ORIGINAL ARTICLE

Real-world multiple myeloma management practice patterns and outcomes in selected Central and Eastern European countries

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KEY WORDS

Central Eastern Europe, multiple myeloma, novel agents, outcomes, treatment patterns

ABSTRACT

INTRODUCTION Multiple myeloma (MM) treatment has evolved substantially in recent years. Solid data on the impact of treatment strategies on patient outcomes beyond clinical trials are scarce, especially in budget-restricted environments with limited access to new treatments.

OBJECTIVES This study investigated treatment practices, patterns, and outcomes in real-world clinical practice in Bulgaria, Croatia, Czech Republic, Poland, Romania, and Slovakia.

PATIENTS AND METHODS This was a noninterventional, observational chart review comprising a cross-sectional and a retrospective longitudinal phase observing adult patients with symptomatic MM at all stages of therapy.

RESULTS The study revealed structural differences in clinical practice compared with a similarly designed study previously conducted in 7 Western European countries. Stem cell transplantation was performed in less than half of newly diagnosed eligible patients. The most frequently used first-line regimens were bortezomib based, with frequent bortezomib retreatment after the first relapse. Lenalidomide-based regimens were predominant in the third and subsequent lines of therapy. Depth of response decreased with each treatment line, with half of patients achieving at least very good partial response (≥VGPR) in the first line, while only one-fourth achieved ≥VGPR in the third or subsequent lines. Time to progression was longer in patients with better response levels.

CONCLUSIONS Inadequate access to advanced antimyeloma regimens and—in some countries—stem cell transplantation highlights the challenges of MM treatment in the region. Information on real-world patient management and its outcomes can provide valuable input for decision makers to effectively allocate limited resources.

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INTRODUCTION Multiple myeloma (MM) is generally considered a cancer of the elderly, with a median age at diagnosis of 69 years.[1] MM accounted for an estimated 38 928 new cases in Europe in 2012 (33 413 in the European Union [EU 27]).[2] The age-standardized mortality rates per 100 000 person-years in 2012 as reported by the European Cancer Observatory (http://eco.iarc.fr) were as follows: 2.7 and 1.8 for men and women, respectively, in Europe

as a whole (40 countries), 3.0 and 2.1, respectively, for EU 27, and 1.7 and 1.3, respectively, for Central and Eastern Europe (CEE).[2] Over the last 3 decades, therapeutic options for MM, especially in the setting of relapsed and refractory disease, have substantially improved. The novel agents, such as immunomodulatory agents, proteasome inhibitors, histone deacetylase inhibitors, and recently, monoclonal antibodies, together with stem cell transplantation (SCT) in eligible patients, have substantially improved the depth of response and increased progression-free and overall survival.[3-6] With the already available novel agents and an ever-increasing number of newly approved drugs and drug combinations, the selection of an optimal treatment strategy at first and subsequent lines, as well as the best sequence of agents to use in relapsed disease, has increased in complexity.

The level of drug reimbursement is a major factor for the choice of treatment worldwide. The therapeutic approaches differ in most European countries, but even higher challenges are faced in CEE, where the health care systems have evolved differently from Western European countries and other economic parameters, such as gross domestic product per capita expenditure for health care, differ substantially. Thus, the level of drug reimbursement is a major limiting factor for the choice of treatment in these countries. Real-world data describing patient management throughout their treatment journey and across different countries are scarce for CEE. Building on previous research from 7 Western European countries (Belgium, France, Germany, Italy, Spain, Switzerland, and United Kingdom),[7,8] we conducted a partly prospective, partly retrospective observational, cross-sectional patient chart review to investigate the management of patients with symptomatic MM in countries with different access to new treatments in order to enhance the understanding of disease burden and current patient management, and to inform health economic analyses.

PATIENTS AND METHODS

Study design This was a noninterventional, observational chart review conducted in 6 countries (Bulgaria, Croatia, Czech Republic, Poland, Romania, and Slovakia) between April 2015 and June 2016. Physicians completed 3 research components (see Supplementary material, *Figure S1*, for details). A questionnaire was used to collect information on hospital policies for drug prescription, guidelines, and diagnostic tests routinely performed in MM. A cross-sectional patient chart review was performed for any patient with symptomatic MM seen during the period of 2 to 4 weeks to enable an estimation of the proportion of patients in each step of the treatment sequence. This included treatment status, line of treatment, and reason for no treatment. Patients with smoldering myeloma or monoclonal gammopathy of undetermined significance were excluded from the cross-sectional phase. A retrospective patient chart review was performed for patients completing their most recent line of treatment within the past 3 months to provide details of current and past treatments. This included details relating to symptomatology, dosages, administration schedule, treatment durations, drug holidays, and reasons for change or discontinuation. Patients who completed their most recent line of treatment more than 3 months prior to enrolment, patients with smoldering myeloma or monoclonal gammopathy of undetermined significance, and patients treated as part of a clinical trial in the most recent line were excluded from the retrospective phase. Patients selected for the cross-sectional chart review were also allowed for the retrospective chart review.

The primary objectives of the study were as follows: 1) to estimate the proportion of patients in each line of the treatment sequence in a real-world setting, including the proportion of patients transplanted, those receiving a maintenance treatment, and those reaching advanced lines of treatment; and 2) to examine differences in treatment patterns (regimen prescribed, dosages, treatment durations, therapeutic pauses, reasons for change or discontinuation, response to treatment, previous treatment [or treatments] received) for each line of therapy for patients with symptomatic MM.

Physicians obtained approval from their respective local ethics committee, where legally required. The study was performed according to the Declaration of Helsinki.

Statistical analyses The data were summarized on a country level to assess outcomes within each country. If country-level analyses were consistent, they were pooled. The present manuscript focuses on pooled data.

Descriptive analyses were planned, and statistical testing was performed for exploratory purposes; no formal hypotheses were tested. For all qualitative variables, sizes and percentages were evaluated; for quantitative variables, distributions, means, standard deviations (SDs), and minimum (min) and maximum values (max) were presented. *P* values from z-tests for quantitative variables (ie, when comparing averages) and χ^2 tests for categorical variables (ie, when comparing the distribution of responses) were reported without adjustment for multiplicity.

