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ORIGINAL ARTICLE

Excellent Response Rates with Bortezomib - Cyclophosphamide – Dexamethasone (VCD) Regimen in Newly Diagnosed Multiple Myeloma (NDMM) from a Resource Constraint Setting in South India

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ABSTRACT

Context: Triplet regimens with proteasome inhibitors, immunomodulatory drugs and steroid are common induction regimens used in Multiple Myeloma patients.

Aims: We did a retrospective analysis of newly diagnosed multiple myeloma patients (NDMM) treated with VCd (Bortezomib, Cyclophosphamide, Dexamethasone) induction therapy in a resource constraint setting.

Settings and Design: Electronic medical records of 26 NDMM patients attending a tertiary medical center in South India were analyzed.

Methods and Material: The response rates of 26 NDMM patients treated with once weekly VCd induction and the clinically significant toxicities with this regimen were studied. Both transplant eligible and ineligible patients were included. Treatment responses after the 2nd and the 6th cycles of VCd were analyzed according to the IMWG uniform response criteria. The severity of toxicities were categorized using NCI-CTAE version 5 grading system.

Statistical analysis used: IBM SPSS version 28 software was used for analyzing the results.

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Results: Of the 26 patients enrolled, 50% were above the age of 65 years. Median follow up was 17.5 months. In an intention to treat (ITT) analysis, the ORR was 57.7% (15/26) with VCd after 6 cycles, with CR of 34.6% (9/26), VGPR 19.2% (5/26) and PR 5.3% (1/19). The major toxicity was ≥ grade 2 peripheral neuropathy (PN). Grade 2 or more cytopenias were seen in 3 patients. 3 patients had grade 2 & 3 infections. 8% patients discontinued the treatment due to adverse events and 32% required bortezomib dose reduction.

Conclusions: VCd is an effective induction regimen for NDMM patients with early deep response rates. This is especially important in LMICs like India, where the out of pocket healthcare expenditure is around 60%. VCd is a feasible regimen even for elderly NDMM patients with comorbidities.

KEYWORDS:

• Myeloma • Induction • Bortezomib • Neuropathy

Key Messages:

VCd is an effective regimen for induction therapy in NDMM patients

VCd has a good toxicity profile even in elderly patients

INTRODUCTION

Bortezomib is the first proteasome inhibitor drug to treat patients with newly diagnosed multiple myeloma and initially, it was given as a single agent or in combination with steroid.[1,2] With the advent of immunomodulatory agents (iMiDs) and proteosome inhibitors, the treatment of Multiple Myeloma and related plasma cell disorders have seen marked improvements in response rates and survival rates. The availability of generic bortezomib has expanded the target population which can reap the benefit of this novel therapeutic agent in lower/middle income countries (LMIC).

Currently, different bortezomib-containing regimens are used as induction therapy for both transplant eligible and transplant-ineligible myeloma patients and high Progression Free Survival (PFS) has been reported with bortezomib-cyclophosphamide-dexamethasone regimen.[3] Bortezomib with dexamethasone and cyclophosphamide (VCd) regimen has been a famous cocktail with significant activity and accetable toxicity profile. VCd is comparitively safe regimen for patients with kidney dysfunction and also a preferred first line regimen in a resource constraint setting.[4]

We did a retrospective analysis of our data of patients with Newly Diagnosed Multiple Myeloma (NDMM) treated with VCd induction therapy in a newly set resource constraint centre. We studied the response rates of NDMM patients who completed 6 cycles of VCd and the clinically significant toxicities with this regimen.

MATERIALS AND METHODS

Patients with NDMM started on induction treatment with VCd regimen from April 2019 to July 2022 at our center were included. Both transplant eligible and ineligible patients were added. Multiple Myeloma was diagnosed if there was more than 10% clonal plasma cells in the bone marrow biopsy, positive Monoclonal band (M band) in Protein Electrophoresis / Immunofixation electrophoresis in either serum or urine, altered free light chain(FLC) ratio in either serum or urine along with one of myeloma defining events (MDE), viz., anemia (Hemoglobin < 10 g/dL), creatinine > 2 mg/dL, plasma calcium level > 11 mg/dL, lytic skeletal lesions in imaging studies. Flourescent In Situ Hybridisation (FISH) for MM was done from bone marrow, albeit, in a limited number of cases due to resource constraints. After getting informed consent from the patients, they were treated with triplet induction regimen containing weekly bortezomib 1.5 mg/m^2 given subcutaneously, cyclophosphamide 300

mg/m^2 orally, and dexamethsone 40 mg given orally.

The dose of dexamethasone was reduced to 20 mg for those above 70 years old and/or for those with difficulty to controlling diabetes mellitus. VCd were given on day 1, day 8, day 15 and day 22 of each 28 day cycle. In case of patients with rapidly progressing renal failure (RPRF) due to myeloma, bortezomib was given intravenously and switched to subcutaneous route once their serum creatinine stabilized, to reduce the incidence of peripheral neuropathy. These patients with RPRF, were given bortezomib twice for the initial one or two weeks to get a rapid disease control and thereby limit renal damage. A skeletal survey/ whole body positron emission tomography scan was done in majority of cases to find out lytic lesions. Patients with creatinine clearance > 50 mL/min, received adjunct therapy with intravenous zoledronic acid (bisphosphonate) for myeloma bone disease.

