Comparison of bortezomib-cyclophosphamide-dexamethasone *versus* bortezomib-dexamethasone based regimens in newly diagnosed multiple myeloma patients

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Abstract

The treatment landscape and clinical outcome of multiple myeloma (MM) patients have changed in the last decades, with an improved median survival of 8-10 years. This study aimed to evaluate the bortezomib, cyclophosphamide and dexamethasone (VCD) regimen *versus* bortezomib and dexamethasone (VD) regimen in patients with newly diagnosed MM. This study has been performed in a retrospective manner. One hundred and three patients with newly diagnosed MM who received chemotherapy at our tertiary care center between the years of 2009 and 2018 were evaluated. A total of 103 patients were included. The 5-year overall survival (OS) for patients who received VD regimen and patients who received VCD regimen were 75% and 83%, respectively. The OS for VD patients was 113.1±12.5 *versus* 122.2±9.5 months for VCD patients with no statistically significant difference (P=0.47). The 5-year PFS (progression free survival) for patients who received VD regimen and patients who received VCD regimen were 66% and 75%, respectively. The PFS for VCD patients was higher than the PFS for VD patients (67.1±7.4 *versus* 97.7±13.4 months), but no statistically significant difference was observed (P=0.59). Relapse rate (P=0.002) and mortality rate (P=0.01) were higher in VD group than VCD group and they were statistically significant. The OS and PFS were clinically longer in patients receiving VCD regimen than in patients receiving VD regimen, although not statistically significant. Cyclophosphamide should be given to patients at physician discretion and depending on patient's frailty function.

Introduction

The treatment landscape and clinical outcome of multiple myeloma (MM) patients have changed in the last decades, with an improved median survival of 8-10 years.[1] The induction therapy of multiple myeloma (MM) has changed significantly in the past decade because of the introduction of new drugs such as the proteasome inhibitor bortezomib (V) and immunomodulatory drugs (thalidomide, lenalidomid).[2] Bortezomib has shown efficacy for the treatment of MM in some clinical trials. Bortezomib-based regimens, including bortezomib plus dexamethasone, are now a cornerstone of treatment for both previously untreated and relapsed and/or refractory MM patients.[3] Bortezomib, dexamethasone based induction therapies are mostly combined with either cytotoxic agents, such as doxorubicin,[4,5] or cyclophosphamide,[6,7] or immunomodulatory drugs (IMiDs, thalidomide and lenalidomide).[8,9] The advantage of bortezomib based regimens to induction therapies without novel agents has been demonstrated in a number of phase III trials.[5,7-9] Three-drug regimens that include bortezomib, such as bortezomib, cyclophosphamide and dexamethasone (VCD), bortezomib, thalidomide, dexamethasone (VTD) and bortezomib, lenalidomide and dexamethasone (VRD) are highly efficient in newly diagnosed MM patients.[10] In this study, we evaluated whether the addition of cyclophosphamide to VD chemotherapy would be effective on survival outcomes in patients with our own experience. This study aimed to evaluate the outcomes VCD regimen *versus* bortezomib and dexamethasone (VD) in patients with newly diagnosed MM.

Materials and Methods

Study design and data collection

This study has been performed in a retrospective manner. Demographic data of the patients, treatment regimen and transplantation data updates were obtained from hospital database. As a result of application standards of the hospitals of Hacettepe Medical School, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care.

Patients and disease characteristics

One hundred and three patients with newly diagnosed MM who received induction therapy at our tertiary care center between the years of 2009 and 2018 were evaluated. The key inclusion criteria were patients 18–70 years of age with newly diagnosed MM who require systemic chemotherapy based on CRAB criteria;[11] with Karnofsky performance status ≥60%; and measurable MM disease.[12] Patients received up to eight 3-week cycles of VD or VCD.[13,14] Bortezomib (1.3 mg/m^2) was administered intravenously on days 1, 4, 8, and 11, dexam-

ethasone (20 mg) was administered orally on days 1, 2, 3, 4, 8, 9, 11 and 12 VD regimen, and additionally cyclophosphamide was administered intravenously 500 mg on 1, 8 days in VCD regimen. Most of the patients (96.1%) received two courses VAD (vincristine, doxorubicin, dexamethasone) chemotherapy before VD or VCD regimen. Antibiotic (co-trimoxazole) and antiviral (valcyclovir) prophylaxis was mandatory throughout induction therapies. Intravenous bisphosphonate administration was recommended every 4 weeks. Response was determined according to the current International Myeloma Working Group response criteria and was evaluated at two time points:[15] prior to ASCT and post ASCT, with the best response at any time after ASCT being captured for analysis. All patients underwent ASCT after induction therapies.