Weighting To adjust for potential selection bias due to frequency of patient visits (usually determined by antitumor treatment and number of consultations during drug-free intervals), patient data collected in the cross-sectional phase were weighted by probability of inclusion in the study using the date of the next scheduled consultation (ie, patients returning sooner were allocated a lower coefficient than those returning later). Due to the weighting, each enrolled patient could be either downweighted (n <1) or upweighted

(n >1) or not impacted (n = 1). As a result, the sum of the base sizes for individual response modalities may be different from the total base size for a particular question.

The retrospective phase was weighted according to the data obtained from the cross-sectional phase using a matching technique.[9,10] The final pooled analysis was adjusted for country distribution size.

RESULTS

Physician characteristics and center practices

In the cross-sectional phase, 39 physicians enrolled a total of 522 patients. In the retrospective phase, 35 physicians enrolled 277 patients. SCT facilities within the hospital were present in 47% of institutions and an additional 34% were part of a network that included a transplant center; 18% had no access to transplant facilities. Notably, in the Czech Republic, all participating centers had their own SCT capabilities. At MM diagnosis, 58% of physicians reported to assess del (17/p13); 55%, t (4;14); 55%, del (13p); 34%, t (14;16); and 34%, 1q amp; 37% of physicians did not test for genetic anomalies. The method of testing used in each center was not documented. There were regional differences in genetic testing: all centers in the Czech Republic and Slovakia tested for genetic anomalies, whereas in Romania genetic anomalies were not assessed at all; all other countries tested for genetic anomalies in over two-thirds of patients. The imaging system usually used for staging was X-ray in 79%, computed tomography in 32%, magnetic resonance imaging in 24%, bone scintigraphy in 5%, and positron emission tomography in 3% of participating centers. Free light chain (FLC) testing was conducted at diagnosis and during treatment in 90% of centers overall, with 29% of Bulgarian centers conducting FLC assessment only at diagnosis and 11% of Romanian centers assessing FLC only during treatment or never, respectively.

Patient population: cross-sectional phase

In the cross-sectional phase (n = 522), the median age was 64 years (range, 21–90 years). The median time since initial diagnosis of symptomatic MM was 27 months (range, 0–248 months). At the time of data collection, time since diagnosis varied widely between countries, with a median of 16 months in Bulgaria and 60 months in Slovakia. Detailed patient characteristics of the cross-sectional phase are shown in Supplementary material (*Table S1*). Of patients undergoing antimyeloma treatment at the time of inclusion in the cross-sectional chart review (n = 296, 57%), 10% were part of a clinical trial and 2% participated in an early-access program; the remaining actively treated patients received standard of care with medication reimbursed in their country. Two percent of patients had never been treated. A total of 217 patients (41%) were not undergoing treatment at the time of data capture. FIGURE 1 shows an overview of the treatment status and history in these respective categories. In the first- and second-line treatment, bortezomib-based regimens were most frequently prescribed; in the third and subsequent lines of treatment, lenalidomide-based regimens were preferred. Details on drugs used in each treatment line are shown in TABLES 1 and 2.

Patient population: retrospective phase

For patients participating in the retrospective phase of the study (n = 277), the median age was 65 years (range, 21–85 years). The median time since diagnosis was 7 months (range, 0–142 months) in patients receiving first-line treatment, 26 months (range, 0–136 months) in those receiving second-line treatment, and 43 months (range, 8–173 months) in those receiving third or subsequent lines of treatment; 33% of patients (n = 92) had received a previous SCT. Detailed patient characteristics of the retrospective phase are shown in Supplementary material (*Table S2*).

The majority of patients (78%, n = 218) were not tested for cytogenetic anomalies. In patients tested for anomalies, the most frequently diagnosed anomaly was 1q amp (60%, n = 26 of the 43 tested). CRAB symptoms of myeloma (hypercalcemia, renal insufficiency, anemia, and bone lesions), were reported as follows: hypercalcemia was present in 7% of patients; renal insufficiency was reported for 15%, anemia was present in 51%; the following bone-related symptoms were reported: bone pain (56%), vertebral fractures (15%), spinal cord compression (9%), and other fractures (9%). Twenty percent of patients (n = 55) had experienced skeletal-related events since diagnosis, mainly pathologic bone fractures and bone surgeries. Disease characteristics are shown in Supplementary material (*Table S3*).

Patient journey

Of data from both phases of the study, a patient journey of the individual steps of myeloma treatment was assembled (FIGURE 2). Of symptomatic patients with a confirmed diagnosis of MM, 38% were eligible for SCT. Of these, 55% did actually receive SCT in the first line, corresponding to 21% of all newly diagnosed patients. After the first-line treatment, 59% moved on to the second-line, 33% received the third-line, 15% received the forth-line, and 8% received the fifth-line treatment.

After the first-line treatment, the most frequently reported reasons for ending treatment were remission or disease stabilization in 39% (n = 42), completion of planned number of cycles in 33% (n = 35), and lack of response or disease progression in 30% (n = 33). After the second-line treatment, similar reasons and frequencies were reported; after the third or subsequent lines, the lack of response or disease progression was the most frequently reported reason for treatment discontinuation (47%, n = 42; TABLE 3; data source, retrospective phase).

