Received: 3 April 2021 | Revised: 18 June 2021 | Accepted: 21 June 2021

DOI: 10.1111/ejh.13683

ORIGINAL ARTICLE

European Journal of Haematology WILEY

Bortezomib-based therapy for newly diagnosed multiple myeloma patients ineligible for autologous stem cell transplantation: Czech Registry Data

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Abstract

Objectives: This study compared the use of bortezomib in different combination regimens in newly diagnosed multiple myeloma (NDMM) patients who were transplant ineligible.

Patients and Methods: We analyzed data from the Registry of Monoclonal Gammopathies (RMG) of the Czech Myeloma Group (CMG) to provide real-world evidence of outcome for 794 newly diagnosed MM transplant ineligible patients. The most frequently used regimen was VCd (bortezomib-cyclophosphamide-dexamethasone) (47.5%) over VMP (bortezomib-melphalan-prednisone) (21.7%), BDd (bortezomib-doxorubicin-dexamethasone) (9.8%), and VTd (bortezomib-thalidomide-dexamethasone) (2.9%).

Results: The overall response rate (ORR) was 69.2% (478/691), including 12.6% (≥ CR); 34.7% very good partial responses (VGPR); and 21.9% partial responses (PR). Among triplet regimens, VMP was the most effective regimen compared to VCd, BDd, and VTd. Median PFS was 22.3 vs. 18.5 vs. 13.7 vs. 13.8 mo, (P = .275), respectively, and median OS was 49 vs. 41.7 vs. 37.9 vs. 32.2 mo (P = .004), respectively. The most common grade 3-4 toxicities were anemia in 17.4% and infections in 18% of patients. **Conclusion:** Our study confirmed that bortezomib-based treatment is effective and safe in NDMM transplant ineligible patients, especially VMP, which was identified as superior between bortezomib-based induction regimens not only in clinical trials, but also in real clinical practice.

KEYWORDS

bortezomib, multiple myeloma, patient, treatment

1 | INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy of plasma cells with median age at diagnosis of approximately 70 years, with 35%-40% of patients older than 75 years.[1]

Autologous stem cell transplantation (ASCT) is the standard of care for this disease; however, less than half of newly diagnosed MM (NDMM) patients are eligible for this treatment due to age, comorbidities, or complications of MM itself. Once ASCT ineligibility is classified, the goal of treatment should lead to the choice of the best regimen for each individual according to laboratory results and clinical status in order to achieve deep and durable responses.[2]

Today, the treatment paradigms change very dramatically with the introduction of novel drugs and their combinations. Generally, the best choices are either proteasome inhibitor-based, IMiD-based, combined, or even with the addition of monoclonal antibodies. The first modern treatment was set up with the introduction of MPT regimen (melphalan-prednisone-thalidomide), which showed superior PFS in comparison with previous golden standard MP (melphalan-prednisone), however with ambiguous results in OS.[3-10] The introduction of bortezomib-based regimens, especially VMP, has soon replaced thalidomide as it provided deeper responses and leads to improvement in OS, too.[11,12]

Even now the bortezomib-based regimens have their place in the treatment of newly diagnosed patients, usually in combination with thalidomide, lenalidomide, or daratumumab.[13-18] They are of special focus especially in patients with renal failure or in MM with adverse features including high-risk cytogenetics or extramedullary disease.[19-21]

While the benefits of bortezomib-based therapy have been exemplified in clinical trials, real-world evidence of outcomes in clinical practice is scarce. Robust, real-world evidence is becoming increasingly important as the efficacy and safety of bortezomib in the treatment of NDMM transplant ineligible patients as reported in the highly controlled clinical trials may differ from experience in everyday oncology practice.

The main endpoint of this registry-based study was to present clinical outcomes for NDMM transplant ineligible patients treated with bortezomib-based induction therapy outside clinical trials. The secondary endpoint was the identification of the most effective bortezomib-based induction regimen with regard to improved survival measures.