Statistical analysis

Statistical analyses were performed using the SPSS software version 25. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorow-Simirnov/Shapiro-Wilk's test) to determine whether they are normally distributed or not. Statistical comparisons were made using Chi-square for categorical data. Student t-test (for two independent samples) was used for comparison of continuous numerical data. Survival analyses were made using Kaplan-Meier test. Multivariate analysis of predictors of survival were performed using Cox regression test. Parameters with P values ≤0.10 in univariate tests were included in the multivariate analysis. P values <0.05 were considered to indicate statistical significance.

Results

Patient characteristics

A total of 103 patients were included. The median age was 59 (35-76) years at the time of diagnosis. The baseline clinical and demographic characteristics of patients are listed in Table 1. Most of the patients were male (62.1%). Neutropenia was seen more VCD group than VD group, however neutropenic fever or neutropenia associated infection were seen two patients in VCD group and one patient in VD. Addition of cyclophosphamide to VD was not associated with neutropenic fever or neutropenia associated infection. Relapse rate (p=0.002) and mortality rate (p=0.01) were higher in VD group than VCD group and they were statistically significant (Figures 1 and 2).

Table 1. Baseline clinical and demographic characteristics of patients.

Parameters	VD group	VCD group	P
N (%)	36 (35)	67 (65)	
Male/female	27/7 (75% / 25%)	37/30 (55.2% / 44.8%)	0.04
Median age at diagnosis (range), years	60 (35-74)	58 (37-76)	0.38
Hb (g/dl)	12.0 (6.3-15-8)	11.2 (7-16)	0.50
Platelets (per/nl)	230 (112-470)	220 (94-663)	0.12
Creatinine (serum, mg/dl)	0.9 (0.4-8)	0.8 (0.4-13.8)	0.51
Calcium (serum, mmol/l)	9.4 (8.2-11.5)	9.5 (9-10.1)	0.42
Karnofsky Performance Status (%)			0.65
100	7 (19.4)	18 (26.9)	
90	19 (52.8)	30 (44.8)	
80	10 (27.8)	19 (29.4)	
Durie Salmon stage at diagnosis (%)			0.74
Stage I	6 (16.7)	17 (25.4)	
Stage II	11 (30.6)	17 (25.4)	
Stage IIIA	11 (30.6)	21 (31.3)	
Stage IIIB	8 (22.2)	12 (17.9)	
LDH>UNL at transplant (%)	23 (63.9)	32 (47.8)	0.11
Neutropenia after chemotherapy (%)	2 (5.6)	22 (32.8)	0.002
Neutropenic fever/infection (%)	1 (2.7)	2 (2.9)	0.95
Disease status pre- transplantation			0.25
CR/VGPR (%)	7 (19.4)	20 (29.9)	
PR or less (%)	29 (80.6)	47 (70.1)	
Disease status post- transplantation (%)			0.77
CR/VGPR	31 (86.1)	59 (88.1)	
PR or less	5 (13.9)	8 (11.9)	
Relapse	13 (36.1)	7 (10.4)	0.002
Mortality	7 (19.4)	3 (4.5)	0.01

LDH: lactate dehydrogenase; UNL: upper normal limit; CR: complete response; VGPR: very good partial response; PR: partial response; ASCT: autologous stem cell transplantation.
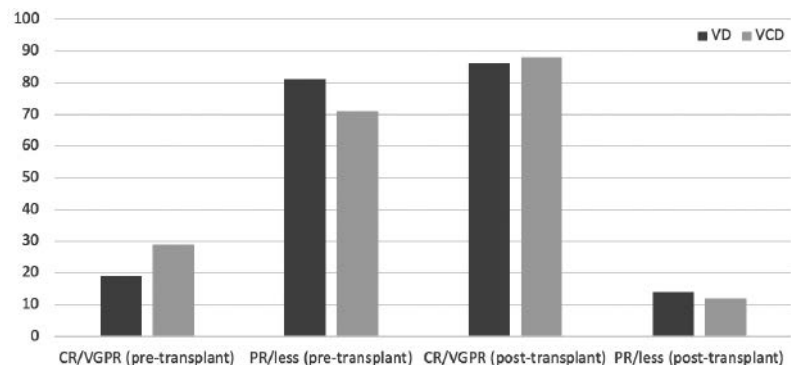

