study. Diagnosis, staging and determining of ISS risk status was done by the medical oncology team as per set international guidelines.¹² After the diagnosis of ISS III multiple myeloma, patients were randomly divided into two Groups by lottery method. Group-I was given Bortezomib, Lenalidomide, Dexamethasone (VDR) in standard doses as per international protocols,¹³ while Group-II was prescribed Bortezomib, cyclophosphamide, Dexamethasone(VCD) as per protocols.¹⁴ Two different bortezomib based triplet therapies were used (1) Bortezomib-lenalidomide-dexamethasone (VDR), (2) Bortezomib-cyclophosphamide-dexamethasone(VCD)Bortezomib-lenalidomide dexamethasone (VDR). Bortezomib was given in a dose of 1.3 mg/m² and dexamethasone 40 mg both at days 1, 8, 15, 22 of the chemotherapy cycle. The third drug included either cyclophosphamide at 300 mg/m² on days 1, 8, 15, 22; or lenalidomide 25 mg at days 1 to 14. Patients in both the Groups were observed closely for four months on regular intervals for any clinical or laboratory adverse effects by the treating team throughout the study period. Response at the end of four months was assessed on the basis of International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma.¹⁶ Complete response and very good partial response were classed as good response while other categories were classed as poor response.¹⁷

Treatment emergent adverse effects (TEAEs) were reported according to the internationally reported adverse events associated with VDR and VCD regimen. The observed adverse effects were graded as per National Cancer Institute common terminology criteria for adverse events (CTCAE) v5.0. For final analysis all grade adverse events were compared between Group I (VDR) and Group II (VCD) as the primary aim of the study was to assess the response rate with these two treatment regimens.

All statistical analyses were conducted using the Statistics Package for Social Sciences version 24.0

(SPSS-24.0). The median and range were computed for the age of patients, while frequency and percentages were determined for the type of response and recorded adverse effects in this study. To compare the response and adverse effects between patients managed with VDR and VCD, the Pearson Chi-square test was employed. A significance level of $p \leq 0.05$ was utilized to establish comparisons between the two study Groups.

RESULTS

A total of one hundred patients of multiple myeloma were included in the final analysis. Median age of the patients was 37.50 years with range 41. Out of total patients, 63 % were male while 37% were female. Table-I summarized the basic characteristics of multiple myeloma patients recruited in this study. In the two treatment Groups 51% patients in Group I underwent VDR treatment while 49% patients in Group II underwent VCD treatment. Overall good response was observed in 47% patients and poor response was observed in 53 % patients. Common adverse effects observed were Neutropenia, anemia and neuropathy.

Table-I: Characteristics of Patients with Multiple Myeloma Recruited in this Study (n=100)

Study parameters	Values
Age (years)	
Median (Range)	37.50 (41.00) years
Gender	
Male	63%
Female	37%
Response at 4 months	
Good response	47%
Poor response	53%
Treatment	
VDR	51%
VCD	49%
Adverse effects	
Neutropenia	27%
Anemia	28%
Neuropathy	25%
Others	05%

Table-II shows the results of statistical analysis. Two Groups were made for the sake of comparison. Good response was seen in 33(64.7%) patients in Group 1 (VDR) whereas in Group II (VCD) 14(28.6%) pts achieved good response. Thus, statistically it was observed that good response (complete and very good partial response) was significantly better in patients who underwent VDR treatment (p -value<0.001) as compared to those who underwent VCD treatment.

All grade significant adverse effects observed were neutropenia, anemia and neuropathy. There was no statistically significant difference in adverse effects between the two Groups (p -value>0.05) in our study.

