RESEARCH

REAL LIFE EXPERIENCE WITH FIRST-LINE THERAPY IN ELDERLY MULTIPLE MYELOMA PATIENTS: CONVENTIONAL OR BORTEZOMIB-BASED? DOUBLE TREATMENT OR TRIPLE TREATMENT?

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Abstract

Introduction: Elderly patients with multiple myeloma have shorter survival outcomes than younger patients. In this study, we aimed to compare the efficacy and toxicity profiles of conventional and bortezomib-based therapy as first-line therapy in elderly patients with multiple myeloma and to determine the prognostic factors.

Materials and Methods: We retrospectively analyzed the survival parameters with bortezomib-based therapy compared to conventional chemotherapy in newly diagnosed multiple myeloma patients over 70 years of age. We also evaluated double and triple therapy in patients receiving bortezomib-based therapy.

Results: A total of 79 patients were included. There was no difference between conventional and bortezomib-based therapy in terms of the overall survival and progression-free survival (p=0.649, p=0.324). The overall survival and progression-free survival of patients who were treated with double bortezomib-based therapy were significantly lower than those of patients who were treated with triple bortezomib-based therapy (p=0.001, p=0.0036). Multivariate Cox regression analysis revealed the parameters to predict the overall survival as triple bortezomib-based therapy (p=0.001), International Staging System (p=0.003), and lactate dehydrogenase level (p=0.004) in elderly patients who received bortezomib-based therapy.

Conclusion: Factors such as frailty, chemotherapy toxicity, comorbidities, and multi-drug use affect the treatment of elderly patients with myeloma. It is important to personalize treatment in elderly patients with myeloma. In this study, there were no differences in survival outcomes between conventional and bortezomib-based therapies. Conventional therapy can still be used as a first-line treatment in some elderly patients. Triple therapy options should also be considered in conventional or bortezomib-based therapies.

Keywords: Multiple Myeloma; Aged; Therapeutics.

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INTRODUCTION

Multiple myeloma is a disease characterized by the clonal proliferation of plasma cells in the bone marrow, which accounts for approximately 10% of all hematological malignancies. The median age of the patients at the time of diagnosis is approximately 65 years. Thirty-five percent of patients are diagnosed at the age of ≥75years, including 10% at the age of 85 years and above (1-3).

The incidence of MM increases with age. It is estimated that the number of elderly patients with newly diagnosed MM will increase in the coming decades as the world's population ages (4-5). Recently, the development of novel treatment modalities has led to significant advancements in the survival outcomes of younger patients with MM. However, elderly patients (defined as ≥75 years) did not show the same outcomes. There may be several reasons for this. First, there are more comorbid conditions and organ dysfunctions associated with aging in the elderly. Second, the risk of frailty is high, which is defined as a physiological decrease in coping with acute stress factors in the elderly and increasing the vulnerability. An increased risk of frailty has been associated with increased functional impairment, hospitalization, dependence, recurrent falls, disability, and death. Moreover, optimal MM treatment may not be applicable in this population because elderly patients are prone to chemotherapy-related adverse events and have a higher risk of chemotherapy toxicity (3, 5-7). Additionally, treatment targets for elderly patients may differ from those of younger patients. For example, in elderly patients with serious illnesses, it may be more critical to control the disease symptoms, maintain independence, and have a better quality of life than prolonged survival (4-5). For these reasons, elderly patients are generally not eligible for high-dose therapy (HDT) plus autologous stem cell transplant (ASCT). As a result, conservative approaches are used more frequently in elderly MM patients than in younger patients with MM.

In this retrospective study, we aimed to examine the survival outcomes of conventional and bortezomib-based treatments as a first-line therapy in newly diagnosed elderly MM patients and the factors affecting the survival of elderly patients. This study also evaluated the results of bortezomib, cyclophosphamide, and dexamethasone (VCD) treatment versus bortezomib and dexamethasone (VD) in patients with newly diagnosed elderly MM patients who were treated with bortezomib-based treatment only.

