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ORIGINAL ARTICLE

Multiple myeloma in elderly patients—a Portuguese multicentric real-life study

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Abstract

Patients older than 75 years old with multiple myeloma (MM) have shorter survival and are usually treated differently from what features in clinical trials. In this study, the authors characterized the Portuguese population of MM patients above 75 years old, treated between 2009 and 2016. We compared the outcomes obtained with bortezomib-based protocols (BBP), thalidomide-based protocols (TBP), and chemotherapy (CT) using univariate and multivariate controlling for age, performance status, International Staging System score, renal impairment, and number of comorbidities. We retrieved data from 386 patients, treated in 12 hospitals. Three hundred thirty-one cases were analyzed: 119 patients treated with BBP, 65 with TBP, 147 with CT. Median age was 79 years; CT-treated patients were older, had a worse performance status, and have more comorbidities. The median follow-up was 25 months. The 2-year OS was 58% and the median OS was 29.5 months. Patients treated with BBP had more frequently very good partial response (VGPR) or better response, and the subgroup of more fit patients had a significantly longer progression-free survival (PFS) and OS. The most frequently grade 3–4 toxicities were hematologic, infectious, and neurologic and were significantly lower in TBP and CT groups vs BBP. The most common second line was CT, followed by lenalidomide. Patients treated with lenalidomide had a higher probability of VGPR or better and a superior 1-year PFS. Despite the limitations of a retrospective study, our cohort represents the reality of older patients with MM in a western country. The hazard of death or progression was higher for old, fit patients treated, in first line, with CT and with TBP compared with that of BBP.

Keywords Multiple myeloma · Real-life study · Elderly patients · Comorbidities

Rui Bergantim, Manuel Neves and Sérgio Chacim qualify as second authors.

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Introduction

Multiple myeloma (MM) is characteristically a neoplastic disease of older adults. The annual prevalence of MM is approximately 31 cases per 100,000 people in the age group 65–74 years old, and it increases to 46 cases per 100,000 people in the age group above 74 years old [1–3]. Additionally, prevalence of myeloma has been increasing due to the prolonged survival of patients and growing life expectancy of general population.

Although novel agents and better supportive care have substantially improved outcome, patients ≥ 75 years old continue to have shorter survival compared with younger patients [4–6]. A meta-analysis of 1435 elderly MM patients treated with bortezomib, melphalan and prednisolone (VMP), or melphalan, prednisolone, and thalidomide (MPT) found that patients aged 75 years or older had worse survival than those under 75 years old; renal failure, cardiac, or gastrointestinal grade 3–4 adverse events were found to negatively correlate with survival among this elderly population [7]. So, the impact of novel agents on long-term survival in a real-life setting is still unclear and, particularly in older patients, may strongly depend on patient's related factors.

Methods for risk stratification of multiple myeloma patients, regardless of age, have evolved over the last decade, effectively segmenting populations that respond to different treatments and have helped to extend life expectancy for up to one decade or more [8, 9]. The most recent proposal for risk stratification is the Revised International Staging System (R-ISS); it offers a unified approach to prognosis, incorporating in the classic ISS prognostic indicators of disease biology such as lactate dehydrogenase (LDH) and cytogenetics [10]. Another risk stratification protocol (mSMART) was developed by the Mayo Clinic providing therapeutic guidance for subjects in different biological risk categories [11].

In the elderly, multiple myeloma is not a highly aggressive biological disease, but the presence of several comorbidities, patients' frailty, and an unsatisfactory immune surveillance makes the treatment of this disease more challenging [12, 13]. At diagnosis, approximately one-third of the MM patients are frail. These patients are poorly characterized in studies and underrepresented in clinical trials as they easily do not fulfill the eligibility criteria, mainly due to comorbidities, organ dysfunction, high number of other medications, and reduced performance status (ECOG > 2 is often an exclusion criteria) [14]. In this setting, frail patients usually are treated with regimens studied for fit patients, risking overtreatment with higher toxicity, early discontinuation, and poor quality of life. On the other hand, fitter patients could be undertreated if treatment is only adapted to their age. Also, they entail a population with diverse comorbidities, and usually less access to novel drugs, giving true importance to real-life data and clinical and population-based registries, which might be able to help providing these data in the future [15].

An adequate and useful definition of frailty is essential for a better assessment of elderly patients and to offer them effective and tailored therapy, aiming to improve their quality of life and progression-free and overall survival. The International Myeloma Working Group (IMWG) recommends a frailty score based on an assessment of physical and cognitive status along with comorbidities using age, the Katz's Activity of Daily Living (ADL), Lawton's Instrumental Activity of Daily Living (IADL), and Charlson Comorbidity Index (CCI) [16]. This scale identifies three categories (fit, intermediate-fitness, and frail) predicting mortality and the risk of treatment toxicity in the elderly MM patients. The same score was applied in the FIRST trial and was also associated with risk of death and PFS [17]. This FIRST's sub analysis also showed that frail patients had a superior cumulative incidence of treatment discontinuation compared with the fit population and a high rate of multiple myeloma–independent deaths was noticed in the frail population. These results point out the importance of applying a robust score to identify frail patients to improve a tailored approach in multiple myeloma treatment.

However, treatment protocols used in real life in most of the western countries may be quite different from what features clinical trials' reality. In this work, the authors retrospectively characterized the Portuguese population of MM patients above 75 years old regarding its demographics, clinical characteristics, and treatment protocols used in first and second lines, from 2009 to 2016. We aim to compare the results in terms of response and time-to-event–related outcomes obtained with different real-life anti-myeloma treatments widely used in elderly patients: bortezomib-based protocols, thalidomide-based protocols, and conventional chemotherapy.

Patients and methods

Study population

This is a retrospective, observational cohort study that includes patients above 74 years old, diagnosed with multiple myeloma defined as per IMWG criteria, needing treatment between January 2009 and June 2016 at 12 Portuguese hospitals (4 university clinics, 2 national oncology institutes, and 6 hospitals). Patients with smoldering MM, plasma cell leukemia, or solitary plasmacytoma were excluded. Patients receiving first-line treatments other than chemotherapy, thalidomide-, or bortezomib-based regimens were also subsequently excluded from analyses (Fig. 1). All data were retrospectively collected from the hospitals' registries and patients' clinical notes. Informed consent was obtained from all patients for being included in the study.

For each patient, data regarding age, gender, comorbidities, ECOG performance status, type of multiple myeloma, date of diagnosis, presence of skeleton disease and/or extramedullary disease, ISS score, cytogenetic, and creatinine clearance at diagnosis were collected (Table 1). Data was also collected concerning the first and second treatment lines administered,

comprising the treatment protocol and total number of cycles administered, date of treatment beginning and ending, reason for discontinuation, toxicity, best response achieved, and its date. In general, published guidelines [18, 19] were followed by the different hospitals in what concerns diagnosis, response evaluation, and treatment protocols. Follow-up information concerning the vital status and occurrence of relapse/progression were collected from the hospital registries; the cut-off date was July 2016.

Outcome definition

Response to treatment was evaluated according to the IMWG criteria [18].