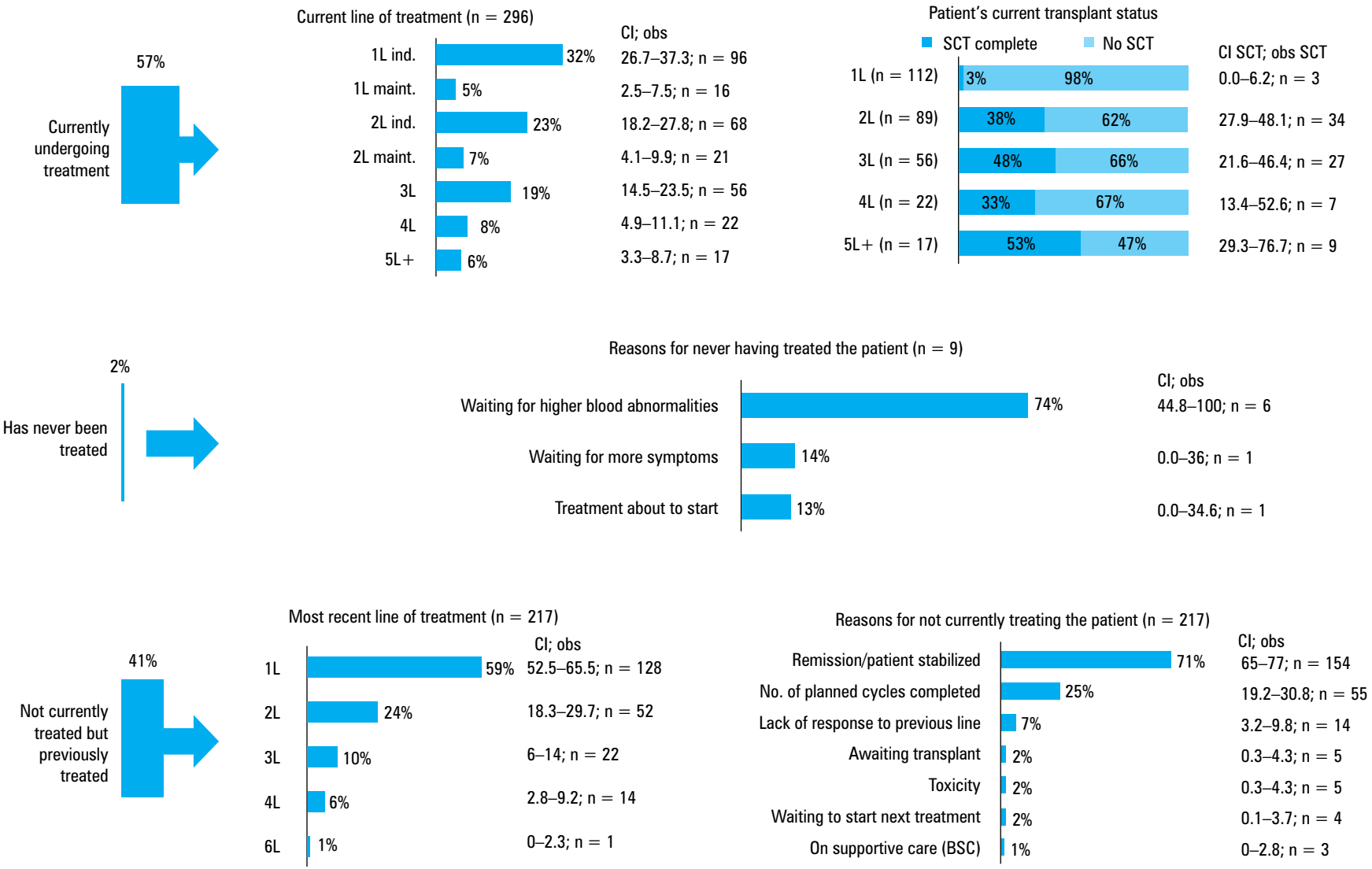


FIGURE 1 Current and past treatments of patients enrolled in the cross-sectional phase. The number with "L" denotes subsequent treatment lines.
Abbreviations: BSC, best supportive care; ind., induction; maint., maintenance; obs, number of observations; SCT, stem cell transplantation

TABLE 1 First-line treatments received by patients in the cross-sectional phase

Treatment	All CEE countries	Bulgaria	Croatia	Czech Republic	Poland	Romania	Slovakia
All first-line treatments, %	n = 112	n = 35	n = 11	n = 11	n = 12	n = 38	n = 6
Bortezomib-based	57	74	8	50	30	63	77
Thalidomide-based	9	0	30	13	46	0	0
Lenalidomide-based	6	0	0	9	0	11	0
Bortezomib + thalidomide-based	5	0	0	28	11	0	15
Carfilzomib-based	1	0	0	0	0	2	0
Others	24	26	62	0	13	25	11
First-line induction treatments, %	n = 96	n = 29	n = 9	n = 10	n = 11	n = 31	n = 6
Bortezomib-based	59	77	9	55	32	63	77
Thalidomide-based	10	0	37	14	42	0	0
Lenalidomide-based	3	0	0	0	0	10	0
Bortezomib + thalidomide-based	6	0	0	31	12	0	15
Carfilzomib-based	1	0	0	0	0	2	0
Others	22	23	54	0	14	26	8
First-line maintenance treatments, %	n = 16	n = 6	n = 2	n = 1	n = 1	n = 6	n <1[a]
Bortezomib-based	46	60	0	0	0	62	0
Thalidomide-based	5	0	0	0	100	0	0
Lenalidomide-based	13	0	0	100	0	19	0
Others	36	40	100	0	0	19	100

a n <1 is due to the weighting procedure.