MATERIALS AND METHODS

Patients

In this retrospective study, multiple myeloma patients aged over 70 years who were diagnosed in the Hematology Department of Health Sciences University, Derince Training and Research Hospital and Kocaeli University School of Medicine between January 2007 and July 2020 were included. The study protocol was approved by the local research ethical committee. All the procedures were performed in accordance with the 1964 Helsinki Declaration. The diagnoses were based on the updated diagnostic criteria International Myeloma Working Group (8). All the data on disease characteristics and treatment protocols were obtained from clinical medical records. The patients were categorized according to the International Staging System (ISS)(9).

The cut-off levels of albumin and B-2 microglobulin(B-2 M) were designated as 3.5 according to ISS (3.5gr/dL, 3.5 mg/L; respectively). The performance status of the patients was classified according to the Eastern Cooperative Oncology Group (ECOG) score. The treatment protocols were divided into two groups conventional chemotherapy, including melphalan-based therapy, VAD (vincristine, adriamycin, and dexamethasone), and novel therapy, including bortezomib-based therapy. According to

the government's health insurance policy, lenalidomide-based regimens could not be used as first-line therapy, regardless of age. Therefore, the first-line novel therapy included only bortezomib-based regimens. The treatment responses were evaluated according to the IMWG criteria (10). Progression-free survival (PFS) duration was calculated from the start of first-line treatment to disease progression or death from any cause. The overall survival (OS) was calculated as the time from diagnosis to death from any cause. The dates of death were determined using the central medical record system. Early mortality was defined as death due to any cause within 12 months of the MM diagnosis (11-12).

Statistical Analysis

Statistical analyses were performed using NCSS (Number Cruncher Statistical System) software(Utah, USA) . The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the normality assumption. Continuous variables were presented as mean ± standard deviation or median (minimum-maximum range), depending on the normal distribution. The categorical variables are summarized as percentages. The Mann-Whitney U test or independent samples Student t test was used to compare non-parametric or parametric variables between the two groups. The Pearson chi-square test or Fisher-Freeman-Halton test was used for comparison to examine categorical variables. The survival durations were calculated using the Kaplan-Meier method. The log-rank test was used to compare the cumulative survival in the patient groups. A multivariate analysis of the predictors of survival was performed using the Cox regression test. The parameters with p values ≤0.20 in univariate tests were included in the multivariate analysis. All statistical analyses were two-sided; the significance was defined as $p < 0.05$.

RESULTS

Patient Outcomes

A total of *79 patients were enrolled in* this *study*. The median age at diagnosis was 74 years (range, 70–90 years); the age range of 61 (77.2 %) patients was 70-79 years, and 18(22.8 %) patients were ≥80 years old. There were 46 men (58.2%) and 33 women (41.8%). The clinical and demographic characteristics of patients receiving conventional and bortezomib-based therapies are shown in Table 1.

The median number of lines of therapy was 2 (1–4). Among the patients who received conventional chemotherapy, 13 patients received melphalan prednisone (MP), 6 patients received melphalan-thalidomide-prednisone (MTP) and 3 patients received VAD. The remaining 57 patients received bortezomib-based therapy, including 22 patients who were treated with bortezomib plus dexamethasone (VD) and 35 patients who were treated with bortezomib, cyclophosphamide and dexamethasone (VCD). A total of 41 patients received second-line treatment,10 patients received third-line treatment and 3 patients received fourth-line treatment. Second-line therapy was initiated due to an adverse event in one patient, refractory disease in 13 patients, and relapsed disease in 27 patients. Maintenance therapy was used as part of the first-line treatment in 12 patients. Seven patients received lenalidomide, four patients received thalidomide and one patient received bortezomib maintenance treatment.

Survival Analysis

The median follow-up time was 15 months (range 1–93 months). The median OS and PFS were 36,5 months (20–56 months) and 11,7 months (5–16 months), respectively.

