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Real-world effectiveness and safety of daratumumab, bortezomib, and dexamethasone in relapsed/refractory multiple myeloma in Slovakia

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Real-world data on regimens for relapsed/refractory multiple myeloma (RRMM) are limited. Daratumumab in combination with bortezomib and dexamethasone is a promising new treatment. The aim of this analysis was to assess the outcomes of daratumumab-bortezomib-dexamethasone (DVd) combination for the treatment of patients with RRMM in a real-world setting. All consecutive RRMM patients who received at least two cycles of DVd treatment between December 2016 and July 2020 were identified. We analyzed the clinical characteristics and survival of 47 patients treated at 7 Slovak centers outside of the clinical trials. The median age was 65 years (range, 35 to 83). The median (range) number of lines of therapy per patient was 3 (2–6). All patients were previously exposed to PIs (proteasome inhibitors) and IMIDs (immunomodulatory drugs), the majority of patients (70.2%) had double refractory (IMIDs and PI) disease and 72.3% of patients were refractory to their last therapy. Most patients presented with high-risk characteristics, including 25.6% adverse cytogenetics and 25.5% extramedullary disease. The majority of patients responded with an overall response rate of 78%, we found complete response in 3, very good partial response in 22, partial response in 12, minor response or stable disease in 9, and progressive disease in 1 patient. After a median follow-up period of 8 months, the median progression-free survival was 10 months. There was a longer progression-free survival in those with 2 vs. >2 prior treatments, with equally good effectivity in standard-risk and high-risk cytogenetic groups. The adverse events were usually mild, none leading to permanent drug interruptions. Daratumumab-bortezomib-based combinations are efficacious and safe regimens in RRMM patients in the real-world setting. This is the first analysis in Slovakia addressing the DVd combination outside of the clinical trial setting.

Key words: daratumumab, bortezomib, relapsed/refractory multiple myeloma, real-world data

The treatment of multiple myeloma (MM) has advanced significantly over the past decade with the approval of novel agents including proteasome inhibitors (PIs), such as bortezomib, carfilzomib, and ixazomib; immunomodulatory drugs (IMiDs) such as lenalidomide and pomalidomide; monoclonal antibodies (mAbs) namely daratumumab, isatuximab, and elotuzumab; and other treatments in development including CAR-T-cell therapy. Patients with disease refractory to both PIs and IMiDs have a particularly poor prognosis, with a median overall survival of 8–9 months [1, 2]. Moreover, relapsed/progressive MM acquires additional mutation or genetic alterations that render the disease more resistant, leading to progressively shorter durations of remission or response to each salvage therapy, and the ultimate development of relapsed/refractory MM (RRMM) [3].

Given the success of targeted immunotherapy with monoclonal antibodies in other cancers, recent research has focused on the development of this class of drugs for multiple myeloma [4–5]. Daratumumab, a human IgGκ monoclonal antibody targeting CD38, has a direct anti-tumor and immunomodulatory mechanism of action [6–9].

In heavily pretreated patients with relapsed or relapsed and refractory multiple myeloma, single-agent daratumumab was associated with an overall response rate of 31%

and a median progression-free survival (PFS) of 4 months and overall survival (OS) of 20.1 months [6]. Treatment with daratumumab in combination with proteasome inhibitors and immunomodulatory agents has resulted in high response rates and acceptable safety profiles [7–15].

The aim of this multi-center retrospective analysis was to evaluate the effectiveness and safety of DVd combination in the real-world practice of Slovak multiple myeloma patients.

Patients and methods

Study design and subjects. This was a multi-centric, retrospective, observational study designed by physicians using data collected from patients with RRMM treated with DVd combination. Patients were treated at 7 different clinical centers in Slovakia between December 2016 and July 2020. Patients who started treatment before September 2019 were treated in the special patient program. To be eligible to receive DVd treatment, adult patients were required to have relapsed MM and completed at least 2 cycles of treatment. Patient care and evaluations were determined by the treating physicians.

Patients received DVd combination therapy in accordance with the regimen employed in the phase III CASTOR study in patients with RRMM [11] and approved by the EMA. Specifically, patients received daratumumab 16 mg/kg once weekly for the first 10 weeks (cycle 1–3), then every 3 weeks for 15 weeks (cycle 4–8), and then once every 4 weeks thereafter (cycles 9 and higher); bortezomib 1.0–1.3 mg/m^2 on days 1, 4, 8, 11 in the first 8 cycles; and dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 until disease progression, unacceptable toxicity, or patient/physician decision to end treatment.