Abbreviations: CEE, Central and Eastern Europe

TABLE 2 Second, third, and subsequent lines of treatment received by patients in the cross-sectional phase

Treatment	All CEE countries	Bulgaria	Croatia	Czech Republic	Poland	Romania	Slovakia
Second-line treatments, %	n = 89	n = 19	n = 15	n = 10	n = 12	n = 23	n = 10
Bortezomib-based	53	37	49	42	57	82	31
Thalidomide-based	11	24	7	5	30	0	0
Lenalidomide-based	13	0	3	44	10	0	51
Bortezomib + thalidomide-based	3	0	0	9	3	7	0
Bortezomib + lenalidomide-based	2	7	0	0	0	0	0
Bendamustin-based	4	18	0	0	0	0	0
Others	14	15	41	0	0	12	18
Third-line treatments, %	n = 56	n = 6	n = 13	n = 2	n = 15	n = 12	n = 7
Bortezomib-based	19	0	6	13	13	48	26
Thalidomide-based	7	18	23	0	0	0	0
Lenalidomide-based	47	0	25	87	88	30	55
Bendamustin-based	8	73	0	0	0	0	0
Others	19	9	46	0	0	23	19
Subsequent treatments, %	n = 40	n = 3	n = 3	n = 3	n = 8	n = 19	n = 4
Bortezomib-based	22	14	9	8	34	24	11
Thalidomide-based	12	43	27	0	19	8	0
Lenalidomide-based	35	0	0	81	48	25	67
Bortezomib + thalidomide-based	1	0	0	11	0	0	0
Bendamustin-based	2	0	0	0	0	0	22
Others	43	64	0	0	44	0	28

Abbreviations: see TABLE 1

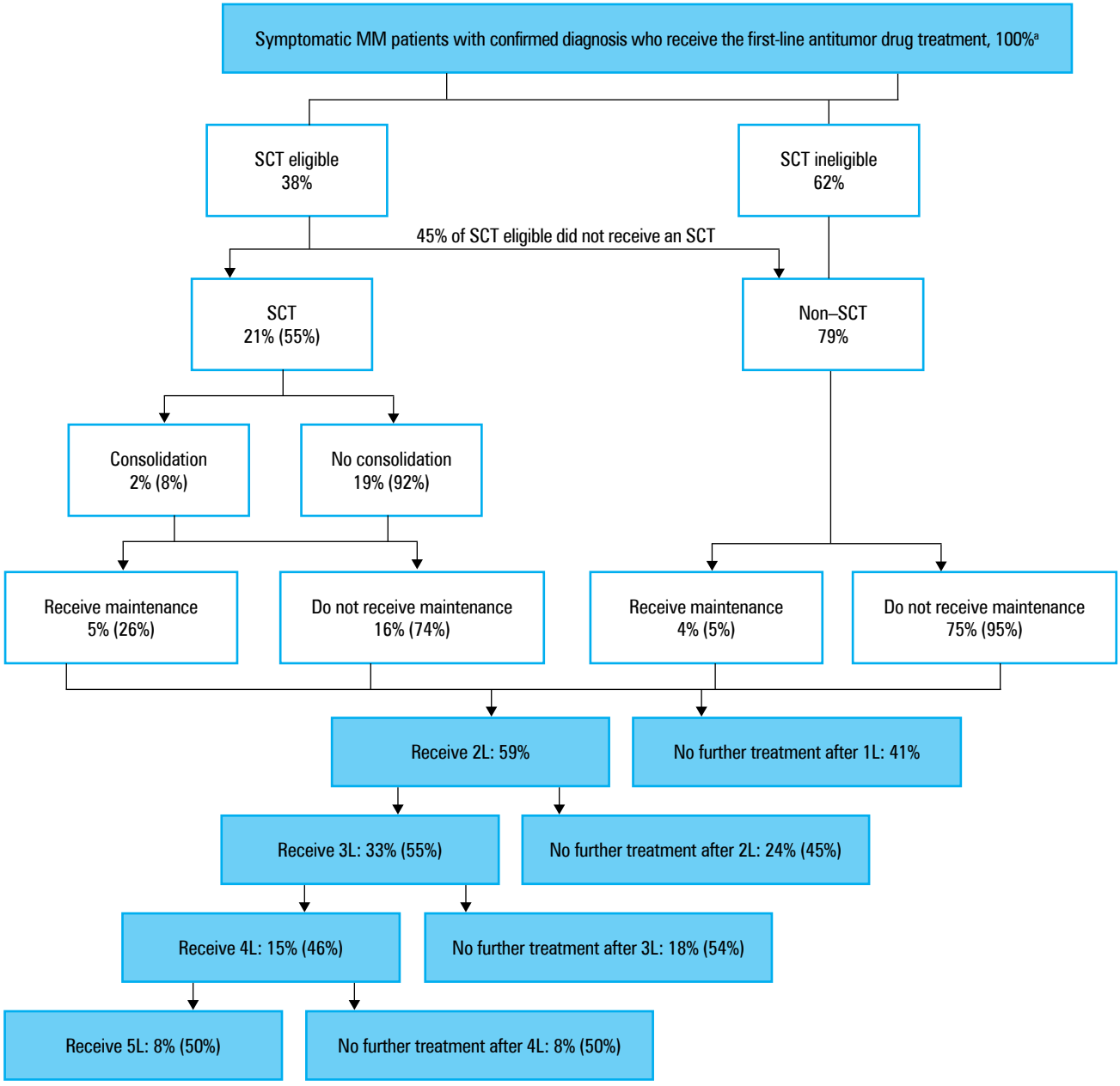


FIGURE 2 Patient pathway of antimyeloma treatment. The number with "L" denotes subsequent treatment lines. Blue boxes indicate information from the cross-sectional phase; white boxes indicate information from the retrospective phase.

a Only patients who had been treated with at least one line of treatment were documented. This was not an inclusion criterion, and therefore may be due to disease management practices.

Abbreviations: MM, multiple myeloma; others, see **FIGURE 1**

Core drug regimens In the retrospective phase, bortezomib-based treatment regimens prevailed in the first-line (57%, bortezomib; 5%, bortezomib–thalidomide) and second-line (53%, bortezomib; 2%, bortezomib–lenalidomide; 3%, bortezomib–thalidomide) treatments; lenalidomide-based regimens were more frequently used in the third line (47%) and the forth or subsequent lines (35%) (**TABLE 4** and Supplementary material, *Figure S2*). There was a considerable variation between countries. While bortezomib-based regimens (all bortezomib-based regimens combined) were most frequently used as the first line in Bulgaria (74%), Czech Republic (78%), Romania (63%), and Slovakia (89%), other regimens, such as vincristine-based, cyclophosphamide-based, or melphalan-based combinations, prevailed in Croatia (62%, followed by thalidomide-based regimens [30%]), and thalidomide-based regimens were predominant in Poland (46%). In the second line, bortezomib-based regimens were most frequently used in Czech Republic (51%, followed by lenalidomide [44%]), Bulgaria (44%; with notable proportions of patients receiving thalidomide [24%]), Croatia (49%, followed by other regimens [41%]), Poland (60%, followed by thalidomide [30%]), and Romania (89%). Lenalidomide-based regimens were most

