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Effectiveness and safety of bortezomib in the treatment of multiple myeloma: a systematic review protocol

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Title: Effectiveness and safety of bortezomib in the treatment of multiple myeloma: a systematic review protocol

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Abstract

Introduction: Multiple myeloma (MM) is an incurable malignant neoplasm that accounts for approximately 1% of all cancers and 10% of hematological malignancies. Bortezomib is one of the most commonly used medications in first-line treatment and subsequent relapses, either as a single agent or in combination with other therapies. We aim to assess the effects of bortezomib on the overall survival (OS), progression-free survival, overall response rate, time to next treatment, health-related quality of life, compliance, adverse events, and treatment-related death in MM patients.

Methods and Analysis: We will perform a systematic review and meta-analysis and will include both randomized and non-randomized controlled studies where the efficacy of bortezomib was compared in similar or dissimilar background therapies in each arm. General and adaptive search strategies were created for the following electronic health databases: Embase, Medline, LILACS, and CENTRAL. Two reviewers will independently select eligible studies, assess the risk of bias, and extract data from the included studies. Similar outcomes will be plotted in the meta-analysis using the Stata Statistical Software 17. The relative risk will be calculated with a 95% confidence interval as the effect size of bortezomib. For the OS and PFS, we calculate the overall odds ratio (OR) from the hazard ratios of each included study. Peto's one-step OR will be calculated for event rates below 1%. We will use the Grading of Recommendations Assessment, Development, and Evaluation system to evaluate the certainty of evidence.

Ethics and Dissemination: As no primary data collection will be undertaken, formal ethical assessment is not required. We plan to present the results of this systematic review in a peer-reviewed scientific journal, conferences, and popular press.

Registration Number: Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on April 24, 2020 (registration number CRD42020151142).

Keywords: Myeloma, Multiple Myeloma, Bortezomib, Systematic Review, Meta-Analysis

Strengths and Limitations of this study

- Trial eligibility evaluation, risk of bias assessment, and data excretion will be performed by teams of reviewers, independently and in pairs.
- We will include randomized clinical trials (RCTs) and non-RCTs.
- We will apply the GRADE approach to evaluate our confidence in the effect estimates of each intervention.
- The potential causes of heterogeneity between studies are anticipated and will be evaluated by subgroup analysis.
- We expect variability in effect estimates among the different treatment interventions.

Introduction

Multiple myeloma (MM) is a malignant neoplasm characterized by clonal proliferation of plasmocytes; it is the neoplastic counterpart of terminally differentiated B cells that suffered oncogenic events during their development. Neoplastic plasmocytes establish firm and precise relationships with the microenvironment of the bone marrow stroma, with a bond of co-dependence and positive feedback. The neoplastic cells secrete varying amounts of a para-immunoglobulin called monoclonal protein (detectable in the blood and/or urine), and leads to the development of organic lesions characterized by anemia, bone lysis (which may lead to pathological fractures), hypercalcemia, and renal failure. Further, this is also associated with recurrent infections due to tumor-induced immunosuppression, and the inability of the immune system to adequately produce physiologically functioning immunoglobulins.[1]

MM accounts for approximately 1% of all cancers and 10% of hematological neoplasms, the second most common in this category.[2] In 2018, approximately 160,000 cases were diagnosed globally, with an estimated incidence in 185 countries.[3] The frequency is slightly higher in men, the occurrence is twice high in blacks than in Caucasians, and the average age at diagnosis is around 65 years.[4]

MM is considered an incurable disease, with periods of remission interspersed with recurrences and retreatment. With each new treatment, the disease tends to respond less, and therefore, remains controlled for decreased duration.[5] The principles of antineoplastic therapy are currently based on the induction period (4–6 month cycles), followed by autologous stem cell transplantation (ASCT) in eligible patients, and subsequent maintenance until disease progression (relapse) or toxicity. Patients not eligible for transplantation receive 2–4 consolidation cycles with the same chemotherapy regimen of induction cycles followed by maintenance.[6]

Treatment paradigms have changed dramatically over the last two decades. By the end of 1990, the therapy was based on corticosteroids, alkylating agents, and anthracyclines (cyclophosphamide, cisplatin, dexamethasone/prednisone, doxorubicin, etoposide, and melphalan), resulting in a median overall survival of approximately 30 months, with a 5-year survival rate of 30–35%.[7] However, new therapies have emerged in the last 20 years and resulted in a significant improvement in the MM patients survivals, especially in developed countries. In the United States and Europe, the 5-year survival rate was increased to 50–55% in this period.[8 9] The initial impact of this transformation was observed after the introduction of thalidomide, bortezomib, and lenalidomide into the therapeutic arsenal.[10-12] In an observational study evaluating 387 patients who relapsed after ASCT, an increased median survival (2 years) was noticed in patients treated with one or more of these three therapies.[7] Additionally, in the last 8 years, several therapeutic options have been made available for relapsed patients, including carfilzomib, ixazomib, panobinostat, elotuzumab, pomalidomide, daratumumab, and selinexor. This has allowed generating a large number of treatment combinations capable of prolonging the patient's survival.[6]

In Brazil, thalidomide, bortezomib, lenalidomide, carfilzomib, elotuzumab, ixazomib, and daratumumab have been approved by the National Health Surveillance Agency (ANVISA) and are available for use. However, the vast majority of these therapies are not available in public health system, and restricted only to private clinic patients, which comprise only 25% of the Brazilian population. The Brazilian health ministry by its "Diagnostic and Therapeutic Guidelines for Multiple Myeloma" has incorporated bortezomib as the first-line MM therapy; however, real-world studies (especially in Latin America) demonstrating the efficacy of bortezomib was missing.[13 14] After the official Brazilian government guidelines, a few studies have shown the benefits of bortezomib in different scenarios in Europe, Asia, and Latin

America. [15-18] A retrospective study of a cohort of 1,103 patients from Latin America (287 from Brazil) showed that the bortezomib treatments were mostly restricted to private clinic patients and yielded better outcomes, despite eligibility for ASCT.[17] After the recent incorporation that bortezomib is an important addition to the limited therapeutic arsenal for individuals with MM in Brazil and other countries, there is an expectation of the overall survival (OS) gain in patients who previously did not have access to new drugs.

In 2016, a systematic review published in the Cochrane database on the use of bortezomib for the treatment of MM highlighted a statistically significant improvement in important clinical outcomes (such as the OS), reinforcing its indication as a standard therapy for the disease.[19] However, this review included only randomized clinical trials (RCTs) published until 2016 and did not include observational studies, therefore lacking real-world data and more recent RCTs.

The objective of this review is to evaluate the efficacy, effectiveness, and safety of bortezomib in the treatment of MM in patients over 18 