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Real-Life Data Comparing Weekly VCD and Twice-Weekly VCD Protocols in Newly Diagnosed Multiple Myeloma Patients

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ABSTRACT

Background This study aimed to evaluate the efficacy and side effects of bortezomib, cyclophosphamide and dexamethasone (VCD) treatment, which is frequently preferred in primary care in patients with multiple myeloma in our country, with two applications per week and one application per week.

Methods A total of 141 patients who received VCD in the induction treatment of newly diagnosed multiple myeloma were retrospectively reviewed and analysed. Both treatment groups were evaluated in terms of efficacy and side effects.

Results A total of 141 patients with newly diagnosed multiple myeloma who received VCD in induction therapy were included in the study. The median age was 62 years. Among 141 patients included in the study, 57 patients received treatment two days a week and 84 patients received treatment one day a week. Sixty-one (43.3%) patients were female and 80 (56.7%) were male. There was no significant difference between the two groups in terms of post-treatment response rates after 2nd cycle VCD regimen (p=0.378) and 4th cycle VCD regimen (p=0.965). Patients receiving weekly VCD regimen had a significantly higher rate of receiving other regimens, and additional VCD regimen of autologous stem cell transplant (ASCT) was significantly higher in patients who received a VCD regimen twice a week compared to the other group (p<0.001). ASCT was performed in 73% of the patients (n: 103). In 54 patients with ASCT at the end of 4th cycle VCD, there was no significant difference between very good partial response/complete response rates and partial response/sub responses between the two groups according to the 3rd month post-transplant responses (p=0.612). Neuropathy was observed in seven (12.3%) patients receiving twice-weekly VCD regimens, while neuropathy was observed in 16 (19.3%) and neutropenia in two (2.4%) patients receiving weekly VCD regimens. The two groups had no significant difference regarding side effects (p=0.387).

Conclusion Our study found no significant difference in the treatment response rates of patients receiving weekly VCD and twice-weekly VCD. The low rates of ASCT in the weekly VCD group were thought to be related to the fact that the patients receiving the weekly regimen were older than the other group and were unsuitable for ASCT due to age. No difference was observed between the two groups regarding the frequency of side effects.

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INTRODUCTION

Combining bortezomib, cyclophosphamide and dexamethasone (VCD) is an effective and widely used induction protocol for newly diagnosed multiple myeloma patients.[1] Since it is difficult to reach the combination of bortezomib, lenalidomide, and dexamethasone in our country's first step of induction treatment, VCD combination is frequently preferred. Different protocols can be applied for VCD. In the weekly VCD protocol, bortezomib is administered subcutaneously once a week, whereas in the twice-weekly VCD protocol, bortezomib is administered twice-weekly.[2] Our study aimed to compare the side effects and response status between these two protocols in newly diagnosed multiple myeloma patients.

MATERIAL AND METHODS

In our study, 141 patients who applied to haematology outpatient clinics between March 2013 and March 2022 and received VCD in the induction treatment of newly diagnosed multiple myeloma were retrospectively screened and analysed. Approval for the study was received from the local ethics committee (dated 24/05/2023 and numbered E1-23-3619 decision).

Demographic data, comorbidities, genetic status at diagnosis, presence of hypercalcemia, renal failure, anaemia and lytic lesions at diagnosis were evaluated. The genetic status of the patients was classified as standard and high risk according to the Mayo Clinic mSMART classification. According to this classification, the presence of trisomy's, t(11;14), t(6;14) was considered standard risk, t(4;14), t(14;16), t(14;20), del 17p, p53 mutation was considered high risk. For prognosis scoring of the patients, the international scoring system (ISS) was calculated based on albumin and beta-2 microglobulin results and revised ISS (R-ISS) was calculated by adding genetic results and LDH values.