The PFS for the conventional chemotherapy group was higher than that of the borte-

Table 1. Baseline clinical and demographic characteristics of elderly MM patients

		All Patients (n:79)	Conventional Therapy (n:22)	Bortezomib-based Therapy (n:57)	p value
Age	Min-Max (Median) Mean±SD	70-90 (74) 75.25±4.98	70-87 (77.5) 77.32±5.52	70-90 (73) 74.46±4.55	[a]**0.037***
	70-79 years ≥80 years	61 (77.2) 18 (22.8)	13 (59.1) 9 (40.9)	48 (84.2) 9 (15.8)	[b]**0.017***
Gender	Female Male	33 (41.8%) 46 (58.2%)	10 (45.5%) 12 (54.5%)	23 (40.4%) 34 (59.6%)	[b]0.680
Type	IgA Kappa IgA Lambda IgG Kappa IgG Lambda Kappa Lambda Non-Secretory	12 (15.2) 8 (10.1) 24 (30.4) 11 (13.9) 9 (11.4) 14 (17.7) 1 (1.3)	5 (22.7%) 4 (18.2%) 7 (31.8%) 5 (22.7%) 0 (0.0%) 1 (4.5%) 0 (0.0%)	7 (12.3%) 4 (7.0%) 17 (29%.8) 6 (10.5%) 9 (15.9%) 13 (22.8%) 1 (1.8%)	[c]0.070
Comorbidities	Diabetes Mellitus Ischemic Cardiac Disease Pulmoner Diseases Renal Diseases Cerebrovascular Disease	11(13.9%) 27(34.1%) 5(6.3%) 23(29.1%) 2(2.6%)	3 (13,6%) 7(31,8 %) 2 (9%) 6 (27,2%) 1 (4,5%)	8 (14%) 20 (35%) 3(13,6%) 17(29,8%) 1 (1,7%)	[c]0.74
ECOG PS Score	0-1 2-4	34 (43.0%) 45 (57.0%)	8 (36.4%) 14 (63.6%)	26 (45.6%) 31 (54.4%)	[b]0.457
ISS	1 2-3	17 (21.5) 62 (78.5)	8 (36.4) 14 (63.6)	9 (15.8) 48 (84.2)	[b]**0.04***
Hb (gr/dl)	Min-Max (Median) Mean±SD	5.1-13.8 (9.9) 9.77±1.76	5.1-13.3 (9.5) 9.55±2.03	6.7-13.8 (9.9) 9.85±1.66	[d]0.506
Creatinine (mg/dL)	Min-Max (Median) Mean±SD	0.6-6.5 (1.16) 1.81±1.39	0.7-5.2 (1.05) 1.48±1.22	0.6-6.5 (1.29) 1.94±1.44	[a]0.082
Calcium (mg/dl)	Min-Max (Median) Mean±SD	8.1-15.7 (9.8) 10.22±1.52	8.1-13.7 (9.7) 9.79±1.22	8.1-15.7 (9.87) 10.38-1.60	[a]0.220
CRP (mg/dl)	Min-Max (Median) Mean±SD	0.1-101 (1) 4.60±13.30	0.1-8 (0.8) 1.86±2.37	0.1-101 (1.64) 5.65±15.50	[a]0.244
LDH (U/L)	Min-Max (Median) Mean±SD	65-560 (167) 199.83±88.15	65-560 (167) 225.38±126.42	99-388 (167) 190.42±68.13	[a]0.524
B2-M (mg/L)	Min-Max(Median) Ort±Ss	2.3-39.2 (6.52) 8.26±6.12	3.1-16 (5.6) 6.39±3.50	2.3-39.2 (6.96) 8.95±6.73	[a]0.088
Bone Lesion at diagnosis	Lytic+ Plasmocytoma No bone lesion	64 (81.0%) 15 (19.0%)	16 (72.7%) 6 (27.3%)	48 (84.2%) 9 (15.8%)	[c]0.337
Response to 1st line therapy	CR-VGPR PR or less	26 (37.1%) 44 (62.9%)	3 (13.6%) 19 (86.4%)	23 (47.9%) 25 (52.1%)	[b]**0.006****
Relapse Patients	Yes No	57 (72.2%) 22 (27.8%)	16 (72.7%) 6 (27.3%)	41 (71.9%) 16 (28.1%)	[b]0.943
Early Death	Yes No	16 (20.2%) 63 (79.8%)	2 (10%) 20 (90%)	14 (24.5%) 43 (75.5%)	[b]**0.029***
All Grade's Adverse Effects	Yes No	51 (64.6%) 28 (35.4%)	13 (59.1%) 9 (40.9%)	38 (66.7%) 19 (33.3%)	[b]0.527
Grade 3-4 Adverse Effects	Yes No	27 (34.1) 52 (65.9)	7 (31.8) 15 (68.2)	20 (35.1) 37 (64.9)	[b]**0.545**