Figure 1. Pre-transplant and post-transplant response rates for VD and VCD regimens.
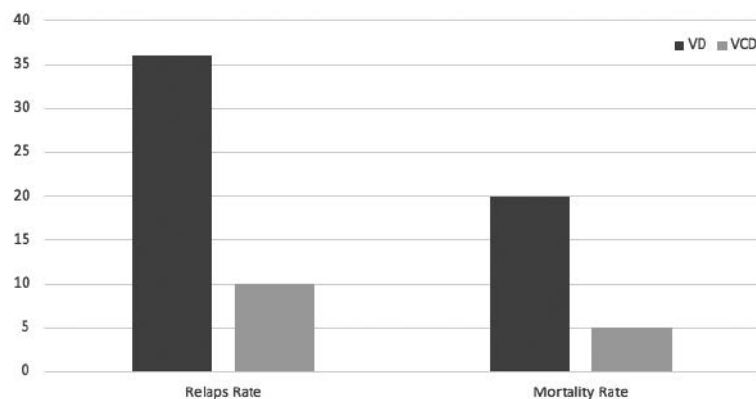

Figure 2. Relapse rate (P=0.002) and mortality rate (p=0.01) for VD and VCD regimens.

Overall survival

Of the 103 patients, 36 (35%) patients received 6-8 courses of VD, 67 (65%) patients received 6-8 courses of VCD regimen. The 3-year overall survival (OS) for patients who received VD regimen and patients who received VCD regimen were 89% and 95%, respectively. The 5-year OS for patients who received VD regimen and patients who received VCD regimen were 75% and 83%, respectively. The OS for VD patients was 113.1±12.5 *versus* 122.2±9.5 months for VCD patients with no statistically significant difference (p=0.47).

The 3-year progression free survival (PFS) for patients who received VD regi-

men and patients who received VCD regimen were 83% and 81%, respectively. The 5-year PFS for patients who received VD regimen and patients who received VCD regimen were 56% and 59%, respectively. The PFS for VCD patients was higher than the PFS for VD patients (67.1±7.4 *versus* 97.7±13.4 months), but no statistically significant difference was observed (p=0.40). The OS and PFS were clinically longer in patients receiving VCD regimen than in patients receiving VD regimen, although not statistically significant (Figure 3).

Cox regression analysis

In univariate analyses, factors affecting

OS were age (p=0.01) and Karnofsky Performance Status of the patients (p=0.01) of the patients, shown in Table 2. Cox regression analysis revealed only parameter to predict OS as Karnofsky Performance Status of the patients (p=0.02) of the patients.

In univariate analyses, factors affecting DFS were age (<50 years) (p=0.006), sex (p=0.03), Karnofsky Performance Status of the patients (p=0.01). Cox regression analysis revealed the parameters to predict DFS as age (<50 years) (p=0.04), sex (p=0.009), Karnofsky Performance Status of the patients (p=0.01).

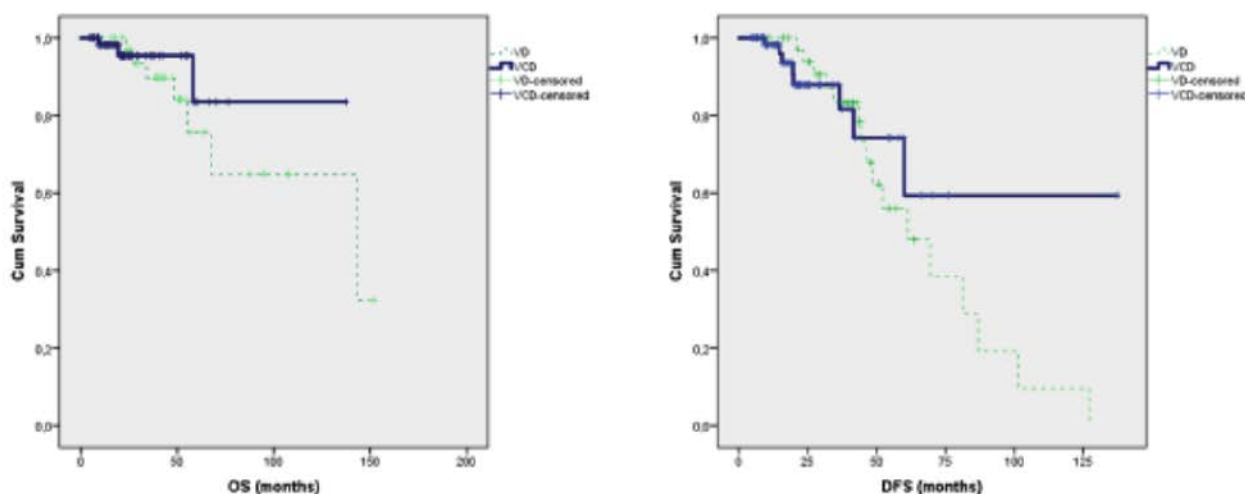**Figure 3. The overall survival (P=0.47) and progression free survival (p=0.40) for VD and VCD patients.**

Table 2. Univariate and Multivariate Analyses of Overall Survival and Disease-Free Survival.