TABLE 3 Clinical characteristics at the end of antimyeloma drug treatment in patients included in the retrospective phase

	End of first line[a] (n = 107)		End of second line[b] (n = 81)		End of third or subsequent lines[c] (n = 89)	
	% (n)	95% CI	% (n)	95% CI	% (n)	95% CI
Reason for treatment discontinuation						
Remission / patient stabilized	39 (42)	29.8–48.2	35 (28)	24.6–45.4	31 (27)	21.4–40.6
Ended as planned	33 (35)[c]	24.1–41.9	26 (21)[f]	16.4–35.6	10 (9)[b,d]	3.8–16.2
Lack of response / progression	30 (33)[f]	21.3–38.7	27 (22)[c]	17.3–36.7	47 (42)[a,e]	36.6–57.4
Death	2 (2)	0.0–4.7	1 (1)	0.0–3.2	1 (1)	0.0–3.1
Toxicity	1 (1)[c]	0.0–2.9	2 (2)	0.0–5.0	12 (10)[a]	5.2–18.8
Other	10 (11)	4.3–15.7	12 (10)	4.9–19.1	12 (10)	5.2–18.8
Best response achieved						
Complete remission	13 (14)	6.3–18.9	15 (12)	7.5–23.3	16 (14)	8.1–23.3
Very good partial response	37 (39)[c,e]	27.6–45.8	23 (18)[d,f]	13.5–31.7	9 (8)[a,e]	3.1–14.9
Partial response	19 (21)[b]	11.7–26.5	35 (28)[a,f]	24.6–45.4	21 (18)[e]	12.1–28.9
Stable disease	11 (12)[f]	5.4–17.4	15 (12)	7.0–22.4	22 (20)[d]	13.4–30.6
Progressive disease	18 (19)[f]	10.3–24.7	12 (10)[c]	5.1–19.5	32 (29)[b,d]	22.6–42.0

Statistical significance (**a**, end of first line; **b**, end of second line; **c**, end of third or subsequent lines): if no letter indicated, no significant differences; letters **a**, **b**, **c** indicate $P < 0.01$; letters **d**, **e**, **f**, $P < 0.05$.

Reasons for discontinuation: disease progression, **b** vs **c** $P < 0.01$, **d** vs **f** $P = 0.02$; ended as planned, **a** vs **c** $P < 0.01$, **e** vs **f** $P = 0.03$; toxicity, **a** vs **c** $P < 0.01$

Best response achieved: very good partial response, **a** vs **c** $P < 0.01$, **d** vs **e** $P = 0.04$, **e** vs **c** $P = 0.02$; partial response, **a** vs **b** $P < 0.01$; **e** vs **f** $P = 0.04$; stable disease, **d** vs **f** $P = 0.05$; progressive disease, **b** vs **c** $P < 0.01$, **d** vs **f** $P = 0.02$

TABLE 4 Core drug regimens across treatment lines (n = 296) in patients included in the retrospective phase

Treatment line	Overall[a]	Core drug regimen[b]							
		Bort	Len	Thal	Bort–Thal	Bort–Len	Carf	Benda	Other
First line	37 (112)	57 (63)	6 (5)	9 (10)	5 (5)	0	1 (2)	0	24 (26)
First line, induction	32 (96)	59 (56)	3 (3)	10 (9)	6 (5)	0	1 (2)	0	22 (20)
First line, maintenance	5 (16)	46 (7)	14 (2)	5 (1)	0	0	0	0	36 (6)
Second line	30 (89)	53 (47)	13 (11)	11 (9)	3 (3)	2 (1)	0	4 (3)	14 (14)
Third line	19 (56)	19 (10)	47 (26)	7 (4)	0	0	0	8 (4)	19 (11)
Fourth or subsequent line	14 (40)	22 (9)	35 (14)	12 (5)	1 (<1)	0	0	2 (1)	28 (11)

Proportions are based on the number of patients in each treatment line.

a Represents the distribution of actively treated patients across treatment lines.

b Represents the distribution of patients treated in each line across core drug regimens.

Abbreviations: Benda, bendamustine-based regimens; Bort, bortezomib-based regimens; Bort–Len, bortezomib–lenalidomide regimen; Bort–Thal, bortezomib–thalidomide regimen Carf, carfilzomib-based regimens; Len, lenalidomide-base regimens; Thal, thalidomide-based regimens

frequently administered in Slovakia (51%, followed by bortezomib [31%]). In the third and subsequent lines, patient numbers were very low and the distribution of core regimens cannot be considered representative of country treatment patterns. Further details on the drug usage patterns are provided in Supplementary material (*Tables S4* and *S5*).

Treatment response and disease evolution A complete remission was achieved in 13% of patients (n = 14) after the first line, 15% (n = 12) after the second line, and 16% (n = 14) after the third or subsequent lines. A very good partial response (VGPR) was achieved in 37% of patients (n = 39) after the first-line treatment. The proportion of patients achieving VGPR declined to 23% (n = 18) after the second line and 9% (n = 8) after the third or subsequent lines of treatment. A partial remission was achieved in 19% (n = 21) after the first line, 35% (n = 28) after the second line, and 21% (n = 18) after the third or subsequent lines of treatment.

Renal function did not deteriorate during the study, with 66% of patients having normal kidney function after the first line, 67% after the second line, and 64% after the third or subsequent lines of treatment. After the first line of treatment, 8% of

patients were on dialysis; after the second line, 1%; and after the third or subsequent lines, 2%.

The proportion of patients with 2 or more bone lesions was 39% after the first line, 26% after the second line, and 36% after the third or subsequent lines of treatment. Further details on treatment response, clinical characteristics, and renal function are shown in Supplementary material (*Table S6*).