Time to next treatment (TTNT) was defined as the time between the start date of first-line and the second-line treatments. Patients that died before starting second-line therapy were censored at the date of death. Event-free survival (EFS) was defined as the time between the start date of first-line treatment and the date of progression, treatment discontinuation due to toxicity, or death from any cause. Progression-free survival (PFS) was calculated as the time from start of first-line treatment to discontinuation due to disease progression or death from any cause. Overall survival (OS) was calculated from the beginning of the first-treatment line until death from any cause. Patients lost to follow-up without any events were censored at the date of the last follow-up. We also evaluated the toxicity associated with first-line treatment which was defined as any grade 3 or 4 adverse reactions according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Statistical methods and data management

The characterization of the demographic and clinical characteristics of our cohort and of the treatment protocols used in first and second lines was done using descriptive statistics. Anti-myeloma treatments were grouped as bortezomib-based protocols (BBP), thalidomide-based protocols (TBP), chemotherapy (alkylating agents), and lenalidomide-based protocols. The comparisons of interest defined a priori between first-line treatment groups were TBP vs BBP and chemotherapy vs BBP. Logistic regression was used to evaluate the association between first-line treatment protocol and the outcome response to first-line treatment (very good partial response or better vs other) and toxicity (at least one grade 3/4 toxicity event vs none). Time-to-event outcome analysis was done using Kaplan-Meier methods. Cox regression was used to assess the association between first-line treatment protocol and the time-to-event outcomes OS, PFS, TTNT, and EFS. For all outcomes, we conducted univariate analyses taking first-line treatment protocol as the only independent variable (results reported as unadjusted OR and unadjusted HR). In order to control for confounding, we also conducted multivariable analyses adjusted for age, ECOG performance status, ISS, creatinine clearance, and number of comorbidities per patient (results reported as adjusted OR and adjusted HR). BBP was defined as the reference category in all fitted regression models. All tests were two-sided. Reported p values concern the likelihood ratio test unless otherwise specified. We considered a significance level of 0.05. Analysis was conducted using R software version 3.1.2 (http://www.R-project.org/).

Results

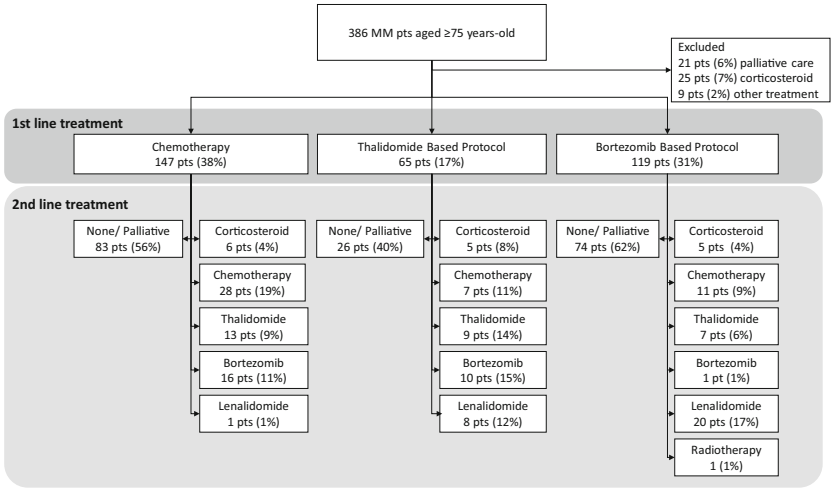
Patient characteristics

We retrospectively identified 386 consecutive MM patients aged above 74 years old who were treated in 12 Portuguese hospitals between January 2009 and June 2016. We excluded from analysis patients receiving, in first line, only symptomatic palliative care ($n = 21$), patients treated with corticosteroids ($n = 25$), and nine patients who were treated with other protocols in the context of clinical trials. The remaining 331 cases, included in the analyses, comprised 119 patients treated with BBP, 65 patients treated with TBP, and 147 that received CT (Fig. 1a). Table 1 shows the baseline clinical and demographic characteristics of these three patient groups. The median age of the entire cohort was 79 years; the CT-treated patients were older (66% aged above 79 years old vs 29% in both BBP and TBP), had a worse performance status (35% with PS > 2 vs 26% in BBP and 16% in TBP), and have more comorbidities (81% with ≥ 1 relevant comorbidity vs 71% in BBP and 75% in TBP). In the TBP group, there was a lower proportion of patients with renal impairment (creatinine clearance < 40 ml/min) and with stage III ISS compared with the other treatment groups (23% vs 41% in both BBP and CT groups and 31% vs 56% in BBP and 59% in CT, respectively). Conversely, the proportion of patients with extramedullary disease was higher in TBP than in the other groups (23% vs 13% in BBP and 14% in CT). The three groups were balanced in what regards the gender distribution, type of MM, and presence of bone disease.

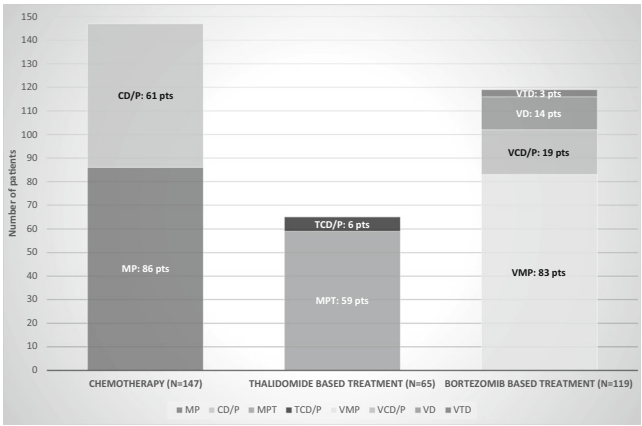
The median time from MM diagnosis to first-line treatment was slightly longer in BBP and TBP groups (Table 1). That may be explained with the need for explicit approvals in Portugal within and/or outside the hospitals, depending on the date of prescription.

In this elderly population, three quarters of the patients (249/331) had at least one comorbidity and 57 (17%) had three or more comorbidities. The most frequent comorbidities were vascular in 46% (153/331) of patients, cardiac in 31% (104), endocrine in 23% (76), pulmonary in 13% (42), gastrointestinal in 11% (37), and psychiatric in 8% (27). Comorbidities were not evaluable in three patients (1%). Twenty-eight patients (12%) had other cancer diagnosis, the most frequent locations being prostate (10 patients) and breast (9 patients).

