Bortezomib-based therapy in non-transplant multiple myeloma patients: a retrospective cohort study from the FABIO project

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Abstract

Introduction: Randomized clinical trials showed that bortezomib, in addition to conventional chemotherapy, improves survival and disease progression in multiple myeloma (MM) patients not eligible for stem cell transplantation. The aim of this retrospective population-based cohort study is the evaluation of both clinical and economic profile of bortezomib-based *versus* conventional chemotherapy in daily clinical practice.

Methods: Healthcare utilization databases of six Italian regions were used to identify adult patients with non-transplant MM, who started a first-line therapy with bortezomib-based or conventional chemotherapy. Patients were matched by propensity score and were followed from treatment start until death, lost to follow-up or study end-point. Overall survival (OS) and restricted mean survival time (RMST) were estimated using the Kaplan–Meier method. Association between first-line treatment and risk of death was estimated by a conditional Cox proportional regression model. Average mean cumulative costs were estimated and compared between groups.

Results: In the period 2010–2016, 3509 non-transplant MM patients met the inclusion criteria, of which 1157 treated with bortezomib-based therapy were matched to 1826 treated with conventional chemotherapy. Median OS and RMST were 33.9 and 27.9 months, and 42.9 and 38.4 months, respectively, in the two treatment arms. Overall, these values corresponded to a HR of death of 0.79 (95% CI 0.71–0.89) over a time horizon of 84 months. Average cumulative cost were 83,839 € and 54,499 €, respectively, corresponding to an incremental cost-effectiveness ratio of 54,333 € per year of life gained, a cost coherent with the willingness-to-pay thresholds frequently adopted from Western countries.

Conclusions: These data suggested that, in a large cohort of non-transplant MM patients treated outside the experimental setting, first-line treatment with bortezomib-based therapy was associated with a favourable effectiveness and cost-effectiveness profile.

Keywords: multiple myeloma, bortezomib, effectiveness, cost-effectiveness, real-world

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Introduction

Multiple myeloma (MM) accounts for 1% of all cancers and about 10% of all haematological malignancies.[1] The incidence in Europe is 4.5–6.0/100,000 per year, with a median age at diagnosis ranging from 65 to 70 years.[2] In Italy, MM accounts for about 5700 incident cases and 3200 deaths per year. Survival estimates at 1 and 5 years are ~80% and ~51%, respectively.[3]

Treatment of MM mainly depends on the patient's age. In young patients (aged ≤65 years) in good clinical condition (fit patients), induction followed by high-dose therapy with autologous stem cell

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transplantation is the standard treatment.[4,5] In older patients (aged >65 years), oral combinations of melphalan and prednisone plus novel agents are considered as standards of care in Europe. Bortezomib (Velcade®, Jannsen-Cilag, Belgium) is the first proteasome inhibitor approved in 2003 by the US Food and Drug Administration (FDA) for the treatment of relapsed and/or refractory MM patients progressing after two prior therapies. In 2008 the FDA, and in mid-2009 the Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA), approved bortezomib also for the treatment of previously untreated MM patients ineligible for stem cell transplantation. This approval was granted after the pivotal phase III VISTA trial showed that 334 previously untreated MM patients not eligible for stem cell transplantation treated with bortezomib in addition to conventional chemotherapy were associated with a 39% reduction of death ($p < 0.001$), as compared with 338 controls, after 2 years of follow-up.[6] Two updated follow-up of the VISTA trial, prolonged to 48 and 60 months, confirmed the main result, showing, respectively, 35% ($p < 0.001$)[7] and 31% reduced risk of death ($p < 0.001$) in patients treated with bortezomib.[8] Despite the efficacy of bortezomib in the prevention of disease recurrence and death that was impressively reported in randomized clinical trials (RCTs), no evidence about its added value is available in real-world populations of patients not eligible for stem cell transplantation. Therefore, the present study aims at evaluating the long-term overall survival (OS) and costs associated with initial treatment with bortezomib-based therapy, compared with conventional chemotherapy, in a wide population-based cohort of non-transplant MM patients in clinical practice. The study is a part of an Italian project funded by AIFA and the Health Department of the Sardinia Region, which supported the so-called FABIO programme (Biologic Drugs in Oncology, the Italian acronym being Farmaci Biologici in Oncologia). The FABIO project aimed at evaluating the profile of safety, effectiveness and cost-effectiveness of biologic drugs approved for treating cancer.

