ORIGINAL ARTICLE

Real-life experience with bortezomib-based regimens in elderly patients with newly diagnosed multiple myeloma and comorbidities: a Polish retrospective multicenter study

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KEY WORDS

bortezomib, efficacy, elderly, newly diagnosed multiple myeloma, safety

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ABSTRACT

INTRODUCTION Bortezomib was the first proteasome inhibitor approved for the therapy of multiple myeloma (MM). Currently, VMP (bortezomib, melphalan, prednisone) is one of the standard regimens recommended as the first-line therapy for patients with MM ineligible for high-dose chemotherapy (HDT) with autologous stem-cell transplantation (auto-SCT).

OBJECTIVES Participants of clinical trials are highly selected populations; therefore, the aim of this study was to present observations from real practice that might provide important information for practitioners.

PATIENTS AND METHODS We retrospectively analyzed the data on the efficacy and safety of bortezomib-based regimens in 154 patients with newly diagnosed MM ineligible for HDT with auto-SCT (median age, 73 years; range, 39–89 years) with particular attention to the effect of age, performance status, and concomitant diseases.

RESULTS Patients aged 75 years or older constituted 53.2% of the study cohort. Performance status was impaired in 34.4% of the patients, according to the Eastern Cooperative Oncology Group scale. Comorbidities were reported in 83.8% of the patients (mainly arterial hypertension and atherosclerotic vascular disease). A total of 798 courses of bortezomib-based regimens (mainly VMP, 86%) were administered. The overall response rate was 81.7%, including 12.7% for complete response and 29.6% for very good partial response. The median progression-free survival (PFS) and event-free survival were 17.3 and 7.1 months, respectively. The impaired performance status and age of 75 or older were negative predictors of PFS. The most common severe adverse events were neuropathy (19.4%), infections (19.2%), and neutropenia (14.9%).

CONCLUSIONS Bortezomib-based regimens are effective and well tolerated in the first-line therapy of elderly patients with MM and comorbidities, with advanced disease, and light chain MM. A more detailed assessment of patients' frailty is needed to increase the efficacy of treatment.

INTRODUCTION

Multiple myeloma (MM) is a clonal proliferation of malignant plasma cells that affects mainly elderly patients. The median age of patients at diagnosis is approximately 70 years, more than 60% of patients are older than 65 years, and more than 30% are 75 years of age or older.[1] The introduction of high-dose chemotherapy (HDT) with autologous stem-cell transplantation (auto-SCT), followed by new drugs such as thalidomide, bortezomib, and lenalidomide, was shown to significantly improve the prognosis of patients with MM by increasing the response rates and survival parameters.[2,3] The improvement could first be seen only in younger patients[4]; however, nowadays, most elderly patients are treated with the new drugs, and survival benefit is observed also in this group.[5]

Thalidomide in combination with melphalan and prednisone has been shown to increase complete response (CR) rates and prolong progression-free survival (PFS) in nontransplant patients with MM, although the effect on overall survival (OS) was unclear.[6] Bortezomib is the first-generation selective reversible proteasome inhibitor initially approved for the therapy of resistant or relapsed MM in 2003. In 2008, San Miguel et al[7] published the results of the phase 3 VISTA trial, which demonstrated superior efficacy of the VMP protocol (bortezomib, melphalan, prednisone) to the MP protocol (melphalan, prednisone) in terms of the response rates, PFS, and OS in untreated patients with MM ineligible for HDT with auto-SCT. The final updated analysis after a median follow-up of 5 years confirmed the continued significant OS benefit with VMP, which became the gold standard in elderly patients with MM ineligible for transplantation.[8]

When used as the first-line therapy, VMP does not lead to more resistant relapses or induction of secondary malignancies.[8] Furthermore, its efficacy was demonstrated also in patients with adverse cytogenetics, since there were no differences in response rates and survival (PFS, OS) between patients with t(4;14), t(14;16), or del 17p and those with normal cytogenetics.[7] VMP was also a well-tolerated, safe, and active regimen in previously untreated patients with MM and renal impairment.[7] Data from the VISTA trail demonstrated that the achievement of CR was associated with improved long-term outcome and clinically relevant improvements in health-related quality of life.[9] This clinical benefit of CR with VMP was independent of whether the CR was achieved early or late during the therapy, which supports the continuation of therapy in patients who tolerate the regimen to achieve the maximum response.[10]

The main adverse effects associated with the VMP regimen are peripheral neuropathy, diarrhea, and myelosuppression. The appropriate management of treatment-related complications is crucial for achieving the best clinical response and quality of life. We conducted a retrospective analysis of the data on the efficacy and safety of bortezomib-based regimens in the first-line therapy of patients with MM ineligible for HDT with auto-SCT.

PATIENTS AND METHODS

Between November 2012 and February 2015, we retrospectively analyzed 154 consecutive patients ineligible for HDT with auto-SCT from 12 Polish centers. All patients fulfilled at least 1 of the following criteria: creatinine clearance below 60 ml/min; presence of at least 1 cytogenetic abnormality: t(4;14), t(14;16), del17p; or age of 75 years or older. According to the reimbursement policy in Poland at that time, bortezomib was reimbursed for the first-line therapy only in patients who were ineligible for HDT with auto-SCT and fulfilled at least one of the above criteria.