Abbreviations: SD: Standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; ISS: International Staging System ; Hb: Hemoglobin; B-2 M: Beta-2 microglobulin; CRP: C-reactive protein; LDH: lactate dehydrogenase; CR: complete remission; VGPR: very good partial remission; PR: partial remission

[a]Mann Whitney U Test, [b]Pearson Chi-Square Test, [c]Fisher Freeman Halton Test, [d]Student-t Test

*p<0.05, **p<0.01

zomib based-therapy group (29.75±6.83 versus 20.92±3.11). The 8-year PFS for patients who received conventional chemotherapy and those who received bortezomib-based therapy were 26% and 28 % respectively); however, no statistically significant difference was observed (p=0.324). The OS for the conventional chemotherapy group was 39.97±5.69 versus 38.15±5.18 months for the bortezomib based-therapy group. The 8-year OS for patients who received conventional chemotherapy and those who received bortezomib-based therapy were 27 % and 46 %, respectively with no statistically significant difference (p=0.649).

Cox regression analysis revealed the parameters to predict the OS as ISS (HR:4.930; 95% CI:2.148-8.647; p=0.001) and CRP level (HR:2.254; 95% CI:1.092-4.651; p=0.028) in all elderly patients. The cox regression analysis revealed the parameters to predict the PFS as CRP level (HR:2.677; 95%CI:1.356-5.285; p=0.005) and response to first-line therapy (HR:2.755; 95%CI:1.328-5.714; p=0,006) (Table 2).

Subgroup analyses of patients who received bortezomib-based first-line therapy were also performed. The PFS of patients who were treated with VD chemotherapy was significantly lower in comparison to the patients who were treated with VCD chemotherapy (13.41±3.25 months vs. 26.78±4.49 months, p= 0.0036). The 8- year PFS of patients who were treated with VD chemotherapy and those who received VCD chemotherapy were 14% and 37%, respectively. The OS in the group receiving VD was signficantly lower in comparison to the patients who were treated with VCD chemotherapy (19.78±3.93 months vs 53.62±7.88, p=0.001). The 8- year OS of patients who were treated with VD chemotherapy and those who received VCD chemotherapy were 10% and 68%, respectively.

In univariate and multivariate analyses, the factors affecting PFS and OS in patients receiving bortezomib-based therapy are shown in Table 3. Cox regression analysis showed the parameters to predict the PFS in response to first-line therapy and CRP level (p=0.023, and p=0.049, respectively). The cox regression analysis showed the parameters to predict the OS as VCD chemotherapy (p=0.001), ISS (p=0.003) and the LDH level (p=0.004) .

DISCUSSION

In this study, we demonstrated that no difference was found between the PFS and OS between conventional chemotherapy and bortezomib-based therapy in elderly patients with newly diagnosed MM. The survival outcomes of the double (VD) and triple (VCD) treatment regimens were also compared in the bortezomib-treated group.The PFS and OS were significantly longer in the VCD regimen than in the VD regimen. The VCD regimen was found to be an independent prognostic factor for a higher OS.

Melphalan-based therapies have formed the backbone of the treatment of elderly MM patients who are not suitable for ASCT. Several studies and meta-analyses have shown a survival benefit from the use of bortezomib or thalidomide in addition to MP (melphalan, prednisolone) in elderly patients unfit for ASCT (7,13-14).