Treatment response was assessed by quantifying the M band, FLC assay and ratio at the completion of cycles 2 and cycles 6 according to the International Myeloma Working Group (IMWG) uniform response criteria. Repeated bone marrow biopsy was not performed routinely for response assessment. We analyzed toxicities which led to delays in administering chemo drugs, dose modification or discontinuation of the regimen using the NCI-CTAE version 5 grading.

RESULTS

Patient charecteristics

Table 1 depicts the patient characteristics. 26 patients were enrolled in the study (16 males; 10 females) with a median follow up of 17.5 months (IQR 8 – 29). Median age was 64 years (ranging from 44 to 79) and 50% of patients were above the age of 65 years. Performance status was ≥ 2 in 13 patients (50%). According to the International Staging System (ISS) 18 (69%) patients were in ISS III. 24/26 patients (92%) had anemia. Renal dysfunction was present in 15/26 patients (57.7%). 16/26 (61.5%) and 6/26 (23%) had skeletal lesions and hypercalcemia respectively. Cytogenetic studies for multiple myeloma related abnormalities were done only in 7 patients due to resource constraints. Of which, 3 patients had del 13q abnormalities.

Table 1: Patient characteristics

Age (years)	
Median age	64 (44-79)
>65 years	13 (50%)
Sex	
Males	16 (62%)
Females	10 (38%)
Stage	
ISS I	3 (12%)
ISS II	5 (19%)
ISS III	18 (69%)
Myeloma Defining Events (MDE)	
Anemia	24 (92%)
Renal dysfunction	15 (58%)
Hypercalcemia	6 (23%)
Bone lytic lesions	16 (62%)

Abbreviations: ISS, International staging system

Treatment results

Patients received weekly VCd with bortezomib dose of 1.5 mg/m2 given by subcutaneous route mostly. Intravenous route was preferred in patients with renal dysfunction in the initial cycles (cycles 1 & 2). Cyclophosphamide and dexamethasone were given by oral route in standard doses. 1 patient was lost to follow up. Of the rest 25 patients, 1 patient discontinued VCd due to bortezomib related bilateral optic atrophy which occurred during the first cycle. Of the 24 patients who completed 2 cycles, the overall response rate (ORR) at 2 cycles was 20/24(83.3%) with complete response (CR) 4/24(16.7%), very good partial response (VGPR) 8/24 (33.3%) and partial response (PR) 8/24(33.3%). 4/24 (16.7%) had stable disease with 2 cycles. 3 patients who had stable disease with 2 cycles of VCd switched to lenalidomide based triplet regimen - VRd. 1 patient switched to lenalidomide-dexamethasone (Rd) regimen due to grade 2 peripheral neuropathy after 2 cycles of VCd. 1 patient preferred to switch to maintenance therapy with bortezomib after 4 cycles. 19 patients who completed 6 cycles VCd were analysed ORR was 15/19 (78.9%) with CR 9/19 (47.4%), VGPR 5/19 (26.3%), PR 1/19 (5.3%). 2/19 (10.5%) had stable disease. Figure 1 illustrates the response rates after 2 cycles and 6 cycles of VCd. No patient had progressive disease during the 6 cycles of VCd. Minimal residual disease (MRD) was not done as the test was not widely available.

In an intention to treat (ITT) analysis (Table 2), the ORR was 57.7% (15/26) with VCd after 6 cycles, with CR of 34.6% (9/26), VGPR 19.2% (5/26) and PR 3.8% (1/26). There were no deaths within the six cycles of VCd induction.