The presence of hypercalcemia was defined as a serum calcium level at least 1 mg/dL above the upper limit of the laboratory or, a serum calcium level above 11 mg/dL, a creatinine clearance below 40 mL/min or a serum creatinine value above 2 mg/dL was defined as the presence of renal insufficiency, a haemoglobin (Hb) level below 10 g/dL was defined as the presence of anaemia. An osteolytic lesion of 5 mm or larger on CT or PET-CT was defined as the presence of a lytic lesion. The presence of extramedullary disease at diagnosis was evaluated. Serum IgG, IgA, IgM, serum-free kappa, serum-free lambda, M protein and bone marrow plasma cell ratio were recorded. Response evaluation of patients receiving VCD at the end of 2nd cycle and 4th cycle according to International Myeloma Working Group (IMWG) criteria; 3rd-month post-transplant responses of patients who received autologous stem cell transplantation at the end of 4th cycle and 6th cycle VCD responses of patients who were not suitable for autologous stem cell transplantation were analysed. Bortezomib-related side effects were evaluated as neuropathy, febrile neutropenia and neuropathy. VCD weekly regimen was administered as cyclophosphamide 300 mg/m^2 intravenously (IV) weekly, dexamethasone 40 mg IV weekly, bortezomib 1.5 mg/m^2 subcutaneously (SC) and VCD twice-weekly regimen was administered as cyclophosphamide 300 mg/m2 IV weekly, dexamethasone 40 mg IV weekly, bortezomib 1.3 mg/m^2 SC.

Patients were divided into two groups: those receiving VCD weekly and those receiving VCD twice-weekly. Differences between the two groups regarding chemotherapy responses and side effects were compared.

Statistically analysis

All statistical analyses were performed using IBM SPSS version 29.0.1 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were presented as mean±SD in the tables. Some categorical variables were presented as numbers (n) and percentages (%), and some were presented in tables. The chi-square test was used for the comparison of categorical variables. Multivariate logistic regression analysis was

performed to determine the variables predicting side effects. P value <0.05 was considered statistically significant.

RESULTS

A total of 141 patients with newly diagnosed multiple myeloma receiving VCD in induction therapy were included in the study. The median age was 62 years (29-83). Among 141 patients included in the study, 57 received bortezomib 1.3 mg/m^2 SC on days 1, 4, 8, and 11, and 84 received bortezomib 1.3 mg/m^2 SC weekly. The median age between the two groups receiving weekly VCD and twice-weekly VCD was 60 and 64 years; according to this analysis, a statistically significant difference was found between age and VCD days (p=0.004). The age of the patients who received weekly VCD was higher. Sixty-one (43.3%) patients were female and 80 (56.7%) were male. According to the ISS staging system, 24.5% (n: 14) of the patients who received twice-weekly VCD regimen were stage I, 35% (n: 20) were stage II, 40.3% (n: 23) were stage III; 21.4% (n: 18) of the patients who received weekly VCD regimen were stage I, 30.9% (n: 26) were stage II, 47.6% were stage III. Only 8.5% (n: 12) of all patients included in the study had high genetic risk. The most common subtype was IgG kappa (30.5%). While 44.7% (n=63) of all patients had no comorbidity, the most common comorbidity was

Table 1. Comparison of clinical and sociodemographic data of patients (n: 141)

Variables	VCD twice a week (n: 57)	Weekly VCD (n: 84)	*P*-value
Gender (Male/Female)	34/23	46/38	0.565[b]
Median age (years)	60	64	0.004[a]
ISS			0.616[b]
I	14 (24.5%)	17 (20.7%)	
II	20 (35.1%)	25 (30.5%)	
III	23 (40.4%)	40 (48.8%)	
R-ISS			0.461[b]
I	11 (19.3%)	13 (15.9%)	
II	38 (66.7%)	62 (75.6%)	
III	8 (14%)	7 (8.5%)	
Genetic			0.494[b]
Standard	51 (89.5%)	77 (92.8%)	
High	6 (10.5%)	6 (7.2%)	
Diagnosis type			0.693[b]
IgA kappa	9 (15.8%)	8 (9.5%)	
IgA lambda	5 (8.8%)	12 (14.3%)	
IgG kappa	17 (29.8%)	26 (31%)	
IgG lambda	13 (22.8%)	16 (19%)	
Lambda light	9 (15.8%)	11 (13%)	
Kappa light	4 (7%)	10 (12%)	
IgM kappa	0	1 (1.2)	
M protein			0.515[b]
<3 g/dL	31	45	
≥3 g/dL	26	36	
Hypercalcemia (No/Yes)	45/12	73/11	0.209[b]
Renal failure (No/Yes)	36/21	57/27	0.563[b]
Anemia (No/Yes)	27/30	49/35	0.391[b]
Presence of lytic lesions (No/Yes)	13/44	24/60	0.445[b]
Extramedullary disease (No/Yes)	41/16	72/12	0.044[b]
Additional therapy before ASCT (No/Yes)	34/17	21/27	0.022[a]
ASCT (No/Yes)	5/52	33/51	<0.001[a]

VCD: bortezomib, cyclophosphamide and dexamethasone; ISS: International Staging System; R-ISS: Revised International Staging System; ASCT: autologous stem cell transplantation

[a] Mann Whitney U test, [b] Pearson Chi-square test.