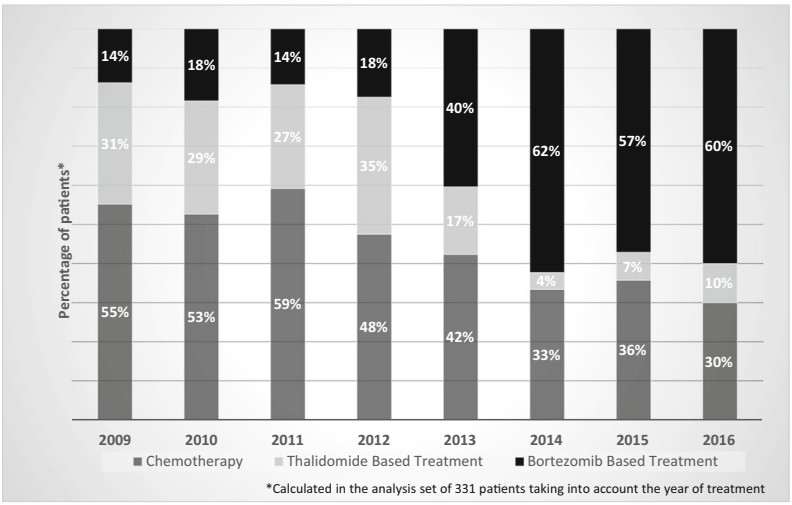
a) Patient flow showing first and second line treatment protocols administered



b) First line treatment regimens administered



c) Distribution of first line treatment protocols per year (2009-2016)



Caption:

C=Cyclophosphamide; D=Dexamethasone; M=Melphalan; P=Prednisolone; T=Thalidomide; V=Bortezomib

◀ **Fig. 1** Treatment characterization. **a** Patient flow showing first- and second-line treatment protocols administered. **b** First-line treatment regimens administered. C, cyclophosphamide; D, dexamethasone; M, melphalan; P, prednisolone; T, thalidomide; V, bortezomib. **c** Distribution of first-line treatment protocols per year (2009–2016)

Treatment options and over time evolution

First-line treatments

Treatment options for the first-line therapy were taken according to local protocols and available drugs in different periods of time. Patients treated with chemotherapy (38%, $n = 147$) received either melphalan and prednisolone (MP) or cyclophosphamide with prednisolone or dexamethasone (CD/P) (Fig. 1b). Patients with thalidomide-based treatment (17%, $n = 65$) received either melphalan, thalidomide and prednisolone (MPT), or thalidomide, cyclophosphamide, and dexamethasone/prednisolone (TCD/P). Patients in which bortezomib was the backbone therapeutic agent (31%, $n = 119$) were mainly treated with bortezomib, melphalan, and prednisolone (VMP, $n = 83$), bortezomib, cyclophosphamide, and dexamethasone/prednisolone (VCD/P, $n = 19$), or bortezomib and dexamethasone (VD, $n = 14$). The association of bortezomib, thalidomide, and dexamethasone (VTD) was only administered to three patients in this time period and was considered a BBP.

During the period ranging from 2009 to 2016, there was a change in the treatment paradigm of these elderly patients with the introduction of novel agents, mainly bortezomib, that became most remarkable after 2012 (54% of the patients treated since 2013) (Fig. 1c). The use of chemotherapy alone was the main option by the end of 2009 with 55% of patients receiving alkylating agents with steroids, decreasing to 30% by 2016. The same pattern was observed with patients that received TBP, which decreased from 31% in 2009 to 10% in 2016. Contrarily, there was a truthful rise on BBP use from below 20% until 2013, to around 60% of patients since 2014 on.

Second-line treatments

Figure 1a shows the second-line treatments administered to the 331 patients included in the study. In the group of patients treated at first line with chemotherapy, 83 (56%) did not undergo further treatment besides palliative care on first relapse/progression. The remaining ones received protocols based on lenalidomide (1%, $n = 1$), based on bortezomib (11%, $n = 16$), based on thalidomide (9%, $n = 13$), corticosteroids alone (4%, $n = 6$), or were retreated with chemotherapy protocols (19%, $n = 28$). From the patients treated with TBP on first line, 40% ($n = 26$) were referred to palliative care on relapse/progression, while the ones eligible for treatment received corticosteroids (8%, $n = 5$), protocols based on chemotherapy (11%, $n = 7$), bortezomib (15%, $n = 10$), lenalidomide (12%, $n = 8$), or retreated with thalidomide-based protocols (14%, $n = 9$). Most patients (62%, $n = 74$) who underwent on BBP at first line were considered to palliative care after relapse/progression. From the group of patients who received a second line after BBP in first line, the majority (17%, $n = 20$) were treated with lenalidomide-based protocols. The remaining ones were treated with corticosteroids alone (4%, $n = 5$), with chemotherapy (9%, $n = 11$), and with TBP (6%, $n = 7$), and only 1 patient (1%) was retreated with a bortezomib-based protocol. There was also 1 patient (1%) that was submitted to isolated radiotherapy.

Response to first-line treatments

Table 2 displays the response to first-line treatment per treatment group. Stringent complete responses, although in small number, were only obtained with BBP. The proportion of patients achieving at least a very good partial response in BBP, TBP, and CT groups was 53% (95% CI 44–66%), 31% (95% CI 21–43%), and 12% (95% CI 7–18%), respectively. Accordingly, the percentage of patients not responding to treatment (stable or progressive disease) was higher in the CT group than that in the TBP or BBP groups (45%, 26%, and 19% respectively) (Table 2). Also, the depth of response (sCR/CR/VGPR vs PR/SD/PD) was associated with the time-to-event outcomes EFS, OS, PFS, and TTNT ($p < 0.001$ for all, logrank test).

Multivariable analysis controlling for age, performance status, ISS, renal impairment, and number of comorbidities confirmed an independent effect of the type of first-line treatment protocol administered in the odds of achieving a very good partial response or better (Table 3). Indeed, TBP- and CT-treated patients have, respectively, a 63% and 90% reduction in the odds of having a very good partial response or better compared with patients receiving first-line BBP (adjusted OR, TBP vs BBP = 0.37; 95% CI 0.18–0.74; adjusted OR, CT vs BBP = 0.10; 95% CI 0.05–0.21).

There was no difference among the three groups in terms of median number of cycles administered (8 cycles in BBP and CT, 9 in TBP) but the median number of cycles to best response was significantly lower in BBP (4 cycles) compared with that in TBP (7.5 cycles) and in CT (7 cycles; p value < 0.001 in both comparisons, Wilcoxon rank-sum test).

Time-to-event outcomes in first-line treatments

The median follow-up in living patients was 25 months (22 months in the BBP group, 47 months in the TBP group, and 30 months in the CT treatment group).

The 2-year OS in the whole cohort of 331 patients was 58% (95% CI 53–64%) and the median OS was 29.5 months (95% CI 25–38 months). The 2-year OS observed in BBP, TBP, and CT