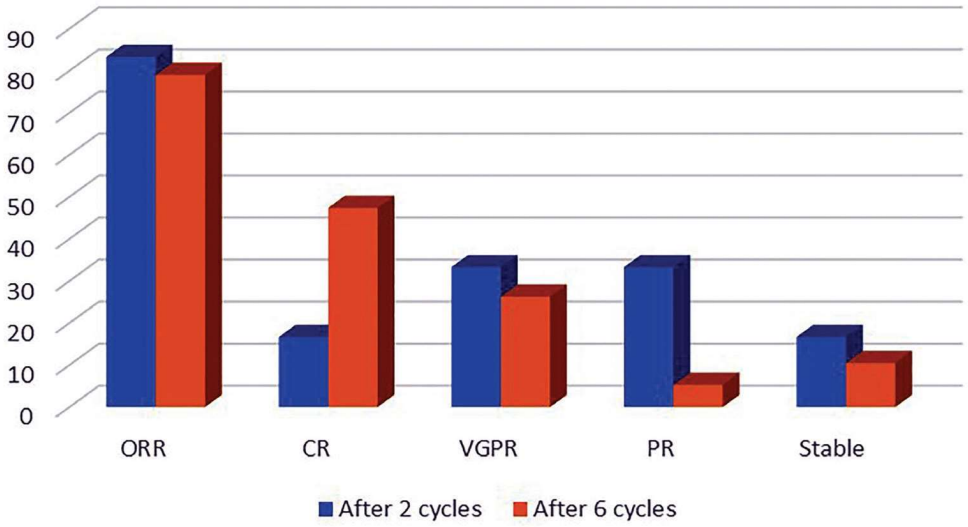

Figure 1: Response rates after 2 cycles and 6 cycles of VCd

Abbreviations: ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response

Table 2: Outcomes by ITT analysis after 6 cycles

ORR	15 (58%)
PR	1 (4%)
VGPR	5 (19%)
CR	9 (35%)
Stable disease	2 (8%)

Abbreviations: ITT, intention to treat; ORR, overall response rate; PR, partial response; VGPR, very good partial response; CR, complete response

Toxicity

The major toxicity was ≥ grade 2 peripheral neuropathy (PN) in 11/25 (44%) with 1 patient having grade 3 PN (Table 3). Notably one patient had bilateral optic atrophy. 2/25 (8%) discontinued bortezomib due to neuropathy. Bortezomib related chalazia of eyelids were seen in 2 patients (8%), one of whom experienced delays in administering therapy due to this. Cytopenias, grade 2 or more were seen in only 3 patients (12%) with two having grade 3 neutropenia - none required colony stimulating factors. 2 patients had grade 2 infections (cellulitis & otitis media) and 1 patient had grade 3 pneumonia due to SARS-CoV-2. Overall VCd was well tolerated, only 2 patients (8 %) discontinued due to adverse events. 8/25 patients (32 %) required bortezomib dose reduction due to neuropathy, six of these patients who required dose reductions, were above the age of 68 years.

Table 3: Adverse events

Neutropenia (≥ grade 2)	2 (8%)
Thrombocytopenia (≥ grade 2)	1(4%)
Neuropathy (≥ grade 2)	12 (46%)
Infections (≥ grade 2)	3 (12%)

DISCUSSION

Induction regimens for multiple myeloma have evolved from dexamethasone-based doublets (e.g., Td, Rd, Vd) to incorporate novel agents. While alkylators like melphalan are effective, their stem cell toxicity limits use in transplant-eligible patients.[5,6] The integration of proteasome inhibitors and IMiDs into triplet regimens has significantly improved ORR and CR rates without compromising stem cell harvest. The VCd regimen balances efficacy, toxicity, and practical considerations in resource-limited settings. Although VRd is a standard induction in high-income countries, the extended lenalidomide exposure required in settings where timely stem cell harvest is not feasible can impair future stem cell mobilization. This makes the non-lenalidomide-containing VCd regimen a pragmatic and preferred choice

in many LMICs.[7,8] Our findings in a South Indian cohort, where most patients bear treatment costs out-of-pocket, demonstrate an ORR of 80% and a ≥VGPR rate of 74% after 2 cycles. These outcomes are comparable to the phase II data from Reeder *et al*.[7] and match or exceed historical rates with older regimens like Td, Rd, Vd, and VTd.[9–12] The achieved VGPR rate is equivalent to more expensive or toxic contemporary regimens. Achieving deep responses (≥VGPR/CR) prior to autologous stem cell transplant (ASCT) is a critical determinant of long-term outcomes.[13,14] Modern, effective induction regimens like VCd have reduced the necessity for tandem ASCT by improving pre-transplant response depth.[15,16] In our study, an ITT analysis showed 53.8% of patients achieved ≥VGPR, underscoring the regimen's capacity for early, deep remission. Toxicity in our cohort was manageable, with peripheral neuropathy being the most common adverse event, consistent with the known profile of bortezomib.[17,18] Proactive dose modification allowed for continued therapy in most cases. Other adverse events, including infections, were manageable with standard care. Our study has limitations inherent to its retrospective design and resource-constrained setting. The lack of comprehensive cytogenetic data limits risk stratification. Furthermore, selection bias may exist, as patients with very high-risk features (e.g., extensive extramedullary disease) might have been directed toward alternative regimens like VRd.

CONCLUSION

The VCd regimen is an effective induction therapy for NDMM, capable of inducing early and deep responses, a prerequisite for prolonged progression-free survival. In our resource-constrained setting, an ITT analysis showed over half of the patients achieved at least a VGPR. With generic bortezomib, the cost of a cycle can be as low as USD 80–90, a critical factor in LMICs like India where out-of-pocket healthcare expenditure is high. Although peripheral neuropathy requires vigilant monitoring, timely dose adjustments make VCd a feasible and well-tolerated regimen even for elderly patients, affirming its value as a cornerstone of myeloma therapy in resource-limited environments.

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Conflict of Interest: The authors have no relevant conflicts of interest to disclose

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