Methods

Setting
The Italian National Health Service (NHS) provides universal and free-of-charge healthcare services considered essential, including cancer medicaments. The service is administered within each of the 21 Italian regions by an automated system of healthcare utilization (HCU) databases that collect a variety of individual-patient-level information, for each of the beneficiaries of the NHS. The FABIO programme was conducted by retrieving HCU data from six Italian regions localized at Northern (Lombardy), Central (Lazio and Marche), Southern (Abruzzo) and Insular (Sardinia and Sicily) Italy. Overall, data covered more than 25 million beneficiaries of the Italian NHS, nearly 42% of the entire Italian population. Details of regional HCU databases of Italy and of the FABIO network have been previously reported.[9] Specific diagnostic and therapeutic codes used for this study are reported in Supplementary material (Table S1).

Cohort selection, exposure definition and follow-up
All NHS beneficiaries with a diagnosis of MM were selected during a recruitment period that varied in a time-span comprised between 2010 and 2016, based on data availability of participating regions. The date of the first hospital admission for MM was defined as the 'index date'. In order to select only incident cases, patients who received diagnosis of malignancy and/or underwent chemotherapy within 5 years before the index date were excluded. Patients younger than 18 years at index date and those who died during the index hospitalization were further excluded. Among the remaining patients, only those who did not undergo stem cell transplantation after the index date and who started drug therapy within 6 months after the index date were included in the study cohort.

The date of the first cancer drug dispensation after MM diagnosis was defined as 'treatment start'. Cohort members were classified as exposed to first-line bortezomib-based therapy or to conventional chemotherapy, according whether during 42 days following the treatment start (i.e. the duration of a treatment cycle with bortezomib[10]) they did or did not receive at least a bortezomib dispensation, respectively.

Each cohort member accumulated person-years of follow-up from the date of treatment start until death (i.e. the outcome of interest), lost to follow-up (i.e. emigration), or study end-point, whichever came first. Study end-point was the last date

with data available within each region (i.e. in a time-span comprised between 31 December 2016 and 30 June 2018).

Baseline characteristics

Baseline covariates included age, gender and year of MM diagnosis. In addition, a previous history of diabetes, bone, renal, circulatory, pulmonary, and stomach disease, mental disorders, as well as a previous history of treatment with bisphosphonates, was assessed for all cohort patients in the 3 years preceding the index date.

Matching cohort arms

To reduce the between treatments heterogeneity, a propensity score (PS) matched analysis was performed.[11] A multivariable logistic regression was used to model the probability of being treated with bortezomib (i.e. the PS), given a set of covariates. The latter were those above-listed as baseline characteristics, in addition to the number of hospitalizations, outpatient services and drug prescriptions in the year before the index date. Each patient belonging to the bortezomib arm (index case) was matched with up to two patients randomly selected from those on standard arm with the same PS value of the corresponding index case, with a tolerated difference of ±0.01.

Statistical analyses

Between-arm differences in baseline characteristics were tested by the chi-square statistics. Overall survival was estimated by using the Kaplan–Meier (KM) estimator. To increase the precision of the estimates, between-region summarized KM curves were estimated. As regional data were not available to be analysed in a pooled analysis, a method for reconstructing individual patients' data starting from each regional KM curve was applied. Briefly, digital software was used to read the coordinates of KM curves within each region. Information on the number of patients still alive at each year of follow-up and the total number of deaths was used to solve the inverted KM equation, which allowed reconstruction of regional data for each arm, so obtaining pooled individual patients' data.[9,12] Median survivals and restricted mean survival times (RMST) were reported as descriptive measures of survival in the two treatment arms. RMST, that is

the area under the KM curve, represents the average survival time experienced by cohort members.[13,14] The association between exposure to bortezomib and risk of death was estimated by means of a conditional Cox proportional hazard model. Estimates were expressed as Hazard Ratio (HR), along with 95% Confidence Intervals (CI). As regional data were not available to be analysed in a pooled analysis, the so-called two-stage meta-analysis was performed to increase the precision of the estimates.[15] Briefly, the proportional hazard model was first fitted separately within each region, and then between-region summarized HR was estimated by means of a fixed-effect model, using the inverse variance weighting.[16] Between-regions heterogeneity was evaluated by using the chi-square statistics[17] and was measured through the I^2 index,[18] which measures the percentage of variation across the regions due to heterogeneity.