2 | METHODS

2.1 | Patients

Data for this study were obtained from the Registry of Monoclonal Gammopathies (RMG) of the Czech Myeloma Group (CMG).[22] All patients provided written informed consent with the inclusion of their data in the RMG and with their assessment. The written consent was approved by the Ethics committees of all hematological centers. The diagnosis, clinical staging, and prognostic score of MM were based on the Durie and Salmon staging system and the International Staging System (ISS).[23,24]

In determination of transplant ineligibility, we followed the recommendations by Spanish myeloma group.[25,26] Presence of frailty, significant comorbidities, advanced age, and poor Eastern Cooperative Oncology Group (ECOG) performance status defined NDMM patients as transplant ineligible. Renal impairment was not an absolute contraindication to transplant.

Disease response and progression were defined according to consensus criteria published by IMWG.[27] Adverse events were assessed according to the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE, v3.0).[28]

Between June 2005 and January 2017, a total of 4204 NDMM patients were diagnosed. Of these, 70.5% (2964/4204) patients were ineligible for ASCT. Out of these NDMM transplant ineligible patients, 43.6% (1293/2964) were treated with bortezomib-based regimens in fifteen hematologic centers in the Czech

Republic. Only 61.6% (794/1293) of NDMM patients were analyzed. The reasons for exclusion from analysis were interruption of bortezomib-based treatment for reasons other than progression in 20.7% (268/1293) of patients; incomplete data in 13.7% (177/1293) of patients; switch of therapy for reasons other than progression in 6.1% (79/1293) patients; and unclear follow-up in 2.4% (31/1294) of patients. At the time of analysis, only 87% (691/794) of patients had definitely finished bortezomib-based treatment without any planned intermissions or continuation of bortezomib-based treatment.

The median age at diagnosis was 70 years (range 39-90) with 78% of patients being >65 years at the time of treatment initiation. A total of 86% (682/794) patients had ECOG 1 or worse; 45.1% (338/794) patients had ISS- 3 stage; 67.5% (521/794) patients had stage III by the Durie-Salmon; and 31.7% (250/794) had substage B by the Durie-Salmon.

Baseline characteristics of the patient cohort are shown in Table 1.

TABLE 1 Clinical characteristics of MM patients at diagnosis

		Patients (N = 794)
Sex	women	375 (47.2%)
	men	419 (52.8%)
Age (years)	≤ 65	176 (22.2%)
	> 65	618 (77.8%)
	median (5th–95th perc.)	70 (56-81)
ISS stage (N = 750)	stage 1	165 (22.0%)
	stage 2	247 (32.9%)
	stage 3	338 (45.1%)
Durie-Salmon stage (N = 772)	I	80 (10.4%)
	II	171 (22.2%)
	III	521 (67.5%)
Durie-Salmon substage (N = 788)	A	538 (68.3%)
	B	250 (31.7%)
M-protein type (N = 788)	IgG	436 (55.3%)
	IgA	152 (19.3%)
	LC only	158 (20.1%)
	other	42 (5.3%)
Light chain type (N = 780)	kappa	463 (59.4%)
	lambda	306 (39.2%)
	biclonal	11 (1.4%)
Extramedullary mass (N = 785)	no	717 (91.3%)
	yes	68 (8.7%)

Note: Median (5th–95th percentiles) for continuous format and count (relative frequencies) for categorical format.

2.2 | Treatment

Bortezomib 1.3 mg/m^2 was given on d 1, 4, 8, and 11 of a 21 d cycle or 1, 4, 8, and 15 of a 28 d cycle. The median number of administered cycles of the bortezomib-based regimen was 8 (range 4-12 cycles). The median cumulative dose of bortezomib was 56 mg (range 24-131.5 mg). Only subcutaneous injections of bortezomib were administered in 395 patients; only intravenous injections of bortezomib were administered in 233 patients. Treatment was discontinued on withdrawal of the patient's consent, disease progression, insufficient treatment response (did not achieve PR or better treatment response after fourth cycle), or the occurrence of unacceptable toxic effects. Patients were given herpes zoster prophylaxis.[29]

The induction regimens were Vd (bortezomib plus dexamethasone) or VP (bortezomib plus prednisone); and VTd, VCd, BDd, VMP, and CVTd (cyclophosphamide plus bortezomib plus thalidomide plus dexamethasone). In total, 81.8% (650/794) of patients were treated by triplet regimens and 10.7% (85/794) with doublet regimens. The most frequent triplet was VCd used in 47.5% (377/794) of patients (treatment is summarized in Table 2). VRD regimen is not included as it has not been approved at the time of the analysis.