No randomized studies have compared melphalan to bortezomib (without melphalan) in transplant-ineligible patients with newly diagnosed MM. The randomized controlled trial of VISTA investigated whether VMP versus MP improved the survival outcomes in patients not eligible for ASCT as first-line therapy. This trial showed that VMP results in a significantly longer OS, time to next treatment, and time to progression than MP. The survival advantage has been demonstrated in patients> 75 years of age, despite the discontinuation of treatment and greater toxicity. The final analysis of the VISTA trial confirmed a persistent significant OS benefit after five years of' follow-up (15-16). We showed that bortezomib-based therapy improved the complete response-very good partial response (CR-VGPR) response rates compared to conven-

Table 2. The effects of clinical parameters on OS and PFS for all elderly MM patients

Parameters of OS		Univariable		Multivariable	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	70-79 ≥ 80	0.913 (0.472-1.764)	0.786		
Gender	Female Male	1.366 (0.754- 2.474)	0.304		
ISS	ISS 1-2 ISS 3	4.409 (2.248-8.647)	**0.001****	4.930 (2.148-8.647)	**0.001****
ECOG	0-1 2-4	2.405 (1.296-4.464)	**0.005****		0.509
Creatinine(mg/dl)	<2mg/dl ≥2mg/dl	2.233 (1.198- 4.162)	**0.011***		0.329
LDH(U/L)	Normal Elevated	2.379 (1.266- 4.473)	**0.007****		0.239
CRP	Normal Elevated	2.948 (1.564- 5.556)	**0.001****	2.254 (1.092-4.651)	**0.028***
Response to 1st line therapy	CR-VGPR PR or less	1.878 (0.912-3.869)	**0.087**		0.559
Parameters of PFS					
Age (years)	70-79 ≥ 80	0.950 (0.509-1.775)	0.873		
Gender	Female Male	1.249 (0.730-2.139)	0.417		
ISS	ISS 1-2 ISS 3	2.371 (1.332-4.222)	**0.003****		0.107
ECOG	0-1 2-4	1.606 (0.936-2.756)	0.085		0.500
Creatinine(mg/dl)	<2mg/dl ≥2mg/dl	1.663 (0.935-2.957)	0.083		0.721
LDH(U/L)	Normal Elevated	3.005 (1.664-5.429)	**0.001****		0.708
CRP	Normal Elevated	3.751 (2.000-7.034)	**0.001****	2.677 (1.356-5.285)	**0.005****
Response to 1st line therapy	CR-VGPR PR or less	3.090 (1.559-6.125)	**0.001****	2.755 (1.328-5.714)	**0.006****

Cox proportional hazards regression analysis; HR: Hazard ratio; CI: Confidence Interval

*p<0.05 **p<0.01

Table 3. The effects of clinical parameters on OS and PFS for elderly MM patients who received bortezomib-based treatment

Parameters of OS		Univariable		Multivariable	
		HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	70-79 ≥ 80	1.409 (0.590-1.714)	0.440		
Gender	Female Male	1.366 (0.754-2.474)	0.210		
ISS	ISS 1-2 ISS 3	7.774 (2.605-18.200)	**0.001****	5.442 (1.759-16.839)	**0.003****
ECOG	0-1 2-4	3.079 (1.385-6.845)	**0.006****	3.654 (1.504-8.877)	**0.004****
Creatinine(mg/dl)	<2mg/dl ≥2mg/dl	3.103 (1.429-6.735)	**0.004****		0.838
LDH(U/L)	Normal Elevated	4.341 (1.980-9.518)	**0.001****		0.599
CRP	Normal Elevated	2.232 (1.052-4.733)	**0.036***		0.190
Response to 1st line therapy	CR-VGPR PR or less	1.687 (0.692-4.111)	0.250		
Chemotherapy regimen	VCD VD	4.302 (1.955-9.464)	**0.001****	5.307 (2.216-12.710)	**0.001****
Parameters of PFS					
Age (years)	70-79 ≥ 80	1,364 (0,596-3,122)	0.462		
Gender	Female Male	1.853 (0.933-3.680)	0.218		
ISS	ISS 1-2 ISS 3	2.117 (1.047-4.281)	**0.037***		0.302
ECOG	0-1 2-4	1.701 (0.903-3.204)	0.100		0.812
Creatinine(mg/dl)	<2mg/dl ≥2mg/dl	1.521 (0.785-2.946)	0.214		
LDH(U/L)	Normal Elevated	2.936 (1.439-5.991)	**0.003****		0.574
CRP	Normal Elevated	3.378 (1.666-6.849)	**0.001****	**2.155(1.070-5.398)**	**0.049***
Response to 1st line therapy	CR-VGPR PR or less	2.852(1.343-6.226)	**0.007****	2.519 (1.135-5.591)	**0.023***
Chemotherapy regimen	VCD VD	1.956 (1.033-3.704)	**0.04***		0.863