Finally, limited to data from the Lombardy Region (i.e. the largest Region among those included in the FABIO programme) cumulative healthcare cost (CHC) in both treatment arms were calculated by means of the Bang and Tsiatis estimator,[19] a method that takes into account censored cost data. For each patient, CHC were calculated by summing up direct costs sustained by the NHS for both inpatient and outpatient services, and drug dispensations supplied during follow-up. The incremental cost-effectiveness ratio (ICER) was measured by dividing the differences in healthcare costs (CHC) and health-related outcomes (measured by the RMST) between the two treatment arms (bortezomib arm and conventional chemotherapy). The ICER represents the healthcare expenditure expected to be saved (or added, depending on the sign) for gaining 1 year of life due to starting therapy with bortezomib. Non-parametric bootstrap method based on 1000 re-samples[20] was used to explore the uncertainty in the cost-effectiveness estimates.[21]

Sensitivity analyses

Two sensitivity analyses were performed in order to assess the robustness of the main results. These analyses were only performed on data from Lombardy Region. First, in the study cohort were included all patients who started cancer treatment after the index date, not limiting the inclusion only to patients treated within 6 months from index date. Second, because of the arbitrariness
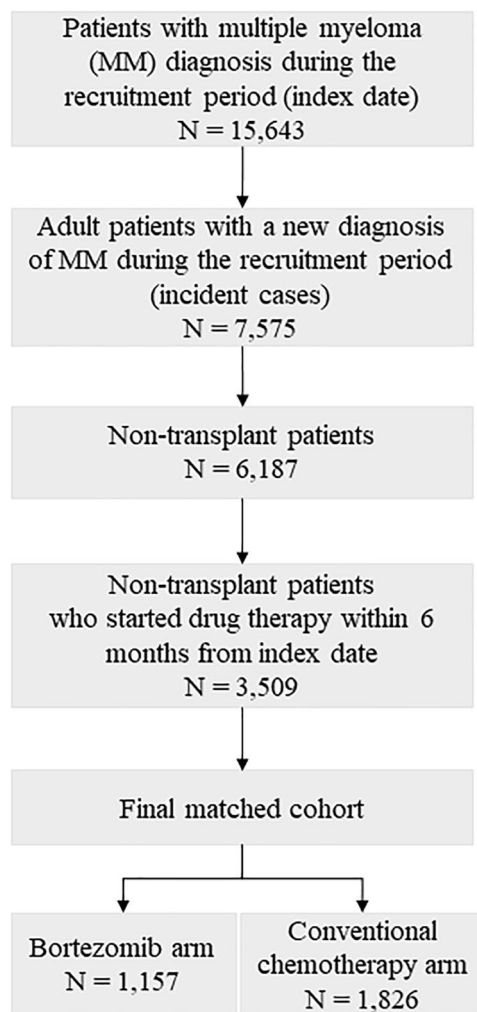
Figure 1. Flow-chart of inclusion and exclusion criteria. FABIO project, Italy, 2010–2016.

in the choice of the time-window used for defining first-line therapy (42 days), a shorter time-window of 21 days was considered for classifying patients into first-line bortezomib of conventional chemotherapy arm.

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All *p*-values were two-sided.

The study protocol was approved by the Ethical Committee of the University of Milano-Bicocca (number 'Prot. 506_2016'), which established the study (i) to be exempt from informed consent

(according to General Authorization for the Processing of Personal Data for Scientific Research Purposes Issued by the Italian Privacy Authority on August 10, 2018; https://www.gpdp. it/web/guest/home/docweb/-/docweb-display/ docweb/9124510), (ii) provides sufficient guarantees of anonymizing individual records, and (iii) was designed according to quality standards of good practice of observational research based on secondary data.

Results

Study cohort
Out of 15,643 MM patients identified during the recruitment period from the six regions participating in the study, 7575 were adult incident cases, surviving after the index hospitalization. Among the 6187 (81.7%) patients who did not undergo stem cell transplantation, 3509 were treated within 6 months after diagnosis with either bortezomib-based therapy ($n = 1325$, 37.8%) or conventional chemotherapy ($n = 2184$, 62.2%). Finally, 1157 patients treated with bortezomib-based therapy were matched to 1826 patients treated with conventional chemotherapy. The process of selection of the study cohort is reported in Figure 1 (region-specific data are reported in Supplementary material, Figure S1).