For infusion-related reaction (IRR) prevention, the patients received premedication comprising methylprednisolone or an equivalent, paracetamol, bisulepin, or montelukast one hour prior to administration of daratumumab.

Definitions and statistical analysis. Response criteria (complete response [CR], very good partial response [VGPR], partial response [PR], minor response [MR], stable disease [SD], and progressive disease [PD]) and survival measures (progression-free survival [PFS] and overall survival [OS]) were defined according to published International Myeloma Working Group guidelines [16]. For the purpose of this study, patients with t(4;14), t(14;16), 1q amplification, and del(17p) were grouped together as a high-risk cohort. Patients who did not have a recorded death date or a documented progression were censored at the time of the last follow-up (July 31, 2020). The adverse events (AEs) associated with DVd treatment were recorded from electronic charts and medication management records. The severity of AEs was classified according to the Common Terminology Criteria for Adverse Events, version 5.0. Statistical analyses were performed using MedCalc Statistical Software version 18.11.3. OS and PFS were estimated using the Kaplan-Meier method. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics. Seven centers responded with 47 patients altogether, including 12 patients from the Department of Hematology and Transfusiology in Bratislava, 10 patients from Banská Bystrica, 9 patients from Košice, 8 patients from National Cancer Institute Bratislava, 5 patients from Martin, 2 from Nitra, and 1 from Ružomberok. The characteristics of the enrolled patients are listed in Table 1.

The median age at the diagnosis was 60 years (range, 32 to 78) and at the daratumumab treatment 65 years (range, 35 to 83).

At data cut-off, the median follow-up for patients included in this analysis was 8 months (95% confidence interval [CI], 6 to 9). FISH results were available in 39 out of the 47 patients and here 10 (25.6%) had high-risk cytogenetics. The International Staging System (ISS) Score was evaluated in 46 patients. The majority had high ISS (stage 2+3): 11 (24%), 24 (52%), and 11 (24%) were in the ISS 1, 2, and 3 groups, respectively. Twelve patients (25.5%) had extramedullary plasmacytoma. Markedly impaired renal function (creati-

Table 1. Baseline characteristics in daratumumab treatment.

Age (years)	Median (range)	65 (35–83)
	<65	19 (40.4%)
	65 to <75	24 (51.1%)
	≥75	4 (8.5%)
Gender	Males	30 (63.8%)
	Females	17 (36.2%)
ISS stage	I	11 (24%)
	II	24 (52%)
	III	11 (24%)
Immunoglobulin isotype	IgG	30 (63.8%)
	IgA	8 (17%)
	FLC only	9 (19.2%)
Cytogenetics	t(4,14)	1/39 (2.6%)
	del17p	3/39 (7.7%)
	t(14,16)	2/39 (5.1%)
	amp1q21	6/39 (15.4%)
	standard risk	29 (74.4%)
	missing	8 (17%)
Extramedullary involvement		12 (25.5%)
Lines of previous therapy	Median (range)	3 (2–6)
Previous PI	Bortezomib	100 (100%)
	Ixazomib	8 (17%)
	Carfilzomib	0 (0%)
Previous IMIDs	Thalidomide	9 (19.1%)
	Lenalidomide	45 (95.7%)
	Pomalidomide	7 (14.9%)
Refractory to	Last line of therapy	34 (72.3%)
	Double refractory	33 (70.2%)
	Triple refractory	19 (40.4%)
Previous HSCT	Autologous HSCT	32 (68.1%)
Renal function	Creatinine ≥177 μmol/l	9 (19.1%)
	Hemodialysis	1 (2.1%)

Abbreviations: ISS – International Staging System; PI – proteasome inhibitors; IMIDs – immunomodulatory drugs; HSCT – hematopoietic stem cell transplantation

Table 2. Overall best response.