Table 2. Comparison of chemotherapy response and side effect data and VCD days of patients (n: 141)

	VCD twice a week (n: 57)	Weekly VCD (n: 84)	*P*-value
After 2nd cycle VCD			0.378
CR	1 (1.8%)	0	
VGPR	27 (47.4%)	32 (38.1%)	
PR	27 (47.4%)	48 (57.1%)	
MR	2 (3.5%)	4 (4.8%)	
4th cycle VCD			0.965
CR	20 (35%)	25 (30%)	
VGPR	15 (26.3%)	23 (27.4%)	
PR	18 (31.6%)	28 (33.3%)	
MR	1 (1.8%)	2 (2.4%)	
SD	0	1 (1.2%)	
PD	3 (5.3%)	5 (6%)	
6th cycle VCD			0.445
CR	1 (12.5%)	10 (28.6%)	
VGPR	3 (37.5%)	15 (43%)	
PR	4 (50%)	10 (28.5%)	
After ASCT 3rd month			0.829
CR	22 (71%)	18 (78.3%)	
VGPR	7 (22.6%)	4 (17.4%)	
PR	2 (6.5%)	1 (4.3%)	
Side effect			0.254
None	50 (87.7%)	65 (78.3%)	
Neuropathy	7 (12.3%)	16 (19.3%)	
Neutropenia	0	2 (2.4%)	

VCD: bortezomib, cyclophosphamide and dexamethasone; CR: complete response; VGPR: very good partial response; PR: partial response; MR: minimal response; SD: stable disease; PD: progressive disease.

hypertension (n: 34, 24.1%). There was no significant difference between both groups in the presence of hypercalcemia (p=0.209), renal failure (p=0.563), anaemia (p=0.391) and presence of lytic lesions (p=0.445) at diagnosis. The number of patients with the extramedullary disease was higher in patients receiving twice-weekly VCD regimens compared to the other group (p=0.044). Table 1 showed the results of the analyses related to comparing various clinical and sociodemographic data of the patients with the days of VCD.

Response rates in twice-weekly VCD treatment group after two cycles were 1.8% complete response (CR), 47.4% very good partial response (VGPR) and 47.4% partial response (PR); these rates were 35%, 26.3% and 31.6%, respectively after four cycles of treatment. CR rate was 0%, VGPR was 38.1% and PR was 57.1% after two cycles in weekly treatment group; after four cycles 30% CR, 27.4% VGPR and 33.3% PR were achieved, respectively. There was no significant difference between the two groups in terms of therapy response after 2nd cycle VCD regimen (p=0.378) and 4th cycle VCD regimen (p=0.965). On the other hand; patients receiving weekly VCD regimen had a significantly higher rate of receiving other regimen and additional VCD regimen before autologous stem cell transplantation (ASCT) compared to the other group (p=0.022). The rate of ASCT was significantly higher in patients who received a VCD regimen twice a week compared to the other group (p<0.001). ASCT was performed in 73% of patients (n: 103). In 54 patients who had ASCT at the end of the 4th cycle VCD, responses three months after transplantation were analysed. No significant difference was found between the VGPR/CR response rates and PR/subresponses between the two groups (p=0.612).

Neuropathy was observed in seven (12.3%) patients receiving twice-weekly VCD regimens, while neuropathy was observed in 16 (19.3%) and neutropenia in two (2.4%) patients receiving weekly VCD regimens. The two groups had no significant difference regarding side effects (p=0.387). Table 2 compared chemotherapy responses and side effect data with VCD days.