In the unmatched cohort, patients treated with bortezomib-based therapy were younger ($p < 0.001$) and had a lower prevalence of bone ($p = 0.047$), circulatory ($p < 0.001$) and pulmonary disease ($p < 0.001$), and there was a lower prevalence of users of bisphosphonates ($p = 0.006$). On the contrary, they had a higher prevalence of renal disorders ($p = 0.012$). However, after matching, no between-arm differences were observed. Baseline characteristics of both unmatched and matched cohorts are reported in Table 1.

Overall survival
After a mean follow-up of 21.4 months, 780 (67.4%) and 1222 (66.9%) deaths were observed among patients on bortezomib-based and conventional chemotherapy, respectively. The pattern of OS among the two treatment arms is shown in Figure 2. Survival estimates at 12, 36 and 60 months from the date of treatment start

Table 1. Comparison between baseline characteristics of multiple myeloma patients belonging to the unmatched and propensity score (PS)-matched cohorts on first-line treatment with bortezomib-based or conventional chemotherapy alone. FABIO project, Italy, 2010–2016.

	Unmatched cohort members		PS-matched cohort members	
	Bortezomib-based therapy (*n* = 1325)	Conventional chemotherapy (*n* = 2184)	Bortezomib-based therapy (*n* = 1157)	Conventional chemotherapy (*n* = 1826)
Gender				
Men	678 (51.2)	1079 (49.4)	581 (50.2)	935 (51.2)
Women	647 (48.8)	1105 (50.6)	576 (49.8)	891 (48.8)
p-value†	0.311		0.599	
Age at diagnosis (years)				
<60	99 (7.5)	169 (7.7)	59 (5.1)	103 (5.6)
60–69	328 (24.8)	375 (17.2)	273 (23.6)	489 (26.8)
70–79	716 (54.0)	902 (41.3)	661 (57.1)	998 (54.7)
≥80	182 (13.7)	738 (33.8)	164 (14.2)	236 (12.9)
p-value†	<0.001		0.187	
Bone diseases	236 (17.8)	449 (20.6)	216 (18.7)	313 (17.1)
p-value†	0.046		0.287	
Renal diseases	365 (27.5)	519 (23.8)	283 (24.5)	412 (22.6)
p-value†	0.012		0.232	
Circulatory diseases	481 (36.3)	938 (43.0)	418 (36.1)	613 (33.6)
p-value†	<0.001		0.152	
Pulmonary diseases	50 (3.8)	195 (8.9)	46 (4.0)	85 (4.7)
p-value†	<0.001		0.378	
Diabetes	239 (18.0)	408 (18.7)	208 (18.0)	379 (20.8)
p-value†	0.634		0.063	
Mental disorders	35 (2.6)	76 (3.5)	30 (2.6)	33 (1.8)
p-value†	0.169		0.146	
Stomach	64 (4.8)	112 (5.1)	208 (18.0)	379 (20.8)
p-value†	0.659		0.063	
Use of bisphosphonates	119 (9.0)	261 (12.0)	109 (9.4)	186 (10.2)
p-value†	0.006		0.495	
†Chi-square test.				
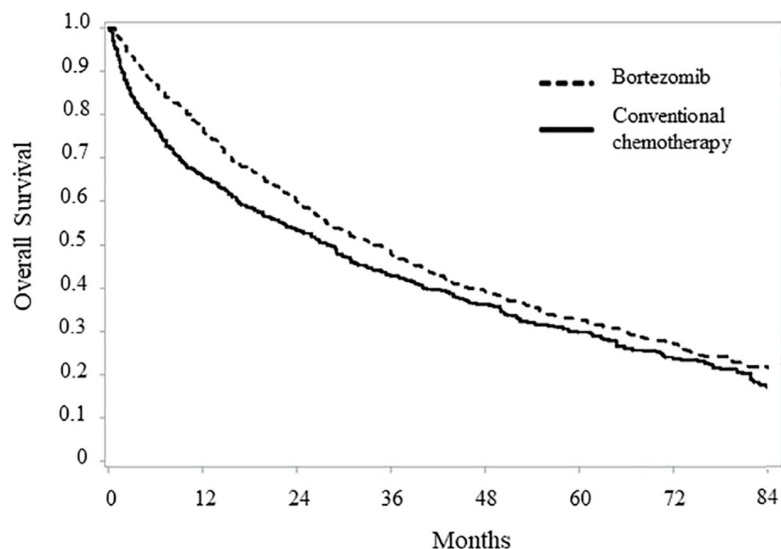
Figure 2. Comparison between Kaplan–Meier overall survival curves of non-transplant multiple myeloma patients on first-line treatment with bortezomib-based or conventional chemotherapy. FABIO project, Italy, 2010–2016.
Cohort members selected with a propensity score matched design were included in this analysis.