Best response	n (%)
ORR	37 (78.7)
CR	3 (6.4)
VGPR	22 (46.8)
PR	12 (25.5)
MR	2 (4.2)
SD	7 (14.9)
PD	1 (2.1)

Abbreviations: ORR – overall response rate; CR – complete remission; VGPR – very good partial remission; PR – partial remission, MR – minimal response; SD – stable disease; PD – progression

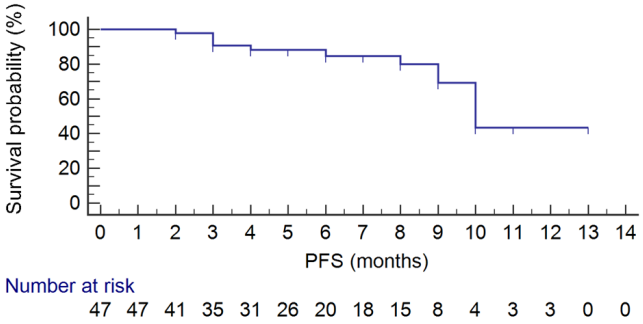

Figure 1. Progression-free survival (PFS).

Table 3. Factors associated with the achievement of CR/VGPR.

Factor	p-value
Age	0.43
Gender	0.02
ECOG	0.01
ISS stage	0.02
Cytogenetics	0.71
Renal function	0.64
Refractory to last line of therapy	0.92
Previous HSCT	0.70
Previous PIs	0.92
Previous IMIDs	0.93

Abbreviations: ISS – International Staging System; PIs – proteasome inhibitors; IMIDs – immunomodulatory drugs; HSCT – hematopoietic stem cell transplantation; CR – complete remission; VGPR – very good partial remission

Table 4. Details of reported infusion-related reactions.

	Any grade	Grade 3 or higher
Infusion-related reaction (IRR)	27 (57.4%)	6 (22.2%)
Dyspnea	10	5
Arterial hypertension	4	1
Throat irritation	4	0
Nasal congestion	4	0
Chills	3	0
Nausea, vomiting	2	0
Erythema	1	0

Table 5. Adverse events.

	Any grade	Grade 3 or higher
Neutropenia	13 (27.6%)	8 (17%)
Thrombocytopenia	11 (23.4%)	7 (14.9%)
Anemia	12 (25.5%)	8 (17%)
Febrile neutropenia	3 (6.4%)	3 (6.4%)
Infection	4 (8.5%)	1 (2.1%)
Herpes zoster reactivation	3 (6.4%)	1 (2.1%)
Worsening of polyneuropathy	7 (14.9%)	5 (10.6%)

nine ≥177 μmol/l) has been reported in 9 cases, including 1 patient who required hemodialysis.

The patients were heavily pretreated with the median line of prior treatment 3 (range 2–6). All patients had prior bortezomib and most had lenalidomide (95.7%) and thalidomide (19%), only 12 (25.5%) patients were previously treated with other innovative drugs. Sixty-eight percent of the patients had prior autologous transplantation. Thirteen (27.6%) patients before daratumumab treatment were relapsed, 34 (72.3%) patients were refractory to their last therapy, 70.2% of patients were double-refractory.

Effectiveness. Among the 47 patients who completed at least 2 cycles of treatment, DVd was effective in the majority of patients. Overall response rate (ORR) was 78%, including CR in 3 patients, VGPR in 22, PR in 12, MR or SD in 9, and PD occurred in 1 patient (Table 2). After 8 months median follow-up, 74.4% of patients are still on treatment, the calculated PFS was 10 months (Figure 1). Factors contributing with the achievement of CR/VGPR are listed in Table 3.

The median overall survival (OS) was 67 months. There was a longer PFS in those with 2 vs. >2 prior treatments (NR vs. 10 months, p=0.01), but there was no significant difference between standard and high-risk FISH patients (NR vs. 9 months, p=0.8) and between the relapsed vs. relapsed/refractory categories (NR vs. 10 months, p=0.4).

Adverse effects. IRR occurred in 27 (57.4%) of the patients. There were 6 cases with grade 3, with no grade 4 or 5 (Table 4). All of the IRR were observed during the first infusion. No patient discontinues the treatment because of IRR.

The most frequent AEs were hematologic toxicities. Grade 4 or 5 and fatal AEs were absent. The summary of toxicity is listed in Table 5. In total, worsening of preexisting polyneuropathy was in 14.9% of evaluable patients (7/47). In our analysis, factors such as age, gender, cytogenetics, ECOG, and previous treatments did not contribute to the development of adverse events (p=0.36) or infusion-related reactions (p=0.11).