2.3 | Statistical analysis

Data were described by absolute and relative frequencies of categorical variables and median (5th–95th percentiles) of quantitative variables, in selected quantitative variables range was reported. Exact binomial 95% confidence interval (CI) was calculated using Clopper Pearson method (reported only for response to therapy). OS, PFS, and TTP were plotted using Kaplan-Meier (K-M) methodology. The K-M estimates were completed by the 95% confidence interval derived using Greenwood formula. Patients were compared in baseline characteristics and endpoints using ML chi-square test (in categorical variables) and Kruskal-Wallis test (in quantitative variables). Log-rank test was used to estimate the statistical significance of the difference between the K-M curves. P-values less than 0.05 were considered statistically significant (all tests two-sided). Analysis was performed in the SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and software R version 3.3.0 (www.r-projec.org).

3 | RESULTS

3.1 | Treatment response

Treatment response could be evaluated in 87% (691/794) of treated patients per IMWG criteria.[27]

Overall response rate (ORR) (defined as ≥PR) was 69.2% (478/691) of patients, including 12.6% (87/691) ≥ CR; 34.7%

(240/691) of VGPR; 21.9% (151/691) of PR; 6.9% (48/691) of minimal response (MR); and 23.8% (165/691) of stable disease (SD)/progression (PG). The median time to progression (TTP) was 18.4 mo [95% CI: 16.6-20.1], PFS was 16.6 mo [95% CI: 14.8-18.3], and the median duration of response (DOR) was 20.0 mo [95% CI: 18.3- 21.6]. The median OS was 44.4 mo [95% CI: 38.8-49.2]. Response rates were not significantly different when subcutaneous and intravenous injections of bortezomib were compared.

TABLE 2 Characteristics of treatment regimen

Frontline therapy, N (%)	Patients (N = 794)
Doublet regimen	85 (10.7%)
Vd therapy (bortezomib +dexamethasone)	81 (10.2%)
VP therapy (bortezomib +prednisone)	4 (0.5%)
Triple regimen	650 (81.8%)
VCd therapy (bortezomib +cyclophosphamide + dexamethasone)	377 (47.5%)
VMP therapy (bortezomib +melphalan + prednisone)	172 (21.7%)
BDd therapy (bortezomib +doxorubicin + dexamethasone)	78 (9.8%)
VTd therapy (bortezomib +thalidomide + dexamethasone)	23 (2.9%)
Other bortezomib –based regimens	59 (7.4%)

Note: Abbreviations

Vd/ VP regimen=bortezomib + corticosteroid (dexamethasone/ prednisone)

VCd regimen =bortezomib +cyclophosphamide +dexamethasone

BDd regimen =bortezomib + doxorubicin +dexamethasone

VMP regimen =bortezomib + melphalan +prednisone

VTd regimen =bortezomib + thalidomide +dexamethasone

Others =BBd regimen (bortezomib +bendamustine + dexamethasone), CVTd therapy (cyclophosphamide +bortezomib + thalidomide +dexamethasone), bortezomib monotherapy

3.2 | Treatment-related toxicity

The most frequent hematological toxicity of grade 3-4 was anemia occurring in 17.4% (133/763) of patients. The most frequent non-hematological toxicities grade 3-4 were infections, occurring in 18% (137/765) of patients. Treatment-related peripheral neuropathy grade 3-4 was found in 4.7% (36/762) of patients (Table 3).