Parameters for OS	Univariate analyses			Multivariate analyses		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age (<50 years)	0.906	0.837-0.981	0.01	0.934	0.867-1.006	0.07
Sex (male)	0.611	0.168-2.220	0.45			
Karnofsky Performance Status	6.393	1.503-27.188	0.01	6.603	1.310-33.272	0.02
Durie Salmon stage at diagnosis (%)	1.482	0.676-3.245	0.32			
LDH>UNL at transplant	0.442	0.052-3.801	0.45			
Induction chemotherapy (VD/VCD)	0.605	0.148-2.464	0.47			
Pre- transplantation disease status	1.257	1.156-10.155	0.83			
Parameters for PFS						
Age (<50 years)	1.022	1.006-1.037	0.006	0.948	0.900-0.998	0.04
Sex (male)	0.402	0.173-0.932	0.03	0.304	0.125-0.738	0.009
Karnofsky Performance Status	2.536	1.264-5.091	0.009	2.668	1.238-5.749	0.01
Durie Salmon stage at diagnosis (%)	1.283	0.802-2.052	0.29			
LDH>UNL at transplant	0.790	0.253-2.468	0.68			
Induction chemotherapy (VD/VCD)	0.697	0.294-1.649	0.40			
Pre- transplantation disease status	0.756	0.252-2.264	0.61			

Discussion and Conclusions

We offer the outcomes of a retrospective analysis of patients with MM who were diagnosed in our center between 2009 and 2018. In this study, newly diagnosed patients who underwent ASCT after induction chemotherapy were included. Baseline age, gender and clinical characteristics of patients were similar between two groups. The use of cyclophosphamide and bortezomib is supported by preclinical data demonstrating synergistic anti-MM efficiency between bortezomib and other alkylating agents.[16] It was effective when combined bortezomib and dexamethasone in previously untreated and relapsed patients with MM.[17] Additionally, different studies have reported improved efficacy associated with adding oral cyclophosphamide to either VD or pomalidomide and dexamethasone.[18,19] Past early-phase clinical evaluation has indicated that the addition of cyclophosphamide to VD regimen is associated with higher response rates, prolong disease control and improved survival in bortezomib-naive MM patients in their first to third relapse.[6]

On the other hand, the addition of cyclophosphamide to VTD led to increased toxicity without associated clinical benefit in patients with previously untreated MM.[20] CR/VGPR was also similar in the VD and VCD arms (86.1 *vs* 88.1%, respectively) in this study, although these response rates differ somewhat when compared with the previous phase II study.[19] In 33 patients with newly diagnosed MM, VCD in 28-day cycles, including 300 mg/m^{2} cyclophosphamide administration on days 1, 8, 15 and 22, reported an 80% reduction in monoclonal protein levels at the end of 2 cycles. The CR rate was 46% and VGPR rate was 71% among the 28 patients who completed all 4 cycles of therapy.[17]

The rate of thrombocytopenia did not appear to be increased with the addition of iv. cyclophosphamide to VD. In this study the rate of neutropenia appeared more in VCD group than VD group. However, the incidence of neutropenic fever or neutropenia associated infection were similar in both groups and very low. Our study had a few limitations. First of all, this study was retrospective. Second in most of patients (until 2017) we could use bortezomib based regimens only after VAD regimen due to the social security reimbursement policies in Turkey. There are several possible reasons for the insufficiency of benefit with the addition of continuous low-dose cyclophosphamide in the present study. One could be the relatively low dose of cyclophosphamide applied. It should also be noted that cytogenetics of patients was not obtained in this study.

OS and PFS were better in VCD group than VD group however, it was not statistically significant in this study. On the other hand, this may be translated as addition of cyclophosphamide to VD may add benefit for OS and PFS if the follow up period was longer and patient numbers were higher in both groups. We feel that longer follow up data is needed to definitely tell that VCD is superior than VD. The addition cyclophosphamide at the first day of chemotherapy cycle is almost non-toxic provided that G-CSF is given; VCD was not associated with neutropenic fever or neutropenia associated severe infection. We prefer VCD over VD with the hope that OS and PFS will be longer in long ran as it was already proved that mortality and relapse rates are lower. The results showed a substantial OS and PFS advantage with the addition of iv cyclophosphamide, although it hasn't reached statistical significance yet. Further trials are needed to determine whether addition of cyclophosphamide to VD at a different dose/schedule confers clinical benefit.

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