Table 1 Baseline clinical and demographic characteristics

Characteristic	Overall ($n = 331$)	Bortezomib-based protocol ($n = 119$)	Thalidomide-based protocol ($n = 65$)	Chemotherapy ($n = 147$)
Age, years old				
Median (range)	79 (75–95)	78 (75–89)	78 (75–85)	81 (75–95)
75–79	181 (55%)	85 (71%)	46 (71%)	50 (34%)
≥ 80	150 (45%)	34 (29%)	19 (29%)	97 (66%)
Gender				
Female	158 (48%)	56 (47%)	31 (48%)	71 (48%)
Male	173 (52%)	63 (53%)	34 (52%)	76 (52%)
ECOG performance status				
0	57 (17%)	25 (21%)	13 (20%)	19 (13%)
1	99 (30%)	35 (29%)	23 (35%)	41 (28%)
2	77 (23%)	27 (23%)	19 (29%)	31 (21%)
3	61 (18%)	18 (15%)	5 (8%)	38 (26%)
4	31 (9%)	13 (11%)	5 (8%)	13 (9%)
Unknown	6 (2%)	1 (1%)	0	5 (3%)
Comorbidities				
0	79 (24%)	35 (29%)	16 (25%)	28 (19%)
1–2	192 (58%)	66 (56%)	37 (57%)	89 (61%)
≥ 3	57 (17%)	15 (13%)	12 (19%)	30 (20%)
Unknown	3 (1%)	3 (3%)	0	0
Multiple myeloma				
IgG K	137 (41%)	52 (44%)	29 (45%)	56 (38%)
IgG L	57 (17%)	21 (17%)	11 (17%)	25 (17%)
IgA K	51 (15%)	12 (10%)	12 (19%)	27 (18%)
IgA L	38 (12%)	14 (12%)	3 (5%)	21 (14%)
Light chain K	25 (8%)	8 (7%)	5 (8%)	12 (8%)
Light chain L	17 (5%)	10 (8%)	2 (3%)	5 (3%)
Oligo/non-secretory	4 (1%)	0	3 (5%)	1 (1%)
IgD L	1 (< 1%)	1 (1%)	0	0
Unknown	1 (< 1%)	1 (1%)	0	0
ISS score				
1	54 (16%)	21 (18%)	15 (23%)	18 (12%)
2	94 (28%)	30 (25%)	26 (40%)	38 (26%)
3	174 (53%)	66 (56%)	21 (32%)	87 (59%)
Unknown	9 (3%)	2 (2%)	3 (5%)	4 (3%)
High-risk cytogenetics				
No	73 (22%)	17 (14%)	9 (14%)	47 (32%)
Yes	37 (11%)	23 (19%)	4 (6%)	10 (7%)
Unknown	221 (67%)	79 (66%)	52 (80%)	90 (61%)
Extramedullary disease				
No	276 (83%)	102 (86%)	50 (77%)	124 (84%)
Yes	51 (15%)	16 (13%)	15 (23%)	20 (14%)
Unknown	4 (1%)	1 (1%)	0	3 (2%)
Bone disease				
No	123 (37%)	47 (40%)	24 (37%)	52 (35%)
Yes	207 (63%)	71 (60%)	41 (63%)	95 (65%)
Unknown	1 (< 1%)	1 (1%)	0	0
Creatinine clearance < 40 ml/min				
No	177 (54%)	59 (50%)	45 (69%)	73 (50%)

Table 1 (continued)

Characteristic	Overall ($n = 331$)	Bortezomib-based protocol ($n = 119$)	Thalidomide-based protocol ($n = 65$)	Chemotherapy ($n = 147$)
Yes	124 (38%)	49 (41%)	15 (23%)	60 (41%)
Unknown	30 (9%)	11 (3%)	5 (8%)	14 (10%)
Time from MM diagnosis to first-line treatment, weeks**				
Median (min–max)	3.0 (0–485.9)	3.4 (0–231.9)	3.1 (0–146.9)	2.8 (0–485.9)

*High-risk cytogenetics comprises at least one of the following cytogenetic findings: del17p; t(4;14); t(14;16); or chromosome 1 abnormalities

**Unknown in 7 patients (5 from chemotherapy group, 1 bortezomib-based protocol, and 1 thalidomide-based protocol)

treatment groups was 65% (95% CI 56–75%), 60% (95% CI 49–74%), and 53% (95% CI 45–62%), respectively (Fig. 2a). The OS was longer in patients treated after 2013 (treated with BBP) when compared with patients treated in the period 2009–2012 with chemotherapy (Fig. 2b); still, that difference did not reach statistical significance ($p = 0.11$). However, in patients aged between 75 and 80 years old with a PS (ECOG) of 0–1 and less than 2 comorbidities ($n = 56$, median follow-up of 26.5 months), there was a significant benefit in terms of longer OS for patients treated with BBP vs both TBP and CT ($p = 0.036$, Fig. 2c).

On univariate analysis, the first-line treatment protocol was significantly associated with OS ($p = 0.014$) with a 76% increase in the hazard of death in the CT group compared with the BBP group (unadjusted HR = 1.76; 95% CI 1.19–2.60) and a 35% increase in the hazard of death in TBP compared with the BBP group (unadjusted HR = 1.35; 95% CI 0.85–2.14). When adjusted for age, ECOG performance status, ISS, creatinine clearance, and comorbidities, the hazard of death was still higher in CT (adjusted HR = 1.50; 95% CI 0.99–2.28) and in TBP (adjusted HR = 1.43; 95% CI 0.89–2.30) compared with BBP, but not statistically significant (Table 4). In the multivariable analysis, the factors showing a trend for an independent association with OS were age and PS (Table 4 and Fig. 3).

The median EFS in our cohort was 14.6 months and the observed 2-year EFS was 28% (95% CI 24–34%), being 22% (95% CI 15–33%) in the BBP treatment group, 30% (95% CI 21–45%) in the TBP, and 31% (95% CI 24–41%) in the CT. No significant differences in EFS between treatment groups could be demonstrated either in univariate (unadjusted HRTBP vs BBP = 1.01; unadjusted HRCT vs BBP = 1.08; $p = 0.904$) or in multivariable analyses (adjusted HRTBP vs BBP = 0.93, 95% CI 0.64–1.36; adjusted HRCT vs BBP = 0.86, 95% CI 0.61–1.20; $p = 0.679$). Similarly, to EFS, no significant differences were demonstrated between treatment groups concerning PFS and TTNT.

As to PFS, the median in the whole cohort was 17 months and the percentage of patients alive without progression at 2 years was 34%, ranging from 32 in TBP (95% CI 22–46%) to 34% in BBP (95% CI 26–46%) and 35% in CT (95% CI 27–44%). For patients aged between 75 and 80 years old with a PS (ECOG) of 0 or 1 and less than 2 comorbidities ($n = 53$), there was a significant benefit of PFS for those

Table 2 First-line treatment responses

	Bortezomib-based protocol ($n = 119$)	Thalidomide-based protocol ($n = 65$)	Chemotherapy ($n = 147$)
Total no. of cycles			
Median (min–max)	8 (1–25)	9 (1–24)	8 (1–44)
Best response IMWG			
sCR	3 (3%)	0	0
CR	13 (11%)	7 (11%)	4 (3%)
VGPR	47 (40%)	13 (20%)	13 (9%)
PR	32 (27%)	25 (39%)	55 (37%)
SD	13 (11%)	10 (15%)	43 (29%)
PD	10 (8%)	7 (11%)	23 (16%)
Not evaluable	1 (1%)	3 (5%)	9 (6%)
No. of cycles to best response in responding patients			
Median (min–max)	4 (1–14)	7.5 (2–24)	7 (2–30)

sCR, stringent complete response; *CR*, complete response; *VGPR*, very good partial response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease

Table 3 Association between type of first-line treatment and very good partial response or better (VGPR/CR/sCR vs PR/SD/PD) controlling for age, performance status, ISS score, creatinine clearance, and comorbidities

	Adjusted OR	95% CI	*p* value*
First-line treatment			
BBP	1		
TBP	0.37	0.18–0.74	0.006
CT	0.10	0.05–0.21	< 0.001
Age at start of treatment			
75–79 years old	1		
> 79 years old	0.79	0.42–1.50	0.473
ECOG PS			
0–1	1		
≥ 2	0.61	0.34–1.11	0.107
ISS score			
1–2	1		
3	1.55	0.77–3.17	0.225
Creatinine clearance			
≥ 40 ml/min	1		
< 40 ml/min	1.31	0.66–2.62	0.446
No. of comorbidities			
0	1		
1–2	1.08	0.56–2.10	0.830
≥ 3	0.78	0.30–1.97	0.602

*Wald test

treated with BBP compared with those treated with TBP or CT ($p = 0.029$, Fig. 2d).