Region-specific survival curves are reported in Supplementary Material, Figure S2, confirming, overall, the national data.

Healthcare costs

Cumulative NHS healthcare costs according to therapeutic strategy are shown in Figure 4. Overall, 82,808 € and 54,154 € were spent, on average, for each patient belonging to bortezomib and standard arms, respectively, over a time horizon of 84 months after starting therapy. The average cost of a patient on treatment with bortezomib therapy included 17,140 € for hospitalization, 8127 € for outpatients services and 58,572 € for drugs. Corresponding figures for a patient on treatment with standard chemotherapy were 17,479 €, 8104 € and 28,916 €, respectively. The cost-effectiveness profile is shown in Figure 5. The ICER value indicated an average cost of 54,333 € for each year of life gained by the treatment with bortezomib. The ICER value was suggestive of clinical effectiveness (longer survival for patients on bortezomib), constrained to higher healthcare costs, in all of the 1000 bootstrap replications.

were 76.8%, 47.7% and 32.9%, among patients on bortezomib therapy, compared with 66.0%, 42.8% and 29.8% among those on conventional chemotherapy. Median OS was 33.9 and 27.9 months, respectively ($p < 0.001$), and RMST was 42.9 and 38.4 months, respectively ($p = 0.001$). Overall, these data correspond to a HR of death of 0.79 (95% CI 0.71–0.89) (Figure 3).

Sensitivity analyses

In the main analysis on Lombardy data, 603 patients treated with bortezomib were 1:1 matched to patients treated with conventional chemotherapy, and the HR of death was 0.72 (0.61–0.85). These results did not change substantially after
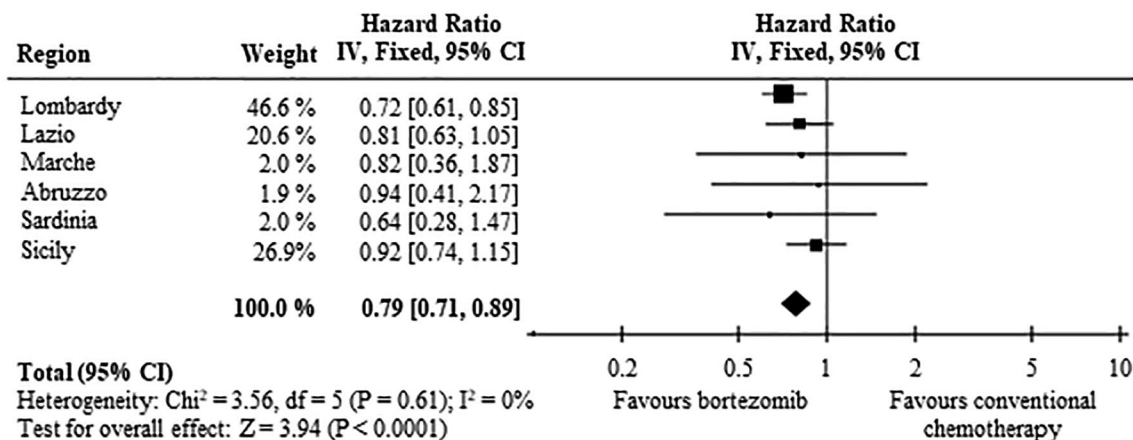

Figure 3. Forest plot of the summarized associations between first-line treatment with bortezomib, compared with conventional chemotherapy, and risk of death. Estimates are shown for each participant region, and by summarizing region-specific hazard ratios.

performing sensitivity analyses. When all patients treated after diagnosis were included in the study cohort (without restricting the entry cohort to those who started therapy within 6 months from diagnosis), 701 matched pairs generated a HR of death equal to 0.70 (0.59–0.82). Further, when a period of 21 days was considered for defining the first-line treatment with either bortezomib or conventional chemotherapy (instead of 42 days), 524 matched pairs gave a HR of death equal to 0.76 (0.63–0.91).