Our analysis included medical records of patients who received at least 1 cycle of a bortezomib-based regimen as the first-line therapy. Bortezomib was given in combination protocols: VMP (bortezomib, melphalan, prednisone), VTD (bortezomib, thalidomide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), and VD (bortezomib, dexamethasone). The choice of the drug combination was based on the performance status, concomitant diseases, specific drug toxicity profile, and local experience.

We assessed the response rates to bortezomib-based regimens, progression free survival (PFS), event-free survival (EFS), overall survival (OS), and treatment-related toxicity. PFS was defined as the time from the start of therapy to the last date when disease activity was assessed, including death from any cause. EFS was defined as the time from the start of therapy to the occurrence of any event such as disease progression, death from any cause, or discontinuation of treatment for any reason (eg, toxicity, patient's preference, introduction of a new treatment without documented progression), or the last date when disease activity was evaluated. OS was defined as the time from the start of therapy to the date of death from any cause, or to the date of censoring at the last time the subject was known to be alive. The response to therapy in patients with MM was assessed according to the International Multiple Myeloma Working Group criteria.[11] Treatment-related toxicity was evaluated using the Common Terminology Criteria for Adverse Events and Common Toxicity Criteria v3.0.[12]

Statistical analysis

Associations between the response rates and patient characteristics were analyzed using the Mann–Whitney test for continuous variables and the χ^2 test for categorical variables. Survival curves were estimated by the Kaplan–Meier method, and the log-rank test was used for comparison. The effect of independent variables on patient survival was tested by the univariate and multivariable Cox proportional hazards regression models; the missing values (range, 0–2) were replaced by means. A P value of less than 0.05 was considered significant.

TABLE 1 The most common concomitant diseases in the study group by age

Concomitant diseases	Age	
	<75 years	≥75 years
Arterial hypertension	41 (51.3)	48 (64.9)
Atherosclerotic vascular disease with ischemia	16 (20.0)	25 (33.8)
Circulatory insufficiency	8 (10.0)	14 (18.9)
Arrhythmia	14 (17.5)	13 (17.6)
Valvular heart diseases	3 (3.8)	3 (4.1)
Diabetes	19 (23.8)	13 (17.6)
Chronic renal impairment	14 (17.7)	5 (6.9)
Chronic obstructive pulmonary disease	5 (6.3)	5 (6.8)
Autoimmune diseases	6 (7.5)	4 (5.4)
Thyroid diseases	14 (17.5)	9 (12.2)
Malignancies	8 (10.0)	3 (4.1)

Data are presented as the number (percentage) of patients.

RESULTS The analysis included a total of 154 patients (69 men [44.8%]; 85 women [55.2%]) treated with bortezomib-based protocols. The median age of patients was 73 years (range, 39–89 years); 116 patients (75.3%) were aged 65 years or older. In 82 patients (53.2%), the inclusion criterion was age of 75 or older, and in 66 patients (42.9%), it was creatinine clearance of less than 60 ml/min; 48 of these patients met both criteria. Adverse cytogenetics was the inclusion criterion in 6 patients (3.9%). However, cytogenetic data were available only in 26 patients. Of these, del17p was found in 4 patients; t(4;14), in 2 patients; and a combination of del17p and t(4;14), in 1 patient. The performance status, evaluated according to the Eastern Cooperative Oncology Group (ECOG) scale, was grade 1 or lower in 99 patients (64.3%); grade 2 in 42 patients (27.3%); and grade 3 or higher in 11 patients (7.1%). Anemia was found in 90.9% of the patients and hypercalcemia—in 48.1%. Polyneuropathy was present in 4 patients (2.6%) before the start of bortezomib therapy. The baseline clinical and laboratory characteristics of the patients are presented in Supplementary material online, *Table S1*.

Concomitant diseases were reported in 129 of the patients (83.8%), with the most common being arterial hypertension and atherosclerotic vascular disease. There were no significant differences in the incidence of concomitant diseases between patients younger than 75 years and those aged 75 or older. The diseases are listed in TABLE 1.

Treatment The most common protocol was VMP, administered in 131 patients (85.1%), while in 23 patients, other combinations based on bortezomib and steroids were used. Bortezomib was administered intravenously in 47 patients (30.5%) and subcutaneously in 107 patients (69.5%).

Assessment of response to therapy Of the 154 patients, 142 were available for the evaluation of response to therapy (92.2%) The others did not achieve the evaluation point for response due to early death or toxicity. The overall response rate was 81.7% (n = 116), including 12.7% of CR (n = 18), 29.6% of very good partial response (VGPR; n = 42), and 39.4% of partial response (PR; n = 56). Stable disease was observed in 9.9% of the patients (n = 14) and disease progression—in 8.5% (n = 12). There was no association between baseline laboratory parameters and achievement of the response to therapy. Patients aged 75 years or older showed a lower CR rate than younger patients (7.2% and 18.1%, respectively) and a higher rate of progressive disease rate (12.9% and 4.2%, respectively); however, the differences were not significant. The rates of VGPR, PR, and stable disease were similar in patients aged 75 years or older and those younger than 75 years (30% vs 29.2%; 38.6% vs 40.3%; and 11.4% vs 8.3%; respectively).