Discussion

The introduction of monoclonal antibodies represented a significant breakthrough in the therapeutic scenario of multiple myeloma. This multi-center retrospective analysis investigated the effectiveness and tolerability of daratumumab, bortezomib, and dexamethasone combination in 47 Slovak RRMM patients. Patients had advanced myeloma with a median number of 3 prior lines of treatment, including PIs and IMIDs. The majority of patients (70.2%) had double refractory (IMIDs and PIs) disease and 72.3% of patients were refractory to their last therapy.

In a recently published analysis, with greater than 3 years of median follow-up, DVd maintains significant PFS and ORR benefits compared to Vd alone (16.7 vs. 7.1 months; 85% vs. 63%, respectively) [17]. Because of the similar median follow-up (8 months vs. 7.4 months), we used for the comparison the first analysis of the CASTOR study [11]. Findings from our real-world cohort reflected the outcome of a broader general patient population, which was more pretreated with bortezomib than that included in the CASTOR study (100% vs. 67.3%, $p<0.001$), and tended to have more advanced stage diseases (ISS II–III, 76% vs. 61%, $p=0.05$) and more patients with disease refractory to the last line of therapy (72.4% vs. 30%, $p<0.001$). Also, although the cytogenetic profiles were only available in 39 patients, the percentages of high-risk abnormalities were comparable to the CASTOR study.

In the CASTOR trial, daratumumab in combination with bortezomib and dexamethasone led to the deep quality of response and high overall response rate in the RRMM subset. Yet despite the differences in baseline characteristics and treatment exposure, treatment response in our study was comparable with the CASTOR trial findings, with a similar ORR (78% vs. 82.9%, $p=0.4$), including 6.4% of CR and 46.8% VGPR. Response rates were, therefore, found to be very similar to those obtained in the CASTOR study with a lower percentage of patients who obtained CR (6.4% vs. 14.6%, $p=0.12$), which can be explained by a higher number of previous lines of therapy. The survival results are a little bit inferior to those obtained in patients from the CASTOR study. The median PFS was not reached (NR) in the CASTOR study versus 10 months in our study, caused also by the number of prior treatment lines (median prior treatment lines 3 vs. 2) and a higher refractory rate. But on the other hand, the same PFS results as in the CASTOR study were obtained in those with 2 vs. >2 prior treatment lines (NR vs. 10 months).

The published real-world data on the DVd combination are lacking. There are only a limited number of publications available in terms of real-world results of daratumumab monotherapy [18–25]. Recently, one Hungarian study has reported new data about daratumumab monotherapy and combination therapies (with bortezomib and lenalidomide) in a real-life setting [26]. Ninety-nine Hungarian patients were included; 48 received monotherapy, while lenalidomide and bortezomib combinations were administered in 29 and 19 cases, respectively. The mean values of prior treatment lines were 2.77±0.869 in patients who received combinations with bortezomib and daratumumab. The overall response rate in this group was in 79% of patients, CR+VGPR in 26% of patients. There was a trend of inferior PFS in the bortezomib combination and monotherapy groups (6.6 months in both), while median PFS was not reached in the lenalidomide group.

IRRs were relatively frequent but generally well manageable and we observed no grade 4 or 5 IRR leading to permanent discontinuation of treatment. The safety profile was compatible with the previously published CASTOR study [11]. Grade ≥3 AEs were reported in 42.5% of the present cohort within the follow-up and in the CASTOR study in 76.1%. However, the lower grade ≥3 AE rate (42.5%) reported here is likely to be attributed to a reporting bias due to the retrospective nature of this analysis.

Major limitations of our work include the small sample size, short median follow-up, and the retrospective study design. In spite of these pitfalls, this is the first analysis in Slovakia addressing the DVd combination outside of the clinical trial setting. Indeed, real-world data are emerging for the use of daratumumab-based combinations in RRMM, but such data are still limited. The findings in the present study are encouraging. Although the follow-up was fairly short (median 8 months), as daratumumab was just introduced in Slovakia in September 2019, our real-world data did demonstrate that the daratumumab-bortezomib-based regimens were active in routine practice for RRMM.

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