Treatment duration and time to progression The median time from diagnosis to the first-line treatment was 1 month (interquartile range [IQR], 0–1). The median duration of active first-line treatment was 6 months (IQR, 3–8) and was comparable (P = 0.12) in patients receiving SCT (6 months; IQR, 4–9) and those not receiving SCT (5 months; IQR, 3–8). The time to second-line treatment was numerically longer in patients receiving SCT (6.5 months; IQR, 2–21) than in those not receiving SCT (1.5 months; IQR, 0–17; P = 0.18). Time to progression after the first-line treatment was 9 months overall (IQR, 4–19), with 16.5 months (IQR, 6–33) in patients receiving SCT and 7 months (IQR, 3–15) in those not receiving SCT (P <0.01). Time to progression was 12 months (IQR, 6–25) in patients receiving a bortezomib-based regimen and 11 months (IQR, 6–21) in those receiving a thalidomide-based regimen (P = 0.41). Only 3 patients received a lenalidomide-based regimen at this stage. Patients achieving a best response of ≥VGPR after the first-line treatment had a longer median time to progression of 22 months (IQR, 14–33) than those achieving <VGPR with 6 months (IQR, 3–12; P <0.01).

The median duration of active second-line treatment was 5 months (IQR, 3–8). The time to third-line treatment was longer in patients receiving SCT (12 months; IQR, 5–22) than in non–SCT patients (6.0 months; IQR, 3–11; P = 0.02). Time to progression by core drug regimens received was the highest in patients receiving thalidomide-based regimens, although the number of patients was very small for this group (n = 5). Differences were observed by degree of best response achieved: patients achieving ≥VGPR in second-line had a median time to progression of 20.0 months (IQR, 11–25), while patients achieving <VGPR had 5.0 months (3–10; P <0.01). Details on duration of active treatment, treatment-free intervals (i.e. time to next line of treatment) and duration of response can be found in TABLE 5 and FIGURE 3.

Adverse events Adverse events and comorbidities as well as their impact on treatment are reported in Supplementary material (*Table S6*). Most frequent adverse events were hematological, followed by neuropathy and fatigue. No assessment of their causal relationship with any given drug was conducted.

DISCUSSION

This study aimed to improve the understanding of clinical practice and outcomes of MM treatment in 6 CEE countries.

Patients diagnosed with MM in the participating countries showed slightly less symptomatic disease with regards to some of the CRAB criteria compared with findings from other regions. Hypercalcemia was present in 7% of patients, which was comparable to literature data (7%–13%; both in the United States) and lower than findings of the Western European sister study (19%).[8] Fifteen percent of patients presented with renal dysfunction, which is slightly less than in the literature (18%–20%).[8,11,12] Anemia was present in 51% of patients. In the literature, anemia was the most inconsistently prevalent CRAB symptom ranging from 39% in the sister study[8] to 45% to 73% in other studies.[11,13] Bone pain was reported by 56% of patients, which was in line with other reports (58%).[12] ISS stage I at diagnosis was reported in 31% of patients; stage II, in 26%; and stage III, in 43%, whereas in the Western European study, the respective values were 16%, 35%, and 49%.[8] However, it is important to note that only patients diagnosed in specialized hospitals were documented in this study. Fitter and less symptomatic patients who were diagnosed and treated exclusively in the outpatient setting were not accessible for documentation within this study.

There was a substantial difference among participating countries and compared with Western Europe in access to SCT, as well as the administered treatment regimens and their sequence. Although SCT is considered a highly effective and cost-efficient procedure in the CEE region, 45% of eligible patients did not receive it. In the Western European sister study, 31% of eligible patients did not undergo SCT.[7] In some countries of the CEE region, logistical challenges may prevent patients from receiving SCT—the number of bone marrow transplant centers is low and transplant waiting lists are correspondingly long.

Data from the cross-sectional phase revealed that, overall, bortezomib-based regimens were most frequently prescribed in the first- and second-line treatment. In the third and subsequent lines of treatment, lenalidomide-based regimens were preferred. Bortezomib was preferably used in Bulgaria (74%), Slovakia (74%), Romania (63%), and Czech Republic (50%). In Poland, thalidomide (46%) was preferred over bortezomib (30%), while in Croatia, other, nonspecified regimens were used in the majority of patients (62%), followed by thalidomide (30%). Combinations of 2 novel agents were only used to a notable degree in Czech Republic, with bortezomib–thalidomide (28%). In the second line, re-treatment with bortezomib was attempted in a notable proportion of patients. Overall, 53% of patients received bortezomib in the second line, with marked differences between countries. According to expert recommendations,[14,15] re-treatment is recommended in case of significant response to the previous treatment, long progression-free survival,