After the therapy (a median of 4 cycles), a significant improvement in hemoglobin concentrations and renal function was observed. Patients who responded to therapy showed a greater increase in median hemoglobin and glomerular filtration rate levels, as compared with patients who did not respond to therapy (1.7 vs 0.0 g/dl, $P < 0.001$ and 9.3 vs 1.78 ml/min, $P < 0.01$, respectively).

Assessment of survival The median PFS was 17.3 months. There was no difference in PFS between patients who achieved CR and those who achieved VGPR. PFS was significantly longer in patients who achieved CR or VGPR, as compared with those who achieved PR (FIGURE 1). In patients with renal failure, PFS was similar to that in patients with normal renal function.

In the univariate analysis, impaired performance status (ECOG grade >2) and older age (≥75 years) were the only negative predictors of survival. The Kaplan–Meier survival analysis and multivariable analysis revealed impaired performance status (ECOG grade >2), older age (≥75 years), and decreased hemoglobin concentrations (<9.0 g/dl) to be independent predictors of survival (FIGURE 2 and TABLE 2). None of the other baseline clinical

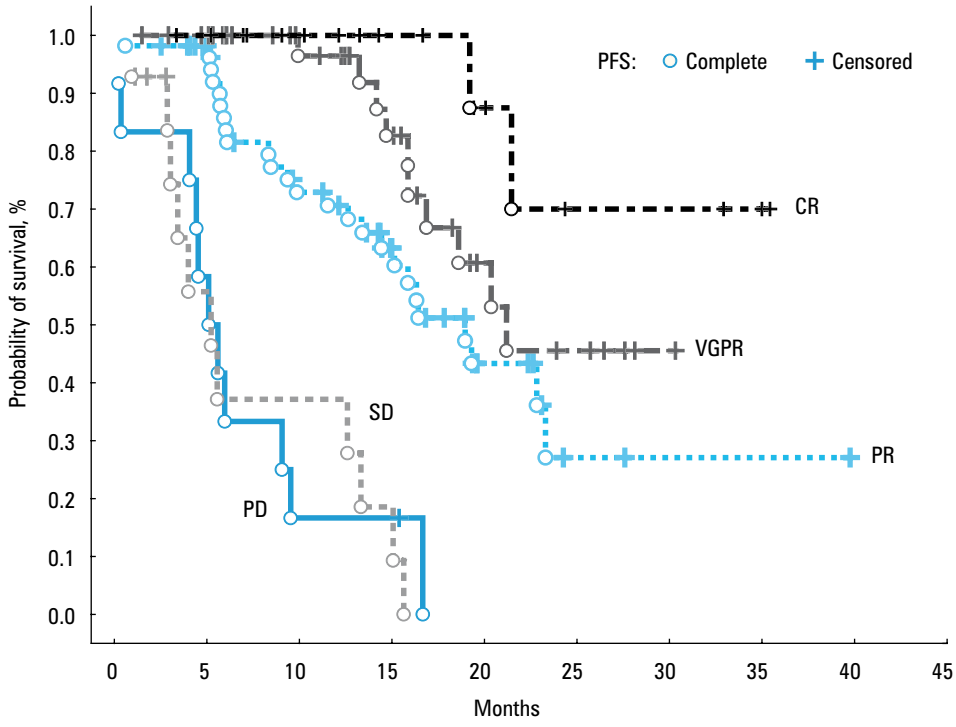

FIGURE 1 Probability of progression-free survival (PFS) by Kaplan–Meier estimates in patients with multiple myeloma treated with bortezomib-based regimens, depending on the response to therapy Abbreviations: CR, complete response; PD, PR, partial response; progressive disease; SD, stable disease; VGPR, very good partial response

and laboratory parameters, including the markers of disease activity, influenced survival.

The median EFS was 7.1 months. In the univariate analysis, the age of 75 years or older and serum creatinine concentration exceeding 2 mg/ml correlated with shorter EFS (FIGURE 3). In the multivariable analysis, only impaired performance status influenced shorter EFS.

The median OS in the whole group was not achieved during the follow-up (FIGURE 4). There were significant differences in OS between patients who responded to therapy as compared with those who did not respond to therapy ("VGPR or better" vs "stable disease or worse", $P < 0.0001$ and "PR" vs "stable disease or worse", $P < 0.01$; FIGURE 4).

Toxicity The most common grade 3/4 adverse events were peripheral neuropathy, infections, and hematological toxicities (TABLE 3). Interestingly, the route of administration did not affect bortezomib neurotoxicity. The incidence of peripheral neuropathy was similar in patients receiving bortezomib intravenously (36.76% for all grades and 19.12% for severe neuropathy) and subcutaneously (41.86% for all grades and 19.97% for severe neuropathy).

Varicella-zoster virus infection was observed in 8 of the 136 patients (5.9%), and the prophylaxis with acyclovir was used routinely in the majority of patients.

The bortezomib dose was reduced in 53 patients (34.4%), and the melphalan dose—in 34 patients (22.1%). Peripheral neuropathy was the main reason for bortezomib dose reduction (28 patients, 20.6%; grade 2 neuropathy with pain, 11 patients; grade 3, 11 patients; and grade 4, 6 patients); other reasons included severe neutropenia in 7 patients (5.1%), severe thrombocytopenia in 5 patients (3.7%), severe anemia in 5 patients (3.7%), and severe diarrhea in 1 patient. Melphalan dose was reduced due to neutropenia in 14 patients (10.3%), thrombocytopenia in 5 patients (3.7%), and anemia in 5 patients (3.7%).