The median TTNT was 24 months, ranging from 21.4 to 24.5 in the three treatment groups. Two-year TTNT observed in the TBP group was 45% (95% CI 33–62%), in BBP was 51% (95% CI 40–65%), and in CT was 52% (95% CI 43–64%).

Toxicities of first-line treatments

The most frequently reported grade 3–4 toxicities were hematologic, infectious, and neurologic (Table 5). There were no significant differences among groups concerning hematologic toxicities, but the odds of grade 3–4 infections were significantly lower in TBP and CT groups compared with those in BBP (unadjusted ORTBP vs BBP = 0.26, 95% CI 0.07–0.72; unadjusted ORCT vs BBP = 0.40, 95% CI 0.19–0.80). Neurologic toxicities were reported in 13% and 16% of the BBT and TBP groups, respectively, but only in 3% of the patients treated with CT (unadjusted ORTBP vs BBP = 1.20, 95% CI 0.47–2.90; unadjusted ORCT vs BBP = 0.20, 95% CI 0.05–0.56). All the other toxicities were reported in 5% or less of the patients. The rate of thromboembolic grade 3–4 events was remarkably low and was only present in 5 patients, 3 in the BBP, 2 in the CT group, and none in the TBP.

Overall, 43% of the patients had at least one grade 3–4 toxicity event to first-line treatment (Table 5). This proportion was higher in BBP (58%) than in TBP (43%) or CT (31%) treatment groups. There was a significant association between the type of treatment protocol and grade 3–4 toxicity in both univariate ($p < 0.001$) and multivariable analyses ($p = 0.001$). Compared to BBP, CT-treated patients had a relative reduction in the odds of grade 3–4 toxicity of 67% (adjusted OR = 0.33, 95% CI 0.18–0.59) controlling for age, ECOG performance status, ISS, creatinine clearance, and number of comorbidities. The reduction in the odds of grade 3–4 toxic events of 41% in the TBP compared to the BBP group was not statistically significant (adjusted OR = 0.59, 95% CI 0.29–1.16). Toxicities were not registered in 22 patients.

Outcomes to second-line treatments

The second-line treatments administered to each first-line treatment group are shown in Fig. 1a.

Overall, among the 132 patients that received second-line treatment (excluding patients treated with corticosteroids or symptomatic palliative care), 29 (22%) patients received second-line treatment with TBP, 27 (20%) with BBP, 46 (35%) with CT, and 29 (22%) with lenalidomide-based protocols.

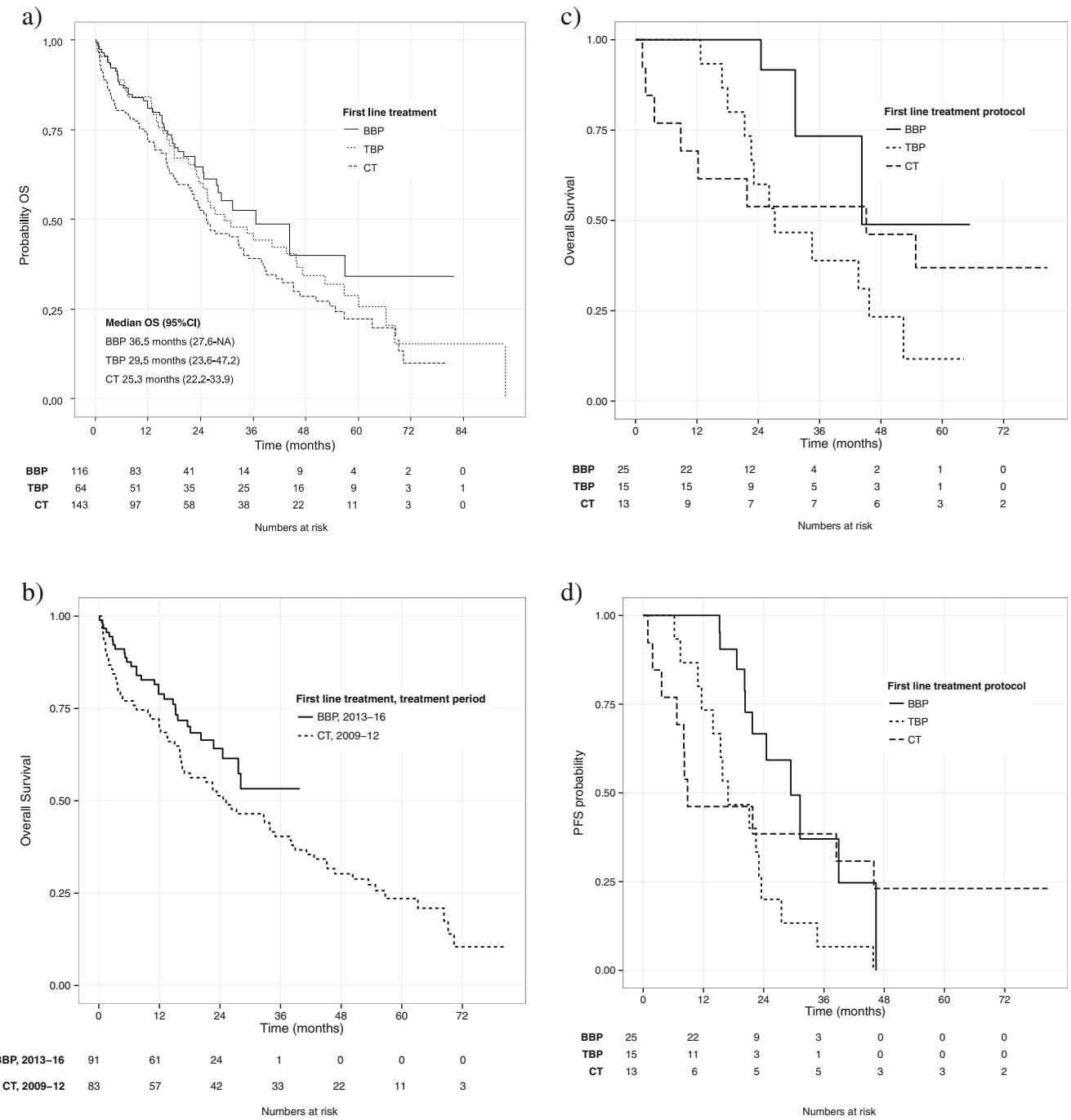
The proportion of patients achieving at least VGPR after second-line treatment was higher for patients treated in second line with lenalidomide-based regimens (48%, compared with 37% in BBP and to only 15% in both TBP and CT groups). The median number of cycles to best response in patients with partial response or better was 3.5 in BBP and 5 in both lenalidomide and TBP.