3.3 | Treatment response stratified by treatment modality

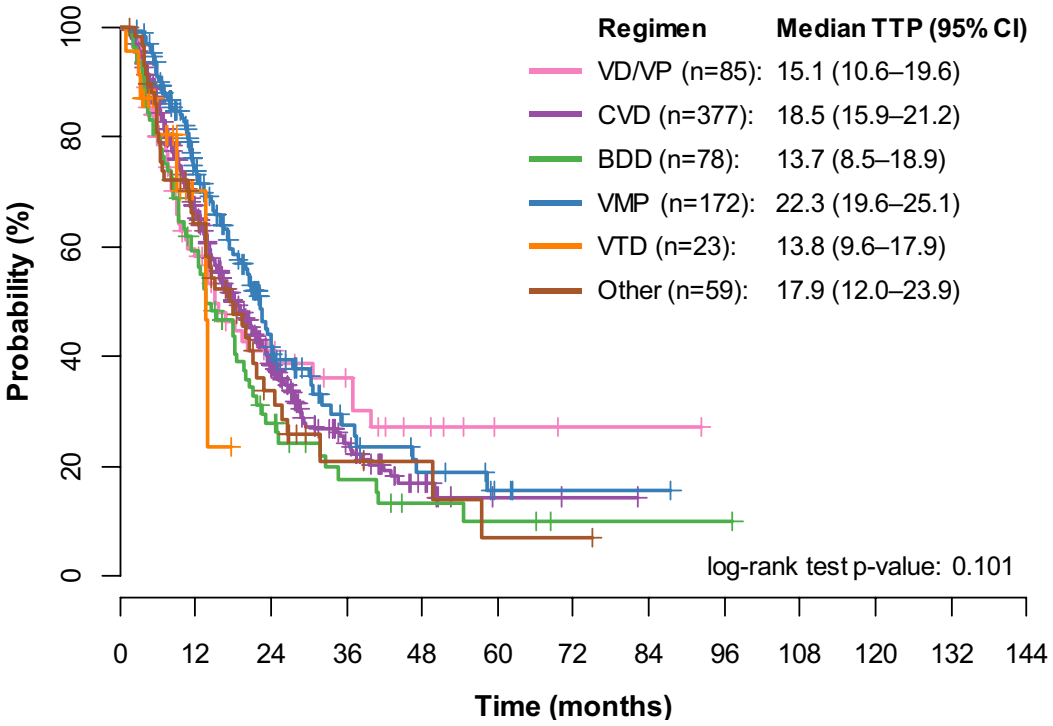
To identify the most effective bortezomib-based regimen, we compared all used induction regimens. VMP showed better outcomes among the triplet regimens compared with VCd, BDd, and VTd regimens. Median PFS was 22.3 vs. 18.5 vs. 13.7 vs. 13.8 mo (P =.101), respectively (Figure 1), and median OS was 49 vs. 41.7 vs. 37.9 vs. 32.2 mo (P =.004), respectively (Figure 2).

There were significant differences (P <.001) between the used regimens and patient's disease characteristics before the induction treatment in the following variables: biological age of patients, the level of β2-microglobulin, creatinine, hemoglobin, and C-reactive protein (CRP) level. Extramedullary involvement and ECOG performance status were not significant variables associated with used regimens.

In our conditions, VMP regimen was preferably used in older patients (median 72; range: 65.0- 82.0), while younger patients were preferably treated by VTd (median 66.0; range 44.0-79.0) or BDd (median 67.0; range 50.0-76.0) regimens. Patients with higher value

TABLE 3 Treatment-related toxicity regardless of treatment regimen (N = 794 patients)

Toxicity, N (%)	grade 1-2	grade 3-4	Missing values
Hematological toxicity			
Anemia (N = 763)	513 (67.3%)	133 (17.4%)	31 (3.9%)
Thrombocytopenia (N = 762)	379 (49.7%)	78 (10.2%)	32 (4.0%)
Neutropenia (N = 761)	282 (37.1%)	118 (15.5%)	33 (4.2%)
Thrombosis (N = 761)	29 (3.9%)	27 (3.5%)	33 (4.2%)
Non-hematological toxicity			
Neuropathy (N = 762)	315 (41.4%)	36 (4.7%)	32 (4.0%)
Infection (N = 765)	279 (36.5%)	132 (17.3%)	29 (3.7%)
Fatigue (N = 765)	384 (50.2%)	29 (3.8%)	29 (3.7%)
Nausea (N = 764)	258 (33.8%)	10 (1.3%)	30 (3.8%)
Diarrhea (N = 765)	168 (22.0%)	21 (2.7%)	29 (3.7%)
Anorexia (N = 763)	174 (22.9%)	4 (0.5%)	31 (3.9%)
Constipation (N = 765)	131 (17.1%)	2 (0.3%)	29 (3.7%)
Any toxicity (N = 752)	381 (50.7%)	359 (47.7%)	42 (5.3%)