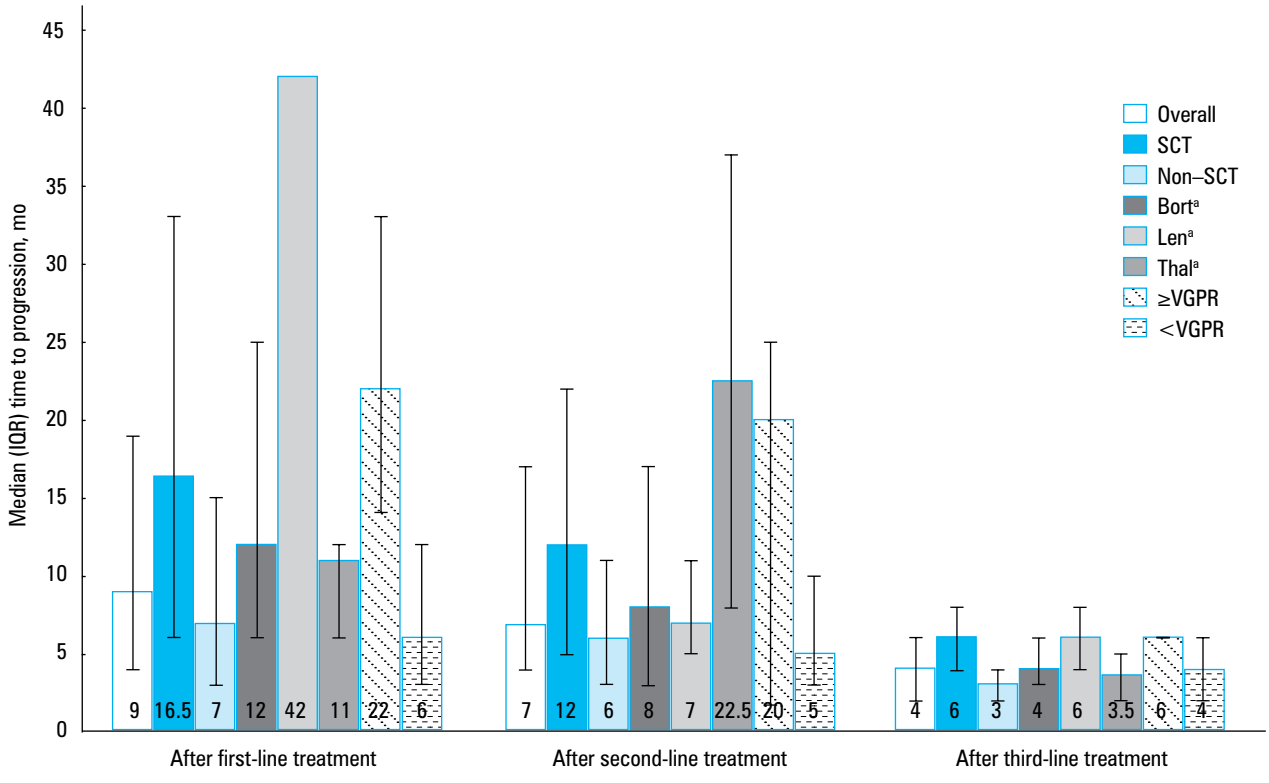
TABLE 5 Treatment duration and drug-free intervals by treatment line in patients included in the retrospective phase

	Overall	Transplant status		Core drug regimen		
		SCT	No SCT	Bort[b]	Len	Thal
Time from diagnosis to first-line initiation	n = 275[a]	n = 92	n = 183	n = 123	n = 3	n = 62
Median (IQR), months	0.0 (0–1)	0.0 (0–1)	0.0 (0–1)	1.0 (0–2)	24.0 (24–24)	0.0 (0–1)
Active first-line treatment	n = 277	n = 92	n = 185	n = 124	n = 3	n = 62
Median (IQR), months	6.0 (3–8)	6.0 (4–9)	5.0 (3–8)	6.0 (4–8)	9.0 (9–9)	7.0 (5–11)
Drug-free interval between first and second lines	n = 170	n = 69	n = 101	n = 108	n = 21	n = 10
Median (IQR), months	4.0 (1–18)	6.5 (2–21)	1.5 (1–17)	3.0 (1–18)	6.0 (1–23)	8.5 (1–19)
Active second-line treatment	n = 170	n = 69	n = 101	n = 108	n = 21	n = 10
Median (IQR), months	5.0 (3–8)	5.0 (3–7)	5.0 (3–9)	5.0 (3–8)	5.0 (4–9)	5.0 (4–14)
Drug-free interval between second and third lines	n = 89	n = 48	n = 41	n = 26	n = 29	n = 13
Median (IQR), months	6.0 (1–14)	10.0 (2–22)	4.0 (1–9)	5.0 (3–32)	8.5 (1–17)	12.0 (0–12)
Active third-line treatment	n = 89	n = 48	n = 41	n = 26	n = 29	n = 13
Median (IQR), months	4.0 (2–7)	5.5 (2–8)	3.5 (3–6)	4.0 (3–6)	6.0 (4–8)	2.5 (2–3)

a Two patients had 127 and 136 months, respectively, between diagnosis and first-line initiation. These outliers were excluded from the calculation.

b All bortezomib triplets (with thalidomide or lenalidomide; see **TABLE 4**) included in the bortezomib data column only; sample size too small to provide separate data for these patients

Abbreviations: IQR, interquartile range; others, see **TABLE 2** and **FIGURE 1**



	Overall	Transplant ststus		Core drug regimen			Best response	
		SCT	Non–SCT	Bort	Len	Thal*	≥VGPR	<VGPR
After first-line treatment	n = 163	n= 55	n = 109	n = 55	n = 3	n = 45	n = 53	n = 110
After second-line treatment	n = 100	n= 48	n = 52	n = 67	n = 10	n = 5	n = 31	n = 69
After third-line treatment	n = 37	n= 20	n = 18	n = 11	n = 11	n = 10	n = 1	n = 36

FIGURE 3 Time to progression by treatment line in patients included in the retrospective phase

a All bortezomib triplets (with thalidomide or lenalidomide) were included in the bortezomib data column only. The sample size was too small to provide seperate data for these patients.

Abbreviations: VGPR, very good partial response; others, see **FIGURE 1**, **TABLE 4**, and **TABLE 5**