The median progression-free survival after the start of second-line treatment with lenalidomide-, bortezomib-, and thalidomide-based protocols and chemotherapy was, respectively, 22, 17.8, and 17 months. PFS observed 1 year after the start of second-line treatment was 65% (95% CI 48–89%) in the lenalidomide group, 56% (95% CI 39–81%) in the bortezomib group, 40% (95% CI 24–69%) in the thalidomide, and 60% (95% CI 47–78%) in the chemotherapy group.

Discussion and conclusions

Despite the limitations of a retrospective study, our cohort represents the reality of the elderly patients with multiple myeloma in a western country. Although the results from this study must be considered within the confines of its inherent limitations, it is important to underline the real nature of these results.

In our national cohort, the median age was 79 and almost half of the patients (45%) were ≥ 80 years old. Moreover, 50% of the patients had ECOG PS ≥ 2 and only 24% of them had



Caption:

BBP=Bortezomib Based Protocols; TBP=Thalidomide Based Protocols; CT=Chemotherapy

Fig. 2 **a** Overall survival by first-line treatment protocol. BBP, bortezomib-based protocols, median OS: 36.5 months, 95%CI: 27.6-NA; TBP, thalidomide-based protocols, median OS: 29.5 months, 95%CI: 23.6-47.2 ; CT, chemotherapy, median OS: 25.3 months, 95%CI: 22.2-33.9. **b** Overall survival 2013–2016 vs 2009–2012. **c** Overall survival for patients < 80 years old and PS 0–1 and < 2 comorbidities. **d** Progression-free survival (PFS) for patients < 80 years old and PS 0–1 and < 2 comorbidities

no comorbidities, 17% had ≥ 3 comorbidities, and 38% had renal impairment (clearance < 40 ml/min). This means that, in real life, we are treating an elderly and frail population often excluded from clinical trials. In our study, both age ≥ 80 years old and ECOG performance status ≥ 2 showed a trend for an independent clinically relevant association with overall

Table 4 Association between type of first-line treatment and overall survival controlling for age, performance status, ISS score, creatinine clearance, and comorbidities

	Adjusted HR	95% CI	*p* value*
First-line treatment			
BBP	1		
TBP	1.43	0.89–2.30	0.136
CT	1.50	0.99–2.28	0.057
Age at start of treatment			
75–79 years old	1		
> 79 years old	1.41	0.99–2.01	0.054
ECOG PS			
0–1	1		
≥ 2	1.39	1.00–1.93	0.052
ISS score			
1–2	1		
3	1.18	0.80–1.72	0.405
Creatinine clearance			
≥ 40 ml/min	1		
< 40 ml/min	1.18	0.81–1.71	0.392
No. of comorbidities			
0	1		
1–2	1.25	0.84–1.87	0.265
≥ 3	1.56	0.94–2.59	0.084

*Wald test

survival in elderly myeloma patients, confirming what is published in other real data studies [5, 6].

Overall, most of the patients were treated with CT (44%), followed by BBP (35.9%) and TBP (19.6%). As expected, the group of patients treated with CT was older, had a higher number of comorbidities, and had a worse performance status than the group of patients treated with protocols that included novel agents (BBP or TBP). From 2009 to 2016, there is an increasing trend of use of bortezomib in first-line treatment (from 14% in 2009 to 60% in 2016) and a consequent reduction of TBP and CT, with impact on the overall survival. Indeed, this change reproduces the ongoing integration of the new agents into the clinical practice but also reflects the heterogeneous reality of our country, with disparities in the access to drugs and innovative protocols. The residual population that are still treated with CT could be explained by a different access of novel agents by centers and the tendency to treat elderly patients in a more conservative way, valuing a cost-benefit ratio and a safety profile very well known. According to these considerations, the authors decided to group all the available anti-myeloma treatment protocols in three groups, which, in fact, reflects real-life decisions.

BBP was the only group of patients that achieved confirmed sCR, and BBP treatment was predictive of VGPR or better in a multivariate analysis, suggesting that BBP performed better

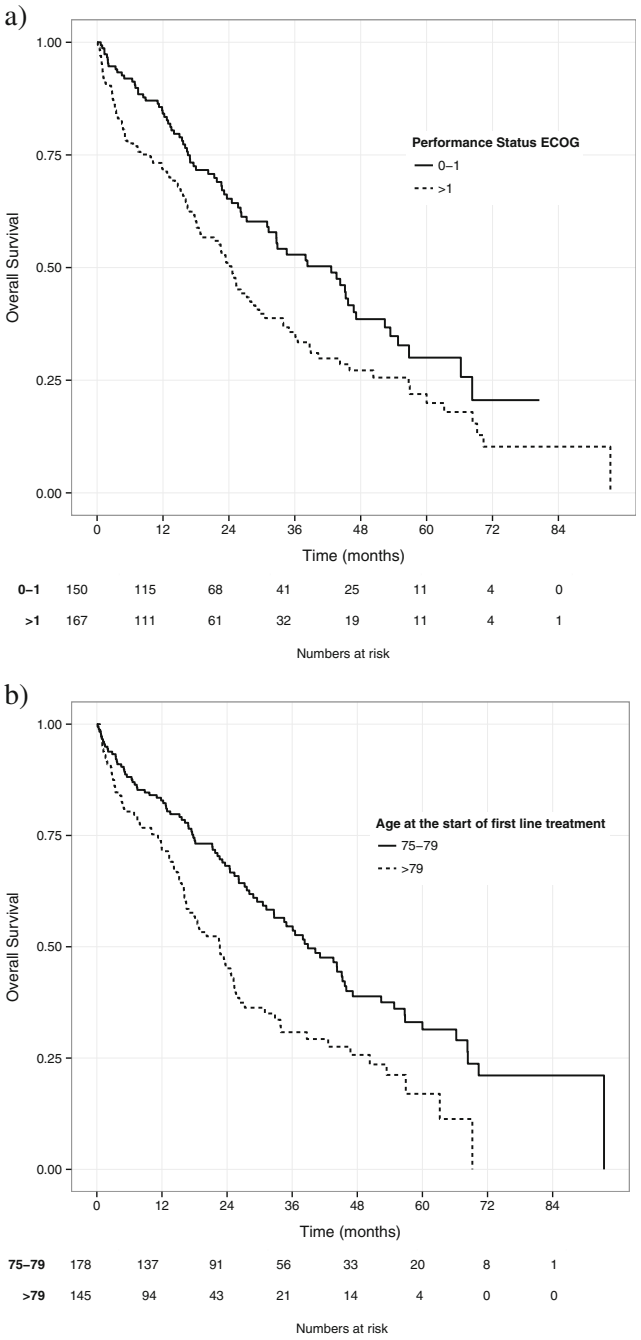


Fig. 3 Overall survival per ECOG (**a**) and age groups (**b**)

than TBP or CT—patients treated with TBP or CT had a 63% and 90% reduction in the odds of having VGPR or better compared with patients receiving first-line BBP. Moreover, the depth of response was associated with the time-to-event outcomes EFS, OS, PFS, and TTNT. However, in such an old population, it is critical to underline that the higher hazard of death found here in patients treated with CT and TBP compared with BBP is tempered when adjusted for important parameters to be considered in old patients' population, as PS, age, kidney function, ISS score, and comorbidities. So, the benefit of more effective regimens ought to be weighted in populations of old