Table-II: Comparison of response and adverse effects in two study Groups (n=100)

Study parameters	Bortezomib, Dexamethasone, and Lenalidomide (VDR Regimen) (n=51)	Bortezomib, Cyclophosphamide and Dexamethasone (VCD Regimen) (n=49)	<i>p</i> -value
Neutropenia			
No	41(80.4%)	32(65.3%)	0.088
Yes	10(19.6%)	17(34.7%)	
Anemia			
No	41(80.4%)	31(63.2%)	0.055
Yes	10(19.6%)	18(36.8%)	
Neuropathy			
No	35(68.6%)	40(81.6%)	0.131
Yes	16(31.4%)	09(18.4%)	
Response at End of 4 Months			
Good	33(64.7%)	14(28.6%)	<0.001
Poor	18(35.3%)	35(71.4%)	

DISCUSSION

Multiple myeloma, manifests as a multi-system disorder, significantly impacting the health-related quality of life across various domains for affected individuals. Standard treatment modalities typically include chemotherapy and stem cell transplantation, with treatment response influenced by both disease-specific and patient-related factors. Various chemotherapeutic regimens may be administered prior to transplantation.

The primary objective of treatment is to achieve either complete or very good partial response in patients. With this objective in mind, we designed this study to compare the response to first-line chemotherapy, specifically Bortezomib, Lenalidomide, Dexamethasone (VDR), against Bortezomib, cyclophosphamide, Dexamethasone (VCD), in diagnosed cases of multiple myeloma at CMH Rawalpindi.

In 2017, Durie *et al.* conducted an open-label trial which concluded that the addition of bortezomib to lenalidomide and dexamethasone significantly improved the progression-free survival of patients with multiple myeloma.¹⁷ Similarly, our study yielded comparable results, with patients managed with VDR demonstrating markedly superior response rates

compared to those managed with VCD. However, it's important to note that our study was limited by its design as it was not a randomized controlled trial but rather a comparative cross-sectional study.

In a study published from China in 2021, the comparison between VDR and VCD chemotherapy in newly diagnosed, transplant eligible cases of multiple myeloma, was conducted. The authors of this study reported that VDR chemotherapy resulted in achieving a deeper response compared to VCD, although survival prognosis did not show a statistically significant difference between the two study Groups.¹⁸ Likewise, in our study, where we evaluated the immediate treatment response after 4 months of treatment, we found that VDR exhibited superior efficacy compared to VCD.

In a study conducted in the USA in 2022, it was found that patients treated with VDR had a more favorable prognosis compared to those treated with VCD.¹⁹ Our study results align with these findings, demonstrating that patients treated with VDR exhibited a superior treatment response compared to those treated VCD. Notably, adverse effects did not show a significant difference between the two treatment Groups.

In a phase II study evolution, overall good response rate was seen with VCD and VDR. No advantage was seen with VDCR (Bortezomib, Dexamethasone, Cyclophosphamide, Lenalidomide).²⁰

Furthermore, Uttervall et al. investigated patients with multiple myeloma treated with VDR and compared them to those treated with VCD. Their study concluded that the overall response rate was better in the VDR Group compared to the VCD Group.²¹

Our study is the first study done in the department of Medical oncology CMH Rawalpindi, comparing the two commonly used regimen in high risk Multiple Myeloma Patients. Findings of our study corroborates the superior treatment outcome results with VDR as compared to VCD reported by most of the studies.

LIMITATIONS OF STUDY

The study had several limitations that need to be acknowledged. Firstly, it was not conducted with the design of a randomized controlled trial, which is gold standard in clinical research. This lack of randomization introduces the potential for bias that may affect the generalizability of the findings.

Secondly, the study only examined short-term treatment responses, and patients were not followed up until transplant or after transplant to evaluate long-term responses. This may not fully capture the overall efficacy and safety of the treatment regimens studied.

To rectify these shortcomings future research should consider conducting randomized controlled trials with long-term follow-up of patients across oncology units in the country. This approach would provide a comprehensive understanding of the relative effectiveness and long-term outcomes of different treatment strategies for multiple myeloma.

CONCLUSION

Patients treated with Bortezomib, Dexamethasone, and (VDR) demonstrated a superior treatment response compared to those treated with Bortezomib cyclophosphamide and Dexamethasone (VCD). However, it's noteworthy that adverse effects did not significantly differ between the two treatment Groups.

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Authors Contribution

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

R & MHB: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

MS & MN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MZ & FM: Conception, data acquisition, drafting the manuscript, 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.

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