DISCUSSION

Multiple myeloma accounts for approximately 17% of haematological malignancies.[3] In myeloma, the treatment goal for young and elderly patients should be to prolong survival by achieving the best possible treatment response without impairing quality of life. Studies have shown that weekly use of bortezomib and subcutaneous administration can be tolerated without any side effects on efficacy.[4,5] CR response after induction therapy and after ASCT is the most important predictor of long-term survival.[6] In recent studies, VCD induction regimens and doses are different and heterogeneous in multiple myeloma patients eligible for transplantation. It is a dose-dependent neuropathy that limits the use of bortezomib.[7] Studies have compared the combination of bortezomib, cyclophosphamide and dexamethasone (CyBorD or VCD) in induction therapy in multiple myeloma patients using different protocols. Most of these studies used bortezomib 1.3 mg/m^2 twice-weekly (days 1, 4, 8, 11) and IV.2,[8-12] Subcutaneous bortezomib has been shown to have similar efficacy with fewer side effects than IV administration, and administration of bortezomib weekly rather than twice-weekly has been associated with reduced toxicity with similar response rates.[2,13]

In a study by McCaughan *et al.*14, the treatment responses of patients receiving weekly VCD were analysed. Stable disease (SD), PR and VGPR responses were obtained in 23%, 43%, and 33% of the patients, respectively, and no progression was detected in any patient. When the response rates after ASCT were analysed, SD was 3%, PR was 35%, and VGPR and higher response rates were obtained in 59% of the patients. In the study by Reeder *et al.*[2], weekly and twice-weekly VCD protocols were compared. Thirty-three patients received VCD twice a week. PR or higher response was obtained in 88% of the patients, VGPR or higher response in 61%, and CR response in 39%. Since toxicity associated with high dose dexamethasone and bortezomib developed in the twice-weekly VCD protocol, the efficacy of the treatment decreased due to postponement/stopping of treatment. Thirty patients received weekly VCD. In the weekly VCD protocol, the bortezomib dose was 1.5 mg/m^2. PR or better response was obtained in 93% of the patients, VGPR or better response in 60%, and CR response in 43%. In this study, it was decided that weekly bortezomib treatment with low-dose dexamethasone should be the first choice protocol for induction in transplant-eligible newly diagnosed multiple myeloma patients.

Although the current treatment guidelines recommend triplet therapies containing a proteozome inhibitor with immunomodulatory drug and dexamethasone for the first line treatment in myeloma patients, this drug combination cannot be used in primary care in our country within the reimbursement conditions and indication list. It is even recommended to add a monoclonal antibody treatment to triplet therapy for especially high-risk patients suitable for ASCT.[15] Therefore, in our study, the differences in treatment response rates and side effects between once-weekly and twice-weekly administration of VCD treatment, which is still used in primary care, were investigated. Weekly treatment has the advantage of reducing the frequency of treatment compared to twice a week. We aimed to investigate whether this advantage differs in terms of response. The efficacy results of our study were similar to the studies in the literature, and no significant difference was found between the two protocols regarding response rates. In our study, the low rate of ASCT in the weekly VCD group was considered to be related to the fact that the patients receiving the weekly regimen were older than the other group and were not suitable for ASCT because of age.

Regarding side effects, the incidence of neuropathy and neutropenia was lower in our study compared to other studies. In the study by Li *et al.*[16], the incidence of neutropenia was 42%, and the incidence of neuropathy was 29%. The low toxicity incidence may be related to incomplete record keeping due to retrospective study.

Although our study was limited due to its retrospective nature and relatively low number of patients, it was thought to contribute to the literature since there was no prospective study data including many patients in our country.

CONCLUSIONS

In conclusion, our study showed no significant difference between weekly VCD and twice-weekly VCD protocols regarding response and side effects. Therefore, it has been shown that the weekly VCD protocol is feasible in induction treatment by reducing the number of hospital admissions in our country, where financial and regulatory constraints exist.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Ankara Bilkent City Hospital, Ankara, Turkey. (Decision number: E1-23-3619, date: 24.05.2023).

Authors' Contribution

Study Conception: EC, AKG; Study Design: FC, EC; Literature Review: EC, FC; Critical Review: EC, İD; Data Collection and/or Processing: ES,; Analysis and/or Data Interpretation: EC, GÖ; Manuscript preparing: EC.

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