Discussion

The present study assessed the long-term survival of non-transplant MM patients, in a large population-based study involving six different geographic areas in Italy. In this setting, patients treated with first-line bortezomib were associated with a HR of death of 0.79 (95% CI 0.71–0.89), as compared with those treated with conventional chemotherapy. These results are coherent with those observed in the pivotal VISTA trial.[6] However, as patients included in our study were older (the median age was 74 *versus* 71 years) and had more concomitant conditions than those included in the trial, a lower OS was observed in our cohort. To the best of our knowledge, the current study represents the only evidence available in the scientific literature about the effectiveness of bortezomib, outside the experimental setting. Only a prospective observational post-marketing study carried out in Germany showed that bortezomib-containing regimens, as compared with standard care, increased overall response rates from 50.0% to 65.9%. However, given the small sample size (353 patients treated with bortezomib-containing regimens and 37 patients treated with conventional chemotherapy), the authors could not perform any statistical test to compare the observed differences.[22] Thus, the evidence on the favourable effect of bortezomib are limited to experimental designs. Two recent network meta-analyses of RCTs showed that bortezomib-containing regimens were superior to conventional chemotherapy in improving OS, indicating a large convergence of the results coming from RCTs.[23,24] Despite this, a prospective clinical cohort study involving Cancer Registries in Germany classified 285 non-transplant MM patients in trial-eligible and trial-ineligible patients, showing that about one-third of the cohort had baseline characteristics that would have precluded their inclusion in clinical trials.
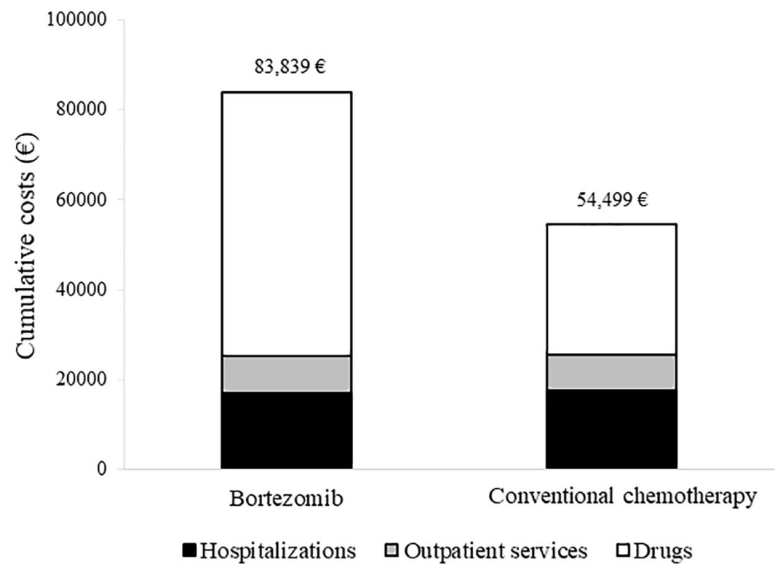
Figure 4. Comparison between cumulative per capita healthcare costs sustained by the NHS for caring non-transplant multiple myeloma patients on first-line treatment with bortezomib or conventional chemotherapy. FABIO project, Italy, 2010–2016.
Cohort members selected with a propensity score matched design were included in this analysis. The Bang and Tsiatis estimator was used for estimating cumulative costs (see text).
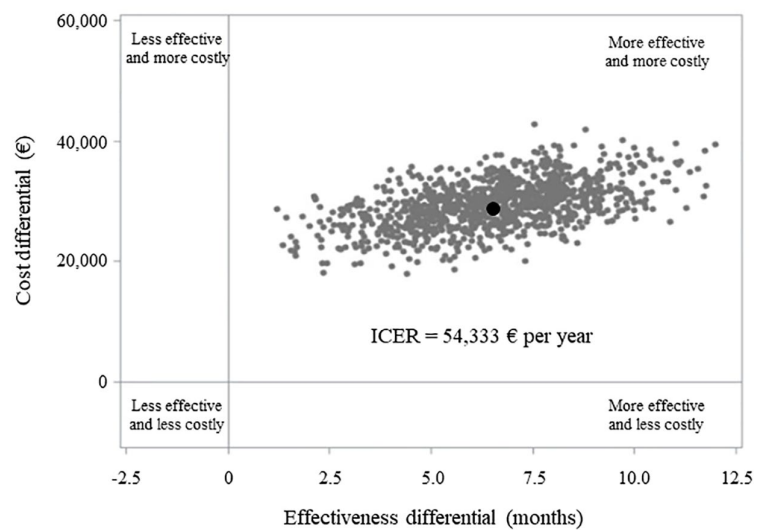
Figure 5. ICER scatterplot comparing non-transplant multiple myeloma patients on first-line treatment with bortezomib or conventional chemotherapy. FABIO project, Lombardy Region, 2010–2015.
Costs were calculated from the amount that the Regional Health Authority reimbursed to health providers. The average survival time was calculated by means of the restricted mean survival time.
The incremental cost-effectiveness ratio (ICER) was measured by dividing the differences in healthcare costs and health-related outcomes between the two treatment arms (i.e. bortezomib and conventional chemotherapy). Non-parametric bootstrap method based on 1000 re-samples was used to explore the uncertainty in the estimates of cost-effectiveness. The black circle represents the ICER observed in our cohort.