Survival rate[1]	VD/VP	CVD	BDD	VMP	VTD	Other
6 months	80.2 (69.8–87.4)	86.0 (82.0–89.1)	80.6 (69.9–87.8)	91.1 (85.7–94.5)	80.3 (54.6–92.3)	80.9 (68.1–88.9)
12 months	59.7 (47.4–70.0)	66.5 (61.3–71.2)	59.2 (47.3–69.3)	73.9 (66.1–80.2)	70.2 (39.3–87.5)	64.3 (50.3–75.4)
24 months	41.0 (29.0–52.7)	38.3 (32.8–43.8)	27.9 (17.9–38.8)	42.8 (33.5–51.9)	–	33.8 (20.8–47.2)
36 months	36.1 (24.1–48.3)	24.2 (18.9–29.8)	17.6 (9.0–28.4)	27.4 (18.1–37.6)	–	20.8 (9.1–35.7)
60 months	27.1 (15.3–40.3)	14.4 (8.6–21.8)	9.9 (3.3–20.8)	15.7 (7.4–26.8)	–	6.9 (0.6–24.8)

[1] Probability of survival without progression or death related to MM (95% CI) in respective time after treatment initiation reported.

FIGURE 1 Progression-free survival (PFS) from treatment beginning by treatment modality

of β2-microglobulin (>2.37 mg/l) were frequently treated with BDd (median 9.4; range 2.9-34.4) and VP/Vd (median 8.2; range 2.4-40.6) regimens (P <.001). Patients with impaired renal function were preferably treated with BDd (median creatinine level was 248.0; range 50.0-912.0) and Vd/VP (median 221.0; range 66.0-706.0) regimens (P <.001) (Table 4).

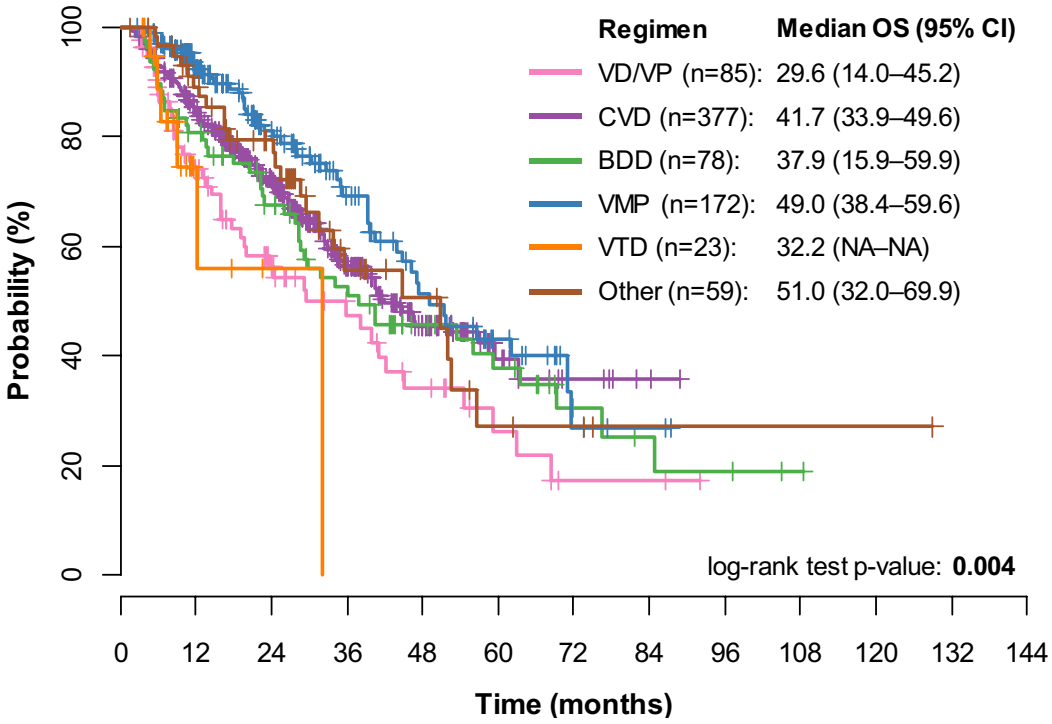
In our study, most patients were treated with VCd (47.5%) or VMP (21.7%) regimens; therefore, we primarily compared these two groups. VMP reached better outcomes in comparison with VCd in all efficacy endpoints (Figure 1, Figure 2). We found that the baseline characteristics of these groups did not differ with the exception of the age, which was higher in VMP (median 72.0; range 65.0-82.0) versus VCd (median 70.0; range 57.0-81.0) (P <.001). Patients treated with VMP experienced more hematologic toxicities, particularly grade 3 and 4 neutropenia (23.5% vs 12.5%, P <.001), respectively, and grade 3 and 4 thrombocytopenia (19.6% vs 6.9%, P <.001), respectively. The rate of venous thrombosis grade ≥1 was also higher in VMP compared to VCd regimen (10.3% vs.5.8%, P =.004, respectively). The rate of infections was similar in both groups (14.7% vs 17.4%, respectively) (Table 5).