Altogether, 798 courses of bortezomib-based regimens were administered (mainly VMP, 86% of the courses). The median number of the courses per patient was 4 (range, 1–9); 63 patients (40.9%) received 1 to 3 courses; 31 patients (20.1%), 4 to 6 courses; and 60 patients (39.0%), 7 to 9 courses. Of these patients, 44 (28.6%) received planned 9 courses of therapy (Supplementary material, *Table S2*). The toxicity of therapy was the main reason for treatment discontinuation (61 patients; 39.6%), which mostly occurred in the early phase of therapy. Another common reason was treatment failure (28 patients; 18.2%), which mostly occurred later during the therapy (TABLE 4). Interestingly, in most cases, discontinuation resulted from new onset of toxicity or exacerbations of comorbidities, mainly cardiovascular ones.

Ten patients died during the treatment (7.4%). The causes of death were disease progression in 2 patients, multiorgan failure in 4 patients, cardiac failure in 2 patients, and infection in 1 patient; in 1 patient, the cause of death remained unknown.

DISCUSSION MM is a disease of elderly patients; therefore, compromised organ function and comorbidities, which are common in these individuals, might contribute to worse tolerance of therapy and negatively affect both the response to therapy and the quality of life. The age over 75 years is considered as one of the features of frailty, although elderly patients constitute a heterogeneous population in terms of the performance status and concomitant diseases. Current standards for the front-line therapy in elderly patients

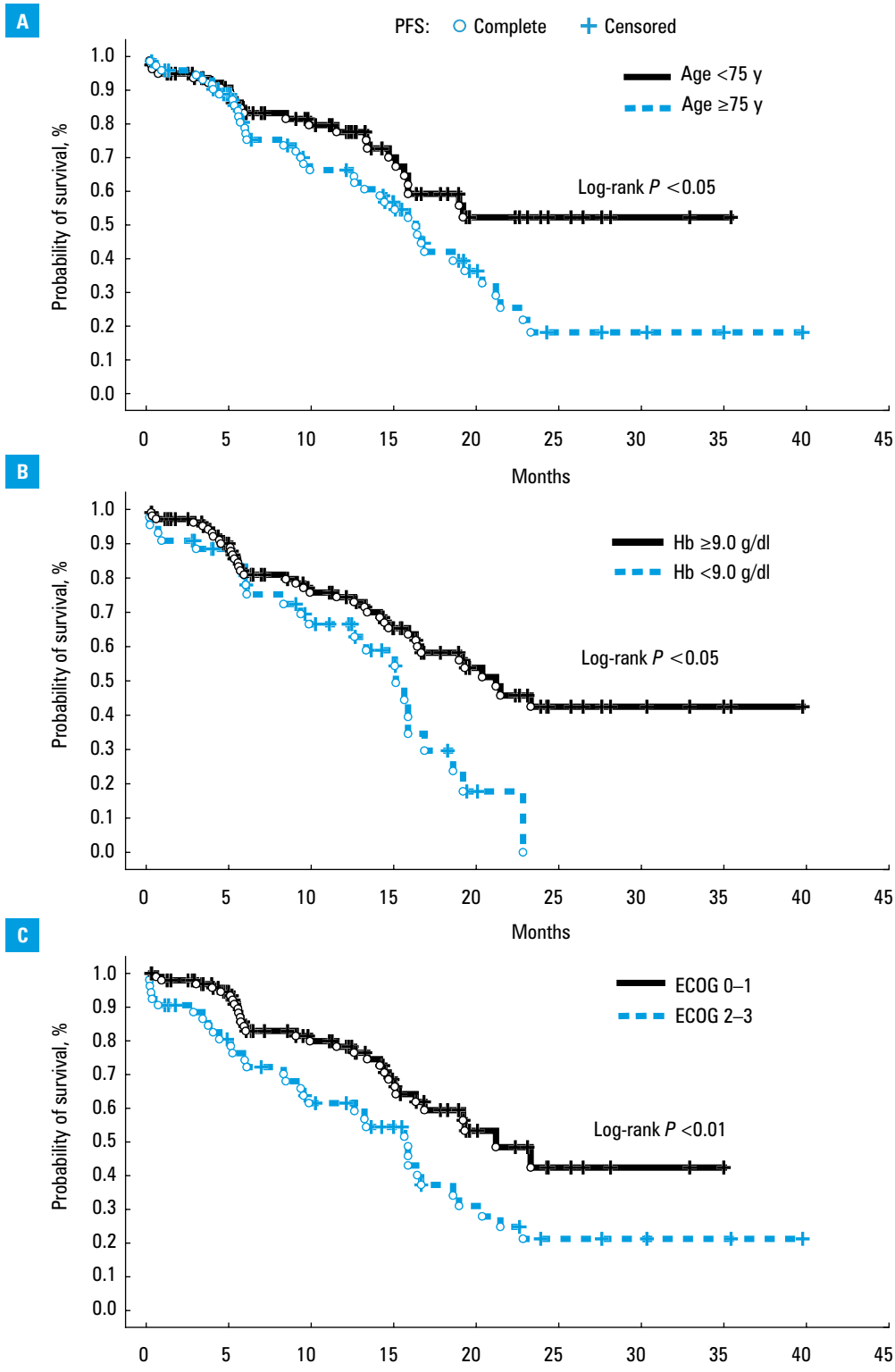

FIGURE 2 Probability of progression-free survival (PFS) by Kaplan–Meier estimates in patients with multiple myeloma treated with bortezomib-based regimens, depending on age (**A**), hemoglobin (Hb) concentration (**B**), and performance status (**C**) (Eastern Cooperative Oncology Group [ECOG] scale)