As expected, survival was considerably shorter for trial-ineligible patients.[25] An evaluation of the clinical impact of bortezomib in the real-world clinical practice was, therefore, essential in this context. Other than the clinical impact, the current study also aimed at evaluating the economic impact of bortezomib on the NHS. A systematic review of published cost-effectiveness analysis showed that bortezomib-based therapy was cost-effective for previously untreated stem cell transplantation-ineligible patients, as compared with conventional chemotherapy, in the USA, Canada, the UK and Sweden.[26] In particular, the USA study found an incremental cost per life-year gained of 86,213 \$.[27] In our cohort, the mean cost for each life-year gained with bortezomib treatment was 54,333 €, a cost coherent with the willingness-to-pay thresholds ranging from €50 thousands to \$100 thousands per year of life gained frequently adopted in Western countries.[28,29]

Our study has several strengths. First, it represents the first study carried out in a real-world setting that evaluated the effectiveness and the cost-effectiveness profile of bortezomib-based therapy, as compared with conventional chemotherapy. Second, the study cohort included patients resident and diagnosed in several geographical areas of Italy, including Northern, Central, Southern and Insular regions, guaranteeing the representativeness of routine clinical practice in Italy and the generalizability of the results, and reflecting the potential heterogeneity in the management of MM. Indeed, the study cohort included all the potential NHS beneficiaries who had a new diagnosis of MM during the recruitment period, with no restriction on age and comorbidities, and the target population from which the study cohort was selected represents almost 42% of the Italian population. Finally, the extended follow-up allowed a long-term evaluation of survival and costs associated with MM patients.

On the other hand, the main weakness of this study is the paucity of data on individual traits, clinical features and drug patterns and regimens, which may result in systematic bias due to confounding. Indeed, as in all observational studies, treatment arms may be unbalanced for some characteristics also associated with the baseline risk of death. Factors such as ethnicity or socioeconomic status can be confidently excluded because Italy population is largely Caucasian and free-of-pay access to cancer care is ensured for all NHS beneficiaries. In addition, in order to better take into account measurable confounding, a PS matching design was used. Other unmeasured factors, however, might affect our conclusions, including clinical features (i.e. performance status or the stage of the disease) and therapeutic regimens (i.e. doses and combination therapies), which were not available in administrative databases.

In conclusion, the current study supports the available evidence about a favourable effect on OS of first-line bortezomib-based therapy, as compared with conventional chemotherapy, in a large real-world cohort of non-transplant MM patients. In addition, the results also confirm the cost-effective profile of bortezomib. However, the recent approval of new therapeutic regimens that combine bortezomib with melphalan and prednisone (VMP) or with lenalidomide and dexamethasone (VRd) require future real-world studies evaluating the value of bortezomib in these new therapeutic strategies.

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Supplemental material

Supplemental material for this article is available online.

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