4 | DISCUSSION

The introduction of bortezomib, thalidomide, and lenalidomide and mainly the more extensive use of high-dose therapy followed by ASCT has helped to change MM from a devastating malignancy with an average survival of 3 years to a chronic disease, where increasing numbers of patients can now expect to live more than 10 years.[30] Unfortunately, more than two-third of NDMM patients are ineligible for ASCT because of age, comorbidities, ECOG performance status, nutritional status, polypharmacy, cognition, and socioeconomic factors.[31]

In the Czech Republic, we performed one of the largest multicenter registry-based analysis of 794 NDMM transplant ineligible patients, treated with bortezomib-based regimens with median follow-up of 23 mo.

In our cohort, we observed that the patients were younger than would be expected in transplant ineligible patients. More than 22% (176/794) of patients were younger than 65 years. However, worse ECOG performance status and advanced MM at the time of diagnosis were the reasons for transplant ineligibility (Table 1).



Survival rate[1]	VD/VP	CVD	BDD	VMP	VTD	Other
6 months	89.0 (79.9–94.1)	93.1 (90.0–95.2)	89.7 (80.5–94.7)	97.1 (93.1–98.8)	88.8 (62.1–97.1)	96.5 (86.7–99.1)
12 months	74.0 (62.5–82.4)	84.8 (80.8–88.1)	80.7 (70.0–87.9)	92.2 (86.6–95.5)	74.6 (44.6–89.9)	89.2 (77.4–95.0)
24 months	56.4 (43.7–67.2)	71.8 (66.6–76.2)	67.6 (55.6–77.1)	81.1 (72.9–87.1)	56.0 (17.5–82.4)	79.3 (65.7–88.0)
36 months	47.4 (34.2–59.5)	56.3 (50.2–61.9)	52.7 (40.0–63.8)	69.3 (58.8–77.6)	–	55.8 (38.4–70.0)
60 months	26.1 (13.3–40.9)	39.4 (30.4–48.3)	37.7 (24.9–50.4)	43.2 (30.6–55.1)	–	27.0 (10.3–47.1)

[1] Probability of survival (95% CI) in respective time after treatment initiation reported.

FIGURE 2 Overall survival (OS) from treatment beginning by treatment modality

TABLE 4 Basic characteristics—continuous variables stratified by treatment modality

	Treatment modality						
Basic characteristics*	Vd/VP	VCd therapy	BDd therapy	VMP therapy	VTd therapy	Other	p[#]
Age (years)	71.0 (56.0-83.0)	70.0 (57.0-81.0)	67.0 (50.0-76.0)	72.0 (65.0-82.0)	66.0 (44.0-79.0)	69.0 (56.0-82.0)	< 0.001
β2 microglobulin (mg/l)	8.2 (2.4-40.6)	4.5 (1.9-20.6)	9.4 (2.9-34.4)	4.5 (2.1-13.7)	6.2 (1.6-50.0)	3.8 (1.8-20.8)	< 0.001
Albumin level (g/l)	36.7 (23.0-45.7)	36.2 (22.3-47.1)	34.7 (25.8-46.8)	36.9 (24.0-45.0)	34.7 (18.9-47.5)	38.0 (27.0-48.0)	0.448
LDH level (μkat/l)	3.3 (1.6-6.3)	3.2 (1.9-6.3)	3.6 (1.7-6.2)	3.1 (2.0-5.2)	3.8 (1.6-6.5)	3.0 (1.8-6.3)	0.041
CRP (mg/l)	6.5 (0.6-85.9)	5.0 (0.6-61.4)	6.3 (1.0-62.0)	3.9 (0.6-46.1)	11.8 (0.4-58.1)	2.9 (0.2-110.9)	0.001
Creatinine level (umol/l)	221.0 (66.0-706.0)	98.5 (54.0-534.0)	248.0 (50.0-912.0)	94.5 (57.0-254.0)	107.0 (64.0-407.0)	87.0 (50.0-421.0)	< 0.001
Calcium total level (mmol/l)	2.3 (1.9-3.1)	2.3 (2.0-3.1)	2.4 (2.0-3.6)	2.3 (2.0-2.7)	2.4 (2.1-3.2)	2.4 (2.0-3.2)	0.022
Hemoglobin level (g/l)	99.5 (73.0-138.0)	103.0 (77.0-142.0)	92.0 (70.0-136.0)	107.0 (82.0-140.0)	98.0 (69.0-142.0)	106.0 (78.0-136.0)	< 0.001