with MM are based on the results of clinical trials designed especially for patients ineligible for HDT with auto-SCT. However, since clinical trials include highly selected populations, observations from real clinical practice may have important practical implications for physicians. In this study, we retrospectively analyzed the data on the efficacy and safety of bortezomib-based regimens (mainly VMP) in 154 patients ineligible for HDT with auto-SCT, with a particular focus on the effect of age, performance status, and concomitant diseases. The overall response rate was 81.7%, and was similar to that achieved in the VISTA trial (80%),[7] GEM2005 trial (80%),[13] and that reported in a German registry by Knauf et al (82%).[14]

The CR rate in our study was lower than that in the VISTA trial (12.7% vs 33%), which might have been caused by several factors. First, in our cohort, there were more patients with more advanced disease (International Staging System [ISS] III) than in the VISTA trial (76% vs 26%) and light chain MM (30% vs 8%). The diagnosis of light chain MM is related with poor prognosis, and in the VISTA study, CR was achieved only in 13% of patients with light chain MM compared with 46% of patients

TABLE 2 Multivariable analysis of factors influencing progression-free survival

Factors	Hazard ratio	95% confidence interval	*P* value
Age (≥75 vs <75 years)	1.93	1.04–3.60	0.04
WBC count (<3.5 G/l or >10.0 G/l vs 3.5–10.0 G/l)	1.38	0.63–2.99	0.4
Hb (<9.0 g/dl vs ≥9.0 g/dl)	2.22	1.13–4.37	0.02
Albumin (<3.5 vs ≥3.5 g/dl)	1.39	0.78–2.48	0.3
Sex (male vs female)	1.06	0.59–1.91	0.8
IgA or light chain vs IgG MM	1.15	0.64–2.06	0.6
λ or nonsecretory chain vs κ chain MM	1.21	0.67–2.21	0.5
ECOG index (2–3 vs 0–1)	2.35	1.27–4.35	0.01
Bortezomib (intravenous vs subcutaneous)	0.57	0.29–1.12	0.1
Bortezomib, dose reduction	0.74	0.39–1.42	0.4
Melphalan, dose reduction	0.94	0.45–1.97	0.9
Hypertension	1.44	0.81–2.59	0.2
Atherosclerotic vascular disease with ischemia	0.90	0.44–1.85	0.8
Circulatory insufficiency	1.30	0.52–3.22	0.6
Arrhythmia	1.02	0.45–2.32	0.9
Diabetes	0.92	0.44–1.90	0.8
Chronic renal impairment	1.92	0.74–4.96	0.2
Chronic obstructive pulmonary disease	1.26	0.38–4.19	0.7
Autoimmune diseases	1.83	0.48–7.08	0.4
Thyroid diseases	0.93	0.40–2.19	0.9
History of cancer	0.99	0.25–3.92	0.9

A *P* value of less than 0.05 was considered significant.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; IgA, immunoglobulin A; IgG, immunoglobulin G; MM, multiple myeloma; WBC, white blood cell

with immunoglobulin-G MM.[10] In patients with atypical symptoms, MM may be difficult to diagnose in routine clinical practice, which may result in the delay of treatment and thus worsening the patients' outcome.[15] Another factor contributing to a lower CR rate might be that the median number of cycles in our study was 4, as compared with 8 in the VISTA study, with the CR rate of 28% achieved between cycles 5 and 9.[10] Additionally, more than half of the patients in our study (53.2%) were aged 75 or older, and the CR rate was lower in these patients. However, the difference was not significant, probably because of a small number of patients in the response subgroups. In the VISTA trial, patients older than 75 years constituted only 31% of the study group, and the CR rate was also lower in this population.

In contrast to the data from clinical trials and meta-analyses showing that PFS was longer in patients achieving CR than in those achieving VGPR or PR, we did not find significant differences in PFS between these patient groups. In the VISTA study,[7] the achievement of CR was associated with longer time to progression, time to next therapy, and treatment-free interval, as compared both with PR and VGPR. In the GEM2005 trial,[13] the achievement of CR was associated with significantly longer PFS and OS both in patients younger than 75 years and in those older than 75 years. The analysis of 3 multicenter clinical trials also demonstrated a significant correlation between CR and longer PFS and OS in elderly patients, including those older than 75 years treated with novel agents (including VMP).[16] Therefore, the achievement of CR is undoubtedly associated with longer OS, and it should be the goal of treatment also in elderly patients with MM. The lack of the correlation between CR and survival in our study might reflect a more detailed evaluation of response in clinical trials than in routine clinical practice, but may also result from the differences in study populations. The median PFS in this study was 17.3 months, as compared with 24 months in the VISTA study and 24.8 months in the VMP-VP trial by Palumbo et al.[17] However, considering that 53% of the patients in our cohort were older than 75 years, 76% had high tumor mass (ISS III), and 29% had light chain MM, these data show high efficacy of bortezomib-based regimens in routine clinical practice. The lack of response to the first-line therapy with bortezomib showed a negative predictive effect on OS, which was only 18 months in patients who did not respond to therapy. The development of new biomarkers predicting response to therapy would allow an identification of patients who should receive other first-line therapeutic regimens as the first-line treatment.[18-20]

As in the previous reports, impaired renal function did not have negative impact on the response rates or PFS. Importantly, patients who responded to therapy showed an improvement in renal function, confirming the efficacy of this protocol in patients with renal failure. Patients who responded to therapy also showed an increase in hemoglobin concentrations.