*p<0.05 **p<.0.01

tional therapy. However, there was no significant difference in the survival outcomes between the two treatment regimens. We believe that there may be several reasons for the difference in the survival outcomes. Patients receiving bortezomib treatment had a higher ISSstage and higher rates of early mortality. Additionally, B2-M and creatinine levels were higher in patients receiving bortezomib-based therapy; however, the difference was not statistically significant. These results suggest that those receiving bortezomib-based therapy have aggressive disease.

Although VCD is not used as first-line therapy in Western countries, it is still frequently used as a first-line treatment in some countries, including our country. No randomized studies have compared VD to VCD in transplant-ineligible patients with newly diagnosed MM. In the Upfront study, the patients aged >65 years who were ineligible for transplantation were randomized into three arms: VD, VMP, and bortezomib-thalidomide –dexamethasone (VTD). No significant differences were observed among the three treatments for median PFS or OS. Side effects were observed to be higher with VTD than with VD or VMP (17). With four cycles of VCD therapy in newly diagnosed MM patients, the CR rate was 46%, and ≥ the VGPR rate was 71% (18). Continuous oral cyclophosphamide addition to VD treatment in relapsed and refractory MM showed an overall response rate of 90% (≥PR 82%); the median event-free survival was 12 months, and the median overall survival was 22 months (19). VCD and VD treatments were compared in a retrospective study of newly diagnosed MM patients. The relapse rate (p=0.002) and mortality rate (p=0.01) were higher in the VD group than in the VCD group. The OS and PFS were better in the VCD group than in the VD group; however, the difference was not statistically significant. In this study, elderly patients were not evaluated as a separate group (20). In our study, we showed that the VCD regimen was associated with longer OS and PFS than the VD regimen. The VCD regimen is an independent prognostic factor for OS. We also showed that the known risk factors for MM (ISS, ECOG, LDH and CRP) are effective in survival outcomes in elderly patients, both in the whole patient group and in the group receiving bortezomib.

Elderly patients with MM are more susceptible to treatment-related side effects; 42-53% of elderly patients experience grade 3-4 adverse events early in treatment with a new agent (21). For this reason, it causes early discontinuation of treatment or lower intensity treatments. In our study, grade 3-4 side effects were found to be slightly lower (34%). Since this was a retrospective study, side effects may have been described less frequently. Early death is another problem in elderly patients. The mortality rate in the first year was approximately 15% in elderly patients with MM. An age ≥ 70 or 75 years was an independent predictor of early mortality (11-12). Contrary to the rate of side effects, early death rates were higher in our study than in the literature. In particular, the early death rate in the bortezomib-based group was significantly higher than that in the conventional chemotherapy group.

Limitations

This study has a few limitations due to its retrospective design and the small number of patients. It is used for genetic evaluation of the MM risk staging system. Since genetic evaluation was not performed in every elderly MM patient, we could not show the relationship between genetic evaluation and the survival outcomes. The myeloma frailty score also could not be evaluated in every patient.

In conclusion, as seen in the real-world data in elderly MM patients, we found that there was no difference in the survival outcomes between conventional and bortezomib-based therapies. In the receiving bortezomib group, the VCD regimen resulted in significantly better survival outcomes than the VD regimen. The treatment of multiple myeloma in the elderly is challenging due to increased side

effects,comorbidities, frailty, and poor adherence to treatment. Therefore, the treatment of elderly MM patients often needs to be individualized. MP or VD treatment may be preferred in patients who are not suitable for more intensive chemotherapy. When the conditions become suitable, triple therapy can be initiated by adding a third drug to patients who receive both MP and VD.

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Declaration of Interest: The authors declare no conflict of interests.

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