Note: Abbreviations

Vd/ VP regimen=bortezomib + corticosteroid (dexamethasone/prednisone)

VCd regimen =bortezomib +cyclophosphamide +dexamethasone

BDd regimen =bortezomib + doxorubicin +dexamethasone

VMP regimen =bortezomib + melphalan +prednisone

VTd regimen =bortezomib + thalidomide +dexamethasone

Others =BBd regimen (bortezomib +bendamustine + dexamethasone), CVTd therapy (cyclophosphamide +bortezomib + thalidomide +dexamethasone), bortezomib monotherapy

*median (5th–95th percentiles)

[#]p-value of Kruskal-Wallis test

TABLE 5 Treatment-related toxicity—VMP and VCd regimen

Adverse events (AE)	grade 1-2	grade 3-4	All grades	*P**
Non-hematological toxicity				
Neuropathy				
VCd (N = 372)	139 (37.4%)	11 (3.0%)	150 (40.4%)	0.187
VMP (N = 154)	63 (40.9%)	9 (5.8%)		
Gastrointestinal AEs§				
VCd (N = 374)	186 (49.7%)	9 (2.4%)		0.083
VMP (N = 155)	83 (53.5%)	9 (5.8%)		
Fatigue				
VCd (N = 374)	177 (47.3%)	9 (2.4%)		0.075
VMP (N = 155)	80 (51.6%)	9 (5.8%)		
Thrombosis				
VCd (N = 374)	8 (2.1%)	14 (3.7%)		0.004
VMP (N = 154)	13 (8.4%)	3 (1.9%)		
Infection				
VCd (N = 374)	132 (35.3%)	65 (17.4%)		0.587
VMP (N = 156)	52 (33.3%)	23 (14.7%)		
Hematological toxicity				
Thrombocytopenia				
VCd (N = 375)	180 (48.0%)	26 (6.9%)		<0.001
VMP (N = 153)	77 (50.3%)	30 (19.6%)		
Neutropenia				
VCd (N = 375)	127 (33.9%)	46 (12.3%)		<0.001
VMP (N = 153)	65 (42.5%)	36 (23.5%)		
Anemia				
VMP (N = 153)	104 (68.0%)	20 (13.1%)		0.596
VCd (N = 375)	262 (69.9%)	55 (14.7%)		

Note: Abbreviations
VCd regimen = bortezomib + cyclophosphamide + dexamethasone
VMP regimen = bortezomib + melphalan + prednisone
**P*-value of ML chi-square test
§Include nausea, anorexia, or diarrhea

Our study showed very good treatment outcomes if we stress that we included all patients who started bortezomib-based therapy even beyond the standard inclusion criteria for clinical trials. The response rates were comparable to the trials (ORR 69.2%; ≥CR 12.6% and ≥VGPR rate 47,3%; median PFS 16.6 mo, median TTP 18.4 mo). Despite the fact that our analysis was performed on unselected patients with ECOG 1 or worse, the results of treatment responses of our analysis are very similar to the results of the VISTA study (Figures 1, 2).[11,12]

The adverse events reported in our study were consistent with established toxicity profiles for bortezomib.[9-11,32] The most frequent grade 3-4 toxicities were anemia in 17.4% (133/763) and infections in 17.3% (132/765) with no significant differences between regimens. The rate of peripheral sensory neuropathy grade 3-4 was reported in 4.7% (36/762) patients in our study. We want to underline that in our real-world analysis, there were also 8.5% (65/762) of included patients with preexisting grade ≥1 peripheral neuropathy. The route of administration of bortezomib in our analysis varied. A total of 57.2% (395/794) patients received subcutaneous bolus and 33.8% (233/794) patients received intravenous bolus of bortezomib. The subcutaneous bolus of bortezomib has similar therapeutic outcomes and toxicity profile as the intravenous bolus. The results of our analysis support previous clinical trials.[33,34]