Table 5 Grade 3/4 toxicities by first-line treatment protocol

Grade 3/4 toxicities, *N* (%)	Overall (*n* = 309)*	Bortezomib-based protocol (*n* = 113)*	Thalidomide-based protocol (*n* = 58)*	Chemotherapy (*n* = 138)*
Any toxicity	65 (43%)	65 (58%)	25 (43%)	43 (31%)
Hematologic	58 (19%)	24 (21%)	11 (19%)	23 (17%)
Infection	43 (14%)	25 (22%)	4 (7%)	14 (10%)
Neurologic	28 (9%)	15 (13%)	9 (16%)	4 (3%)
Asthenia	7 (2%)	3 (3%)	2 (3%)	2 (1%)
Gastrointestinal	6 (2%)	4 (4%)	0	2 (1%)
Cardiovascular	6 (2%)	2 (2%)	3 (5%)	1 (1%)
Thrombotic event	5 (2%)	3 (3%)	0	2 (1%)
Hyperglycemia	3 (1%)	1 (1%)	0	2 (1%)
Psychiatric	2 (1%)	1 (1%)	0	1 (1%)
Cutaneous	1 (< 1%)	0	0	1 (1%)
Myopathy	1 (< 1%)	0	1 (2%)	0

*Information concerning toxicity was not available in 22 patients (6 patients from BBP, 7 from TBP, and 9 from CT treatment group)

and frail patients. Accordingly, in our real-life old patients' cohort, the subgroup of patients aged 75 to 80 years old with a good performance status (0 or 1) and with few comorbidities (less than 2) treated with BBP have a statistically significant benefit of PFS and OS when compared with those treated with TBP or CT. Moreover, the median number of cycles needed to obtain response was lower in BBP than that in TBP or CT. These results confirm in real-life patients' data indirectly extracted from clinical trials [20] and justify the progressive preference of bortezomib over thalidomide from 2009 to 2016. It is clear here that these real-life results follow the results of clinical trials but also highlight the difficulty of reflecting the clinical trial results in the broad real-life population of old patients. Accordingly, the clear advantage of BBP in PFS and OS found in the subgroup patients between 75 and 80 years old, with low number of comorbidities (< 2) and better PS (< 2), obviously closer to those represented on clinical trials, is difficult to reproduce in patients over 80 years old.

The most prevalent grade 3–4 toxicities were hematological (19%), infectious (14%), and neurological (9%). There were no significant differences among groups concerning hematologic or other toxicities, but the odds of grade 3–4 infections were significantly lower in TBP and CT groups compared with those of BBP. The number of grade 3–4 thromboembolic events was very low in our cohort and, surprisingly, there were no grade 3–4 thromboembolic events in the TBP group. This finding might be explained by the generalized use of thromboprophylaxis in these patients. The differences between PFS and EFS in each treatment group account for the number of patients stopping treatment due to toxicity. As expected, this difference was higher in BBP.

With a median follow-up in living patients of 25 months (22 months in the BBP group, 47 months in the TBP group, and 30 months in the CT treatment group), the median OS was 25 months and the median EFS was 14.6 months. The observed OS in our cohort is inferior to the survival of patients ≥ 75 years old reported in a previously published meta-analysis [7]. Nevertheless, only one of the studies included in this meta-analysis [21] did not excluded patients due to comorbidities or ECOG. So, our results may in fact show the real impact of comorbidities and performance status on survival of elderly patients.

The 2-year OS observed in BBP, TBP, and CT treatment groups was 65%, 60%, and 53%, respectively. On a multivariate analysis controlling for age, performance status, ISS score, creatinine clearance, and comorbidities, the hazard of death was higher in CT (adjusted HR = 1.50; 95% CI 0.99–2.28) and in TBP (adjusted HR = 1.43; 95% CI 0.89–2.30) compared with that of BBP, although not statistically significant. The non-significant difference between the median OS of patients in the BBP and TBP groups might be related with the next line of treatment, as in the BBP group only 24% patients did a second line with new agents (thalidomide, lenalidomide, or bortezomib), and in the TBP, 41% of patients had a second line with one of these 3 agents. However, patients treated in more recent years with BBP live longer compared with patients treated between 2009 and 2012, mainly with chemotherapy. Also, patients with less comorbidities, with good PS, and with age up to 80 years old have a significant increase in PFS and OS when treated with BBP. This reflects either the impact of better supportive therapy used in recent years as well as the actual effect of novel drugs in real-world data, especially in fit old populations.

There was no difference in EFS and TTNT between treatment groups. This might be explained by the retrospective nature of this real-life study, where the exact time of progression and other censoring events are leverage by the schedule of the clinical appointments and laboratory assessments, which are not so precisely defined as in clinical prospective

studies. Furthermore, TTNT may be not representative, as the line of treatment after relapse might have been postponed due to the high number of toxicities and comorbidities in this elderly and frail population.

The diversity of treatment options over the years and the missing data inherent to the retrospective nature of this study may also hamper the clear demonstration of the relation between classic prognostic factors, such as ISS score and cytogenetics, and survival outcomes. In this retrospective cohort, a very high percentage (67%) of these patients had no cytogenetics analysis at the diagnosis, representing the reality in some countries. This finding should be understood in guidelines and treatment protocol guidance.

The most common second line was CT (46 patients), followed by lenalidomide and thalidomide (29 patients each) and bortezomib (27 patients). Patients treated with lenalidomide-based treatment had a higher probability of VGPR or better than patients treated with bortezomib- or thalidomide-based regimen or CT and had a superior 1-year PFS (65%) than patients treated with bortezomib (56%). These findings are in line with results of phase III clinical trials and highlight the relevance of lenalidomide-based protocols in this subset of patients. Nevertheless, it should also be mentioned that patients exposed to lenalidomide in second line were more commonly treated with BBP in first line and have a better PS, which might contribute for the overall performance of the therapeutic option.

In summary, the presented data highlights that option for more efficient protocols, like BBP, is associated with a better outcome in elderly patients, validating data from clinical trials, where these patients are underrepresented. Patients treated with BBP have faster responses, higher response rates (> VGPR), and longer OS. Furthermore, it should also be noted that the association between quality of response and OS, already extensively validated in clinical trials, seems to be applicable in this subset of patients, justifying the pursuit of the best possible response in elderly patients. Nevertheless, the higher rate of grade 3/4 toxicity associated with BBP stresses the importance of an adequate frailty assessment in these patients.

Author Contribution CJ collected data, designed the analysis, critically reviewed the analysis of the data, and wrote and review the manuscript.

RB, MN, SC, GE, and PL collected data, designed the analysis, and reviewed the manuscript.

SE analyzed the data and reviewed the manuscript.

CA, JB, MB, HC, CF, CG, CG, AJ, AM, TM, AM, AR, AS, FT, and HV collected data and reviewed the manuscript.

