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

Iwona Hus1, Adam Walter-Croneck2, Anna Masternak3, Artur Jurczyszyn4, Lidia Usnarska-Zubkiewicz5, Łukasz Bołkun6, Agnieszka Druzd-Sitk7, Marcin Rymko8, Jadwiga Łętowska9, Ewa Lech-Marańda10, Marcin Pasiarski11, Anna Dmoszyńska1

1  Department of Clinical Transplantology, Medical University of Lublin, Lublin, Poland
2  Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland
3  Department of Hematology, Regional Hospital, Opole, Poland
4  Department of Hematology, Jagiellonian University Medical College, Kraków, Poland
5  Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wrocław Medical University, Wrocław, Poland
6  Department of Hematology, Medical University of Białystok, Białystok, Poland
7  Department of Lymphoid Malignancies, Institute of Oncology, Warsaw, Poland
8  Department of Hematology, Specialist Municipal Hospital, Toruń, Poland
9  Department of Hematology, Ludwik Rydygier Memorial Specialized Hospital, Kraków, Poland
10 Centre of Postgraduate Medical Education, Warsaw; Institute of Hematology and Transfusion Medicine, Warsaw, Poland
11 Department of Hematology, Institute of Oncology, Kielce, Poland

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

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 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. 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. The improvement could first be seen only in younger patients; however, nowadays, most elderly patients are treated with the new drugs, and survival benefit is observed also in this group.

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. 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. 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.

When used as the first-line therapy, VMP does not lead to more resistant relapses or induction of secondary malignancies. 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. VMP was also a well-tolerated, safe, and active regimen in previously untreated patients with MM and renal impairment. Data from the VISTA trial demonstrated that the achievement of CR was associated with improved long-term outcome and clinically relevant improvements in health-related quality of life.

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.

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, comorbid 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. Treatment-related toxicity was evaluated using the Common Terminology Criteria for Adverse Events and Common Toxicity Criteria v3.0.

Statistical analysis  Associations between the response rates and patient characteristics were analyzed using the Mann–Whitney test for continuous variables and the χ² 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.
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%. Polynuropathy 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.

| Concomitant diseases                                      | <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.

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
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 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
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%), GEM2005 trial (80%), and that reported in a German registry by Knauf et al (82%).

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 study (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         | 1.04–3.80               | 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

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. 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. 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, the achievement of CR was associated with longer time to progression, time to next therapy, and treatment-free interval, as compared with immunoglobulin-G MM. 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. 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. 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, the achievement of CR was associated with longer time to progression, time to next therapy, and treatment-free interval, as compared with immunoglobulin-G MM. 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. 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. 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, the achievement of CR was associated with longer time to progression, time to next therapy, and treatment-free interval, as compared with immunoglobulin-G MM. 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. 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. 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, the achievement of CR was associated with longer time to progression, time to next therapy, and treatment-free interval, as compared with immunoglobulin-G MM. 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. 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. 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, the achievement of CR was associated with longer time to progression, time to next therapy, and treatment-free interval, as compared with immunoglobulin-G MM. 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. 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. 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, the achievement of CR was associated with longer time to progression, time to next therapy, and treatment-free interval, as compared with immunoglobulin-G MM. 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. 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. 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.
A network meta-analysis of randomized clinical trials by Weisel et al\textsuperscript{27} showed survival benefit of lenalidomide combined with low-dose dexamethasone versus other first-line treatments such as VMP, VTP, and MP\textsuperscript{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\textsuperscript{7} nor in the VMP-VP trials.\textsuperscript{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 co-morbidities, as compared with patients observed 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  | 23  |
| Thrombocytopenia  |                                  | 103 | 19  |
| Anemia            |                                  | 87  | 17  |
| Polyneuropathy    |                                  | 91  | 30  |
| Diarrhea          |                                  | 133 | 4   |
| Infections        |                                  | 113 | 26  |
| Cardiovascular disease |                              | 136 | 16  |

Data are presented as the number (percentage) of patients.
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, but in agreement with the results of a retrospective study.

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, 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, but in agreement with the results of a retrospective study.

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, 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, but in agreement with the results of a retrospective study.
analysis by Minarik et al., 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 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. 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.

The rate of treatment discontinuation due to adverse events was higher in our study than in the VISTA trial (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, 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.

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.

Acknowledgments We would like to thank Darzia Zawirska (Kraków, Poland), Agnieszka Szudy (Lublin, Poland), Małgorzata Raźny (Kraków, Poland), Patrycja Zielińska (Katowice, Poland), and Renata Guzicka-Kazimierczak (Szczecin, Poland) for data collection.