Before introduction of VRd, VMP was recommended as the gold standard of treatment for NDMM transplant ineligible patients.[11] However, as can be seen from the results of our analysis, the most frequently used regimen in our conditions was VCd (47.5%) over VMP (21.7%) and BDd (9.8%) regimen. Owing to the lack of cumulative stem cell damage, cyclophosphamide, unlike melphalan, preserves the ability to harvest stem cells during induction. Therefore, VCd regimen was preferably used in patients who would be otherwise transplant eligible based on biological age but their clinical conditions at the beginning of treatment did not allow enrollment

to transplant program. The second most commonly used regimen in our conditions was VMP, preferably used in elderly patients (median 72.0, range 65.0- 82.0) who were not candidates for ASCT. The third most commonly used regimen was BDd, preferably used in patients with impaired renal function (median creatinine level was 248.0; range 50.0-912.0).

When we compared the patient groups of two most common used regimens, VMP reached better outcomes in comparison with VCd in all efficacy endpoints, including OS, TTP, and PFS. However, VMP compared to VCd had also more hematological side effects, in particular thrombocytopenia (69.9% vs. 54.9%, P <.001) and neutropenia (66.0% vs. 46.1%, P <.001). The rate of venous thrombosis was also higher in VMP compared to VCd regimen (10.4% vs. 5.9%, P =.004). A partial explanation for this result may be the fact that VMP was used in elderly patients with higher risk of cardiovascular and thromboembolic complications (Table 5).

Generally, we can conclude that VMP has been the optimal bortezomib-based front-line treatment for NDMM transplant ineligible patients who are 65 years or older without impaired renal function. Regimens VCd, VTd, or VCTd could be recommended for younger NDMM patients with aggressive disease (advanced ISS stage, D-S stage, extramedullary disease). The best treatment choice for younger MM patients with renal failure without severe cardiac complications is BDd. For "frail" NDMM patients with/without impaired renal failure, Vd or VP regimen could be optimal treatment with good balance of efficacy and safety.

In contrast to the VISTA or other clinical trials with highly selected patients, we analyzed an unselected group of NDMM transplant ineligible patients regardless of baseline laboratory results, presence of extramedullary mass, comorbidities, and ECOG performance status. The assessment of transplant ineligibility, treatment regimen, dose, route of administration of bortezomib, and duration of treatment were decided by the hematologist. Therefore, in this study, there are various treatment regimens, different routes of bortezomib applications, and non-uniform duration of treatment—the real picture of the clinical practice.

5 | CONCLUSION

Our real-world analysis using data of 794 unselected NDMM transplant ineligible patients treated by bortezomib-based induction regimens confirmed the efficacy and safety of bortezomib-based induction regimen. VMP has been the gold standard for a whole decade, and this study confirmed this claim even in real-life setting outside of clinical trials. Other regimens combining bortezomib with cyclophosphamide, adriamycin, or thalidomide are usually used in specific situations with fair results still they had worse outcomes in our analysis than the VMP regimen.

ACKNOWLEDGEMENTS

The authors would like to thank all members of the Czech Myeloma Group and especially all patients and their caregivers whose participation made this study possible. We would also like to thank all the participating centers for their involvement and enthusiasm during the study.

This research was funded by MH CZ—DRO (UHHK, 00179906), PROGRES Q40/8, MH CZ—DRO (FNBr, 65269705), CZ.02.1.01/0.0/0.0/16-019/0000868, NV18-03-00500, MH CZ—DRO (FNOI, 00098892), and IGA-LF-2021-001.

CONFLICT OF INTEREST STATEMENTS

The authors declare that there are no competing financial interests in relation to the work described.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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How to cite this article: Sandecká V, Pour L, Špička I, et al. Bortezomib-based therapy for newly diagnosed multiple myeloma patients ineligible for autologous stem cell transplantation: Czech Registry Data. *Eur J Haematol*. 2021;107:466–474. https://doi.org/10.1111/ejh.13683