Compliance with ethical standards

Conflict of interest CJ has received a research grant from Takeda and has received speaker honorarium/participation in advisory boards from Celgene, Janssen, Takeda, and Amgen. MN received a speaker honorarium from Janssen, Takeda, Amgen, and Celgene. RB has received a research grant: from APCL/SPH/AMGEN and Celgene and speaker honoraria/advisory board from Celgene, Janssen, Takeda, and Amgen. SC has received speaker honorarium or participation in Advisory Boards from Takeda, Janssen, Celgene, Sanofi, Bristol-Myers Squibb, and Abbvie. CG has received honoraria from Janssen, Celgene, Amgen, and Takeda for lectures and participation in advisory boards. JB declares that he has no conflict of interest. HV has received honoraria from Celgene and Amgen for participation in advisory boards. ABS declares that she has no conflict of interest. TM declares that she has no conflict of interest. AM declares that she has no conflict of interest. AR declares that she has no conflict of interest. SE declares that she has no conflict of interest. AM declares that she has no conflict of interest. FT has received honoraria for speaker services from Takeda, Amgen, Celgene, Janssen, and attendance at advisory boards for Takeda, Amgen, Celgene, and Janssen. HC declares that he has no conflict of interest. CG has received honoraria from Celgene, Amgen, and Janssen for participation in advisory boards. CF has received honoraria for speaker services, attendance at advisory boards, and travel reimbursement from Sanofi Genzyme. MB has received honoraria for speaker services from Janssen and attendance at advisory boards of Celgene, Amgen, Janssen, Takeda, and Merck. GE has received research grants and speaker honorarium from Celgene, Janssen, and Amgen. CA has received honorarium for participation in advisory boards from Amgen, Celgene, Janssen, and Takeda. AJ received a speaker honorarium from Celgene, Janssen, and Novartis. PL has received speaker honorarium/participation in advisory boards from Celgene, Janssen, Takeda, and Amgen.

Ethical approval All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. (2017) National Cancer Institute SEER. In: National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER). 2017. http://www.seer.cancer.gov. Accessed 2017
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386. https://doi.org/10.1002/ijc.29210
3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, Forman D, Bray F (2013) Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer (Oxford, England : 1990) 49:1374–1403. https://doi.org/10.1016/j.ejca.2012.12.027
4. Fonseca R, Abouzaid S, Bonafede M, Cai Q, Parikh K, Cosler L, Richardson P (2017) Trends in overall survival and costs of multiple myeloma, 2000-2014. Leukemia 31:1915–1921. https://doi.org/10.1038/leu.2016.380
5. Schaapveld M, Visser O, Siesling S, Schaar CG, Zweegman S, Vellenga E (2010) Improved survival among younger but not among older patients with multiple myeloma in the Netherlands, a population-based study since 1989. Eur J Cancer (Oxford, England : 1990) 46:160–169. https://doi.org/10.1016/j.ejca.2009.07.006
6. Pulte D, Gondos A, Brenner H (2011) Improvement in survival of older adults with multiple myeloma: results of an updated period

analysis of SEER data. Oncologist 16:1600–1603. https://doi.org/10.1634/theoncologist.2011-0229
7. Bringhen S, Mateos MV, Zweegman S, Larocca A, Falcone AP, Oriol A, Rossi D, Cavalli M, Wijermans P, Ria R, Offidani M, Lahuerta JJ, Liberati AM, Mina R, Callea V, Schaafsma M, Cerrato C, Marasca R, Franceschini L, Evangelista A, Teruel AI, van der Holt B, Montefusco V, Ciccone G, Boccadoro M, Miguel JS, Sonneveld P, Palumbo A (2013) Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials. Haematologica 98:980–987. https://doi.org/10.3324/haematol.2012.075051
8. Anderson K (2014) Multiple myeloma: advances reported in 2013 are useful in the clinic. J Natl Compr Cancer Netw 12:808–811
9. Kristinsson SY, Anderson WF, Landgren O (2014) Improved long-term survival in multiple myeloma up to the age of 80 years. Leukemia 28:1346–1348. https://doi.org/10.1038/leu.2014.23
10. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S, Gay F, Attal M, Passera R, Spencer A, Offidani M, Kumar S, Musto P, Lonial S, Petrucci MT, Orlowski RZ, Zamagni E, Morgan G, Dimopoulos MA, Durie BGM, Anderson KC, Sonneveld P, San Miguel J, Cavo M, Rajkumar SV, Moreau P (2015) Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 33:2863–2869. https://doi.org/10.1200/JCO.2015.61.2267
11. Mikhael JR, Dingli D, Roy V, Reeder CB, Buadi FK, Hayman SR, Dispenzieri A, Fonseca R, Sher T, Kyle RA, Lin Y, Russell SJ, Kumar S, Bergsagel PL, Zeldenrust SR, Leung N, Drake MT, Kapoor P, Ansell SM, Witzig TE, Lust JA, Dalton RJ, Gertz MA, Stewart K, Rajkumar SV, Chanan-Khan A, Lacy MQ (2013) Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clinic proceedings Mayo Clinic 88:360–376. https://doi.org/10.1016/j.mayocp.2013.01.019
12. Zweegman S, Palumbo A, Bringhen S, Sonneveld P (2014) Age and aging in blood disorders: multiple myeloma. Haematologica 99:1133–1137. https://doi.org/10.3324/haematol.2014.110296
13. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, Kapoor P, Dingli D, Hayman SR, Leung N, Lust J, McCurdy A, Russell SJ, Zeldenrust SR, Kyle RA, Rajkumar SV (2014) Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 28:1122–1128. https://doi.org/10.1038/leu.2013.313
14. Larocca A, Palumbo A (2015) How I treat fragile myeloma patients. Blood 126:2179–2185. https://doi.org/10.1182/blood-2015-05-612960
15. Bergin K, McQuilten Z, Moore E, Wood E, Spencer A (2017) Myeloma in the real world: what is really happening? Clin Lymphoma Myeloma Leuk 17:133–144.e1. https://doi.org/10.1016/j.clml.2016.12.002
16. Palumbo A, Bringhen S, Mateos M-V, Larocca A, Facon T, Kumar SK, Offidani M, McCarthy P, Evangelista A, Lonial S, Zweegman S, Musto P, Terpos E, Belch A, Hajek R, Ludwig H, Stewart AK, Moreau P, Anderson K, Einsele H, Durie BGM, Dimopoulos MA, Landgren O, San Miguel JF, Richardson P, Sonneveld P, Rajkumar SV (2015) Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood 125:2068–2074. https://doi.org/10.1182/blood-2014-12-615187
17. Facon T, Hulin C, Dimopoulos MA, et al (2015) A frailty scale predicts outcomes of patients with newly diagnosed multiple myeloma who are ineligible for transplant treated with continuous lenalidomide plus low-dose dexamethasone on the FIRST trial
18. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BGM, Miguel JFS (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15:e538–e548. https://doi.org/10.1016/S1470-2045(14)70442-5
19. Rajkumar SV (2016) Updated diagnostic criteria and staging system for multiple myeloma. Am Soc Clin Oncol Educ Book 35:e418–ee23. https://doi.org/10.14694/EDBK_159009
20. Kumar A, Hozo I, Wheatley K, Djulbegovic B (2011) Thalidomide versus bortezomib based regimens as first-line therapy for patients with multiple myeloma: a systematic review. Am J Hematol 86:18–24. https://doi.org/10.1002/ajh.21904
21. Palumbo A, Bringhen S, Caravita T et al (2006) Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 367:825–831. https://doi.org/10.1016/S0140-6736(06)68338-4