Our retrospective analysis revealed that cytogenetic tests were performed in few patients in routine clinical practice in Poland, even though low test results were one of the criteria for reimbursement of bortezomib-based regimens. However, this trend may probably change now that cytogenetic parameters are included in the revised ISS criteria.[21]

There is an ongoing debate on the use of alkylators in the therapy of MM. Mateos et al[22] demonstrated significantly longer PFS and OS in patients treated with bortezomib-based regimens compared with VTP in patients aged 65 years. In a retrospective analysis of 6 randomized trials, Morabito et al[23] also showed longer PFS and OS in patients treated with VMP, as compared with VTP. These data show an important role of alkylator for achieving longer survival. Recently, the regimens with lenalidomide have been approved as the first-line therapy for patients with MM ineligible for HDT with auto-SCT. Based on the results of the phase III FIRST trial,[24-26] continuous lenalidomide dexamethasone treatment has been proposed as a new standard of

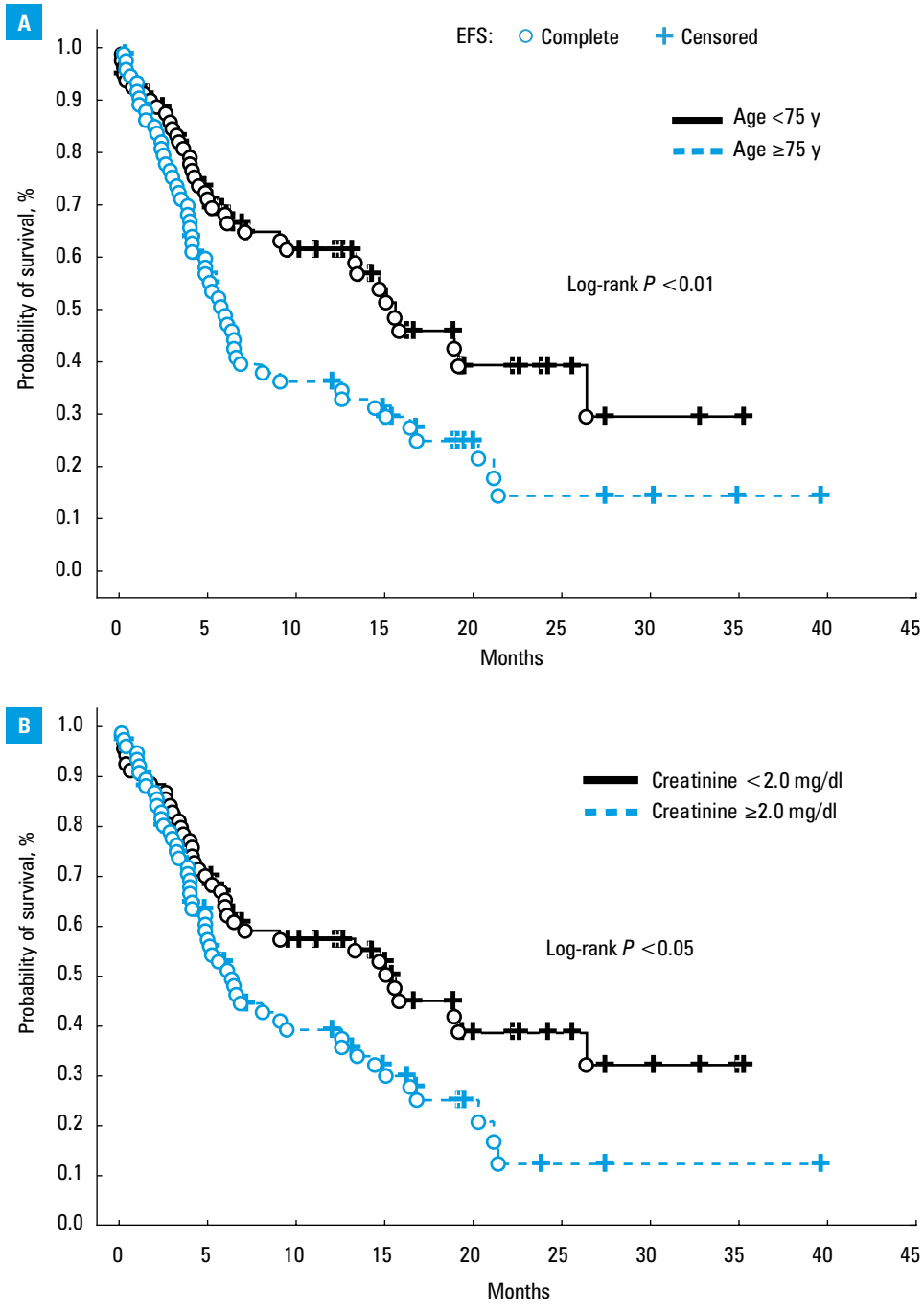

FIGURE 3 Probability of event-free survival (EFS) by Kaplan–Meier estimates in patients with multiple myeloma treated with bortezomib-based regimens, depending on age (**A**) and creatinine concentration (**B**)

TABLE 3 Toxicity of bortezomib-based regimens

Toxicity	Grade (Common Toxicity Criteria)	
	0–2	≥3
Neutropenia	92 (59.7)	23 (14.9)
Thrombocytopenia	103 (66.9)	19 (12.3)
Anemia	87 (56.5)	17 (11.0)
Polyneuropathy	91 (59.1)	30 (19.4)
Diarrhea	133 (86.4)	4 (2.6)
Infections	113 (73.4)	26 (19.2)
Cardiovascular disease	136 (88.3)	16 (10.4)

Data are presented as the number (percentage) of patients.

care for transplant-ineligible patients with newly diagnosed MM. A network meta-analysis of randomized clinical trials by Weisel et al[27] showed survival benefit of lenalidomide combined with low-dose dexamethasone versus other first-line treatments such as VMP, VTP, and MP[27]; however, there are countries where this regimen is not available.

Two parameters that negatively predicted PFS and EFS both in the univariate and multivariable analyses were older age (≥75 years) and worse performance status (ECOG >1). The survival was not affected by age neither in the VISTA[7] nor in the VMP-VP trials.[17] A possible explanation of these conflicting findings is that elderly patients participating in clinical trials are a highly selected group of more fit individuals with fewer comorbidities, as compared with patients observed

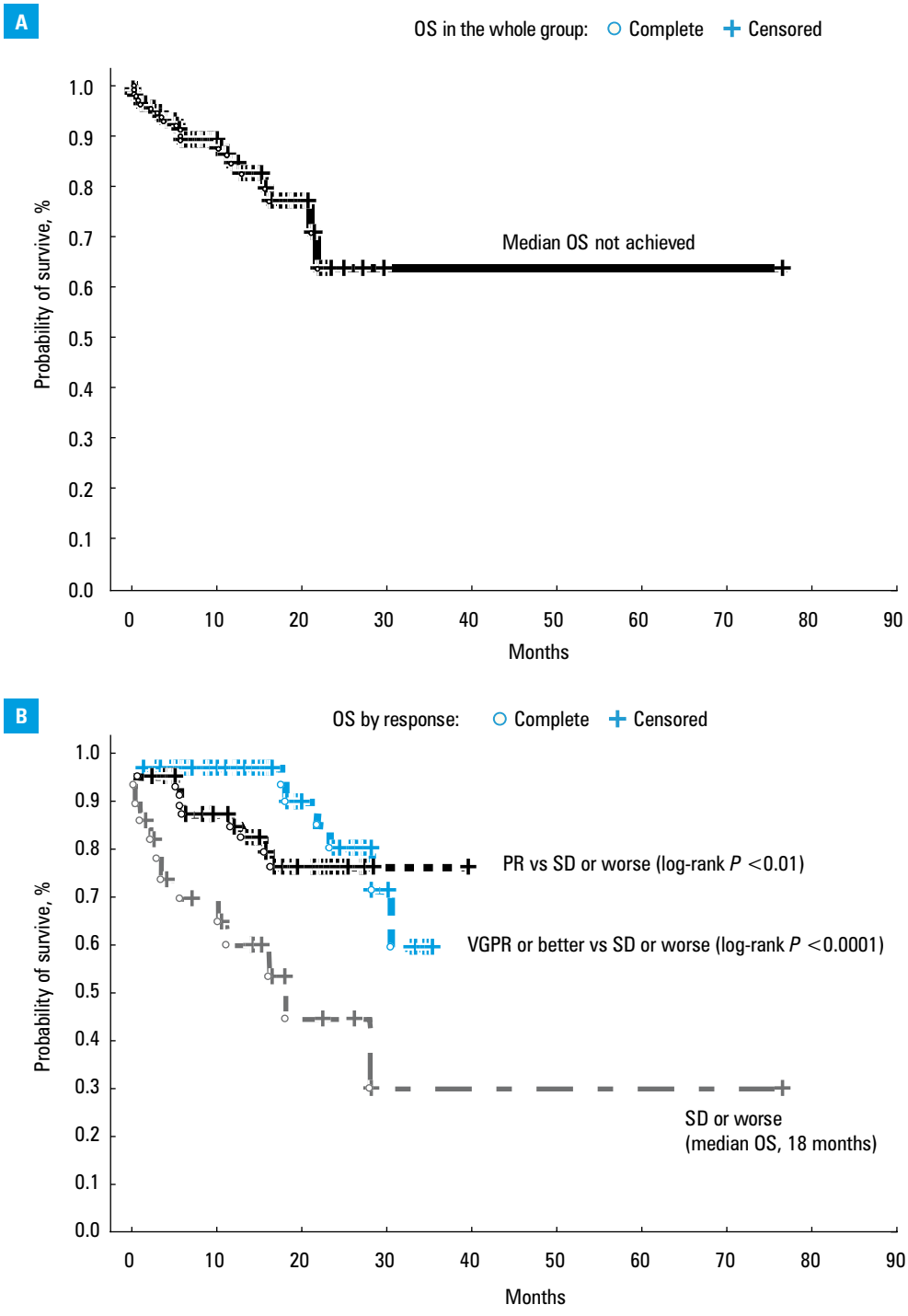

FIGURE 4 Probability of overall survival (OS) by Kaplan–Meier estimates in all patients with multiple myeloma treated with bortezomib-based regimens (**A**) and depending on the response to therapy (**B**) Abbreviations: see **FIGURE 1**

in routine clinical practice. On the other hand, in a meta-analysis of 4 randomized European phase 3 clinical trials with thalidomide and/or bortezomib, involving 1435 patients, age above 75 years was one of the negative predictors of survival.[28]

We did not observe a higher frequency of the toxicity of therapy in patients aged 75 years or older, and concomitant diseases were not shown to affect the tolerance of therapy. In the GEM2005 study,[22] the frequency of hematological toxicities in patients treated with VMP was similar between those aged 75 years or older and the younger patients. Although there was a trend for a higher incidence of nonhematological adverse effects, the cumulative dose of different drugs was lower in patients aged 75 years or older.

In our study, the most common grade 3/4 adverse events were peripheral neuropathy and infections. Grade 3/4 hematological adverse effects were rare. The relatively high incidence of infections might be associated with a high proportion of elderly patients and with advanced disease. The most important adverse effect was peripheral neuropathy, which remained the main reason for treatment discontinuation. The incidence of polyneuropathy was similar irrespective of the route of bortezomib administration (intravenous vs subcutaneous). This is in contrast to the data from randomized clinical trials,[29,30] but in agreement with the results of a retrospective

TABLE 4 Primary reasons for treatment discontinuation

Reason of discontinuation		Cycles administered			Total events
		1–3	4–6	7–9	
Polyneuropathy	Total	21 (13.6)	4 (2.6)	2 (1.3)	27 (17.5)
	Exacerbation	2 (1.3)	1 (0.7)	0	3 (1.9)
	New onset	19 (12.3)	3 (1.9)	2 (1.3)	24 (15.6)
Cardiovascular disease	Total	9 (5.8)	4 (2.6)	0	14 (9.1)
	Exacerbation	7 (4.5)	4 (2.6)	0	11 (7.1)
	New onset	2 (1.3)	0	0	2 (1.3)
Infection		9 (5.8)	3 (1.9)	1 (0.7)	13 (8.4)
Hematological toxicity		3 (1.9)	2 (1.3)	2 (1.3)	7 (4.5)
Myeloma progression		5 (3.3)	10 (6.5)	11 (7.1)	26 (16.9)
Patient decision		1 (0.7)	0	0	1 (0.7)

Data are presented as the number (percentage) of patients.

analysis by Minarik et al,[31] including 446 patients with MM treated with bortezomib. They suggested that the lower dose of bortezomib is more important for reducing neurotoxicity. Data from the randomized phase 3 GIMEMA trial[32] showed that reducing the bortezomib regimen from twice- to once-weekly infusions decreased the incidence of grade 3/4 peripheral neuropathy from 28% to 8%. Larocca et al[33] demonstrated a low incidence of peripheral neuropathy associated with low-dose intensity bortezomib-based regimens in patients aged 75 years or older with newly diagnosed MM.[33]

The rate of treatment discontinuation due to adverse events was higher in our study than in the VISTA trail (39.6% vs 15%). Nine cycles of bortezomib-based regimens were given only in 28.6% of the patients in our study. Both treatment discontinuation and dose reductions were more common in our cohort than in the previous prospective clinical trials, despite a lower incidence of adverse events. These observations reflect a less stringent approach to administering a full number of planned cycles of therapy in routine clinical practice. Therefore, rather than due to serious adverse events, the treatment is often discontinued at the discretion of the treating physician to avoid toxicity, especially in elderly and frail patients. All participants in our analysis started bortezomib as a twice-weekly regimen; however, starting the therapy with a once-weekly dose in patients aged 75 years or older or in those with comorbidities would probably allow an administration of more cycles, especially that neuropathy was the most common cause of therapy discontinuation.

It is important to carefully evaluate patients, especially those aged 75 or older, in terms of the efficacy of therapy. It is now generally agreed that the choice of MM treatment based only on the criteria of age and performance status is not adequate. According to the IWMG report, a geriatric assessment consisting of the Katz Activity of Daily Living, Lawton Instrumental Activity of Daily Living, and Charlson Comorbidity Index predicts survival and toxicity of therapy much more precisely in elderly patients with MM,[34] and comprehensive algorithms for treatment decision making should be developed. The results of a recently published phase 2 trial comparing 3 low-dose intensity regimens with bortezomib (VT, VCT, and VMP) suggest that 2-drug regimens followed by bortezomib maintenance should be the therapy of choice in frail elderly patients.[33]

In conclusion, the results of this retrospective analysis showed high efficacy of bortezomib-based regimens as the first-line therapy of patients with MM ineligible for HDT with auto-SCT, even though there was a high percentage of patients with advanced disease and light chain MM. Since older age (≥75 years) and worse performance status (ECOG >1) were the most important parameters negatively predicting PFS, a more detailed evaluation of patients' frailty with geriatric assessment tools would allow practitioners to increase the efficacy of treatment.

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

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