and acceptable tolerance. The median time to progression was 12 months in patients treated with bortezomib in the first line, 42 months in patients receiving a lenalidomide-based regimen, and 11 months in those receiving a thalidomide-based regimen; the difference was not significant. In the third-line treatment, lenalidomide was preferred in Czech Republic (87%), Poland (87%), and Slovakia (55%), while bendamustine was used in Bulgaria (73%), bortezomib in Romania (48%), and other regimens in Croatia (46%). The median time to progression in the second line was 8 months with bortezomib, 7 months with lenalidomide, and 22.5 months with thalidomide. The surprisingly long median time to progression in patients receiving first-line lenalidomide-based regimens (42 months; n = 3), as well as patients receiving second-line thalidomide (22.5 months; n = 5) is most likely due to the very low patient numbers and may not reflect the true clinical situation. However, the finding that patients receiving thalidomide-based regimens in the first-line setting achieved a similarly long time to progression as patients receiving a bortezomib-based regimen, warrants some further investigation. In the CEE countries, thalidomide is often administered in combination with bortezomib in the bortezomib–thalidomide–dexamethasone (VTD) regimen or as part of the cyclophosphamide–thalidomide–dexamethasone (CTD) combination. Both are highly effective regimens.[16-19] Thalidomide is also often used as part of the induction regimen in the SCT program where efficacy and cost-effectiveness was satisfactory as assessed by the UK National Institute of Health Care and Excellence.[20] In Western European countries, bortezomib was preferred as the first-line treatment (36% overall), while lenalidomide was more widely used as the second-line (59%) and third-line (51%) treatments (Supplementary material, *Figure S3*). However, newer drugs such as pomalidomide as well as triplet combinations of a proteasome inhibitor plus an immunomodulatory drug (plus dexamethasone) were also used as early as the first line.[7] However, the Western European sister study was conducted during 2014 and treatment patterns have evolved since then, with the approval of novel agents.[21]

The rates of VGPR or better were very low in the present study, and subsequent treatment-free periods and time to progression were short. Possibly, first-line protocols were of low efficacy and more effective treatment combinations are only reimbursed once certain standard treatments have failed. Reimbursement applications for novel agents in the CEE region often take one month or longer to be decided, and bridging regimens are commonly administered until a decision on coverage of novel agents is made. These data show that more effective drug combinations, which have been approved and are continuously being approved, need to be made available to patients in the region, and models of reimbursement in budget restricted areas urgently need to be developed. Country-specific data on cost effectiveness of novel agents regarding direct and indirect costs and benefits would certainly support decision makers in the region.

Cytogenetic risk assessment was not done in all patients as recommended by the European Society for Medical Oncology or International Myeloma Working Group guidelines.[22,23] In the present study, 78% of patients were not tested for cytogenetic anomalies, with physicians in the Czech Republic conducting cytogenetic testing in the largest proportion of patients of all participating countries (65%), covering all relevant cytogenetic assays. An ongoing observational study in relapsed and refractory MM found a rate of cytogenetic testing of 51% in the European Union and United States in their 2013 interim analysis.[24] Cytogenetic risk status currently only determines the overall treatment strategy, but possibly has no to limited clinical consequence in the selection of individual agents, as the evidence from randomized clinical trials is still immature.[25]

In budget-restricted areas such as the assessed countries, participation in international clinical trials is a possibility to obtain access to high standards of diagnostics and treatment. However, only 36% of patients participated in clinical trials and 8% in early-access programs, indicating an area for improvement in clinical practice. On the other hand, clinical trials are not a sustainable strategy to improve patients' outcomes as they are dependent on the scientific interest in the area and the execution of trials. Long-term improvement of standard of care is needed for all patients independently of the availability of clinical trials.

This study has some limitations. Patient numbers in each participating country were small, especially for drug usage in first-line maintenance and third or subsequent treatment lines. Pooling data necessarily introduced some bias, as clinical practice differs between countries due to different reimbursement regulations. Some secondary study objectives, such as an estimation of the association between patient characteristics or a patient's clinical history and the treatment regimen for each line, could not be carried out due to low patient numbers. The study was not designed to detect differences between groups with regard to treatment duration or time to progression. Multiple statistical tests were performed without formal adjustment for multiple testing; therefore, the chance of a spurious finding was increased. Since the patient numbers were very small for many of the comparisons, the results should be interpreted with caution. Factors influencing a patient's frequency of visits, such as antimyeloma treatment received or the number of visits during drug-free periods, potentially led to variations in the probability of inclusion. To adjust for possible recruitment bias, a weighting strategy (described in the previous section) was employed. Potentially, some degree of positive selection bias was

introduced in patients who were in subsequent lines of treatment, because of the limited access situation. Generic bortezomib became available in the region in the second half of 2015. The implications of market entry of generics on treatment patterns, however, have not been studied in this chart review.

In summary, in this evaluation of patterns of decision making in clinical practice in 6 CEE countries, treatment strategies differed compared with a similarly designed study conducted in 7 Western European countries. Of transplant-eligible patients, a larger proportion did not undergo transplantation in CEE than Western Europe. The first--line treatment and subsequent re-treatment with bortezomib were common in the assessed region, with lenalidomide-based regimens being used in a notable proportion of patients only in the third or subsequent lines, both only rarely as triplet combinations. Newer novel agents were rarely used. Complete response rates were lower compared with the Western European countries, while VGPR rates were comparable after the first-line treatment, but markedly lower after the second line. These results of treatment standards and decision making in real-world clinical practice provide useful information and indicate areas for improvement of access to more effective treatments.

SUPPLEMENTARY MATERIAL Supplementary material is available with the article at www.pamw.pl.

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CONTRIBUTION STATEMENT DC and DD contributed equally to the manuscript. DN and LF designed the research study, building on a similarly designed Amgen study conducted in Belgium, France, Germany, Italy, Spain, Switzerland, and the UK.[7,8] LF analyzed the data. DN, KST, LF, and KB reviewed the raw data and statistical analysis results and interpreted the data. DC, DD, IS, IM, GM, and SOK acquired and interpreted the data. All authors critically reviewed the manuscript and provided an important intellectual contribution. All authors approved the final and submitted version.

CONFLICT OF INTEREST DD, IM, and GM declare no conflict of interest. DC declares to have received consulting fees or other remuneration (payment) from Novartis, Amgen, Pfizer, Takeda, and Janssen. IS declares to have received research grants from Celgene, consulting fees from Bristol-Myers Squibb, Celgene, Janssen-Cilag, Novartis, Takeda, and Amgen, and to be a member of the speakers bureau for Celgene, Janssen--Cilag, Amgen, and Bristol-Myers Squibb. SOK is a member of the speakers' bureau for Takeda, Amgen, and Roche. LF received honoraria from Amgen to conduct the research. DN, KST, and KB are employees of Amgen and hold Amgen stock.

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