Contribution statement AW-C and IH equally contributed to the work in the concept and design of the study, acquisition, analysis and interpretation of data and drafting the article. AM, AJ, LU-Z, ŁB, AD-S, MR, JŁ, EL-M, and MP contributed to the acquisition of data and revising the manuscript critically for important intellectual content. AD conceived the idea for the study and revised the manuscript critically for important intellectual content. All authors critically reviewed the manuscript and approved the final version of the manuscript for submission.

**Table 4** Primary reasons for treatment discontinuation

| Reason of discontinuation     | Cycles administered | Total events |
|-------------------------------|---------------------|--------------|
|                               | 1–3 | 4–6 | 7–9 |    |
| Polyneuropathy                |     |     |     |     |
| Total                         | 21  | 4   | 2   | 27 |
| Exacerbation                  | 2   | 1   | 0   | 3  |
| New onset                     | 19  | 3   | 2   | 24 |
| Cardiovascular disease        |     |     |     |     |
| Total                         | 9   | 4   | 0   | 14 |
| Exacerbation                  | 7   | 4   | 0   | 11 |
| New onset                     | 2   | 0   | 0   | 2  |
| Infection                     | 9   | 3   | 1   | 13 |
| Hematological toxicity        | 3   | 2   | 2   | 7  |
| Myeloma progression           | 5   | 10  | 11  | 26 |
| Patient decision              | 1   | 0   | 0   | 1  |

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

1. SEER Cancer Statistics Review 1975-2002; Previous Version - SEER Cancer Statistics. https://seer.cancer.gov/archive/scr/1975_2002/#citation. Accessed July 2017.

2. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med. 1986; 335: 91-97.

3. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008; 111: 2516-2520.

4. Brener H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. 2008; 111: 2521-2526.

5. Palumbo A, Magargotto V. Novel treatment paradigm for elderly patients with multiple myeloma. Am J Blood Res. 2011; 1: 190-204.

6. Palumbo A, Bringhen S, Caruxita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet Lond Engl. 2006; 367: 825-831.

7. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008; 359: 906-917.

8. San Miguel JF, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. J Clin Oncol Off J Am Soc Clin Oncol. 2013; 31: 448-455.

9. Deforge M, Dhavan R, Robinson D, et al. Health-related quality of life in elderly, newly diagnosed multiple myeloma patients treated with VMP vs. MP: results from the VISTA trial. Eur J Haematol. 2012; 89: 16-27.

10. Harousseau JL, Palumbo A, Richardson PG, et al. Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with bortezomib and melphalan in the randomized phase III FIRST Trial. J Clin Oncol. 2012; 30: 1031-1037.

11. Durie BGM, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20: 1467-1473.

12. NCI Common Terminology Criteria for Adverse Events Files. https://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed July 2017.

13. Mateos MV, Orist A, Martinez-Lopez J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised controlled trial. Lancet Oncol. 2010; 11: 934-941.

14. Knauf W, Abenhardt W, Alabsoud A, et al. Treatment of non-transport patients with multiple myeloma: routine treatment by office-based haematologists in Germany - Data from the Prospective Tumour Registry Lymphatic Neoplasms (TLN). Oncol Res Treat. 2014; 37: 635-644.

15. Chababalski O, Golab T, Dereczynk M, et al. 99mTc-MIBI scintigraphy in the diagnosis of multiple myeloma. Pol Arch Med Wewn. 2016; 126: 190-192.

16. Gay F, Larocca A, Wijermans P, et al. Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. Blood. 2011; 117: 3025-3031.

17. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol Off J Am Soc Clin Oncol. 2010; 28: 5101-5109.

18. Luczak M, Kubicki T, Rzetelska Z, et al. Comparative proteomic profiling of sera from patients with refractory multiple myeloma reveals potential biomarkers predicting response to bortezomib-based therapy. Pol Arch Intern Med. 2017; 127: 392-400. doi:10.20543/pamw.4032

19. Fuch C. Proteomic analysis of serum for identification of potential biomarkers predicting response of patients with refractory multiple myeloma to bortezomib-based therapy. Pol Arch Intern Med. 2017; 127: 386-387. doi:10.20543/pamw.4057

20. Kamitsuka J, Kaper OM, Dymicza-Piekarska V, et al. Serum soluble CD26/Slc12A4 concentration depending on the stage of multiple myeloma and its correlation with selected angiogenic cytokines. Pol Arch Med Wewn. 2016; 126: 321-329.

21. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol Off J Am Soc Clin Oncol. 2015; 33: 2863-2869.

22. Mateos MV, Orist A, Martinez-Lopez J, et al. GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? Blood. 2014; 124: 1887-1893.

23. Morabito F, Bringhen S, Larocca A, et al. Bortezomib, melphalan, prednisone (VMP) versus melphalan, prednisone, thalidomide (MPT) in elderly newly diagnosed multiple myeloma patients: A retrospective case-matched study. Am J Hematol. 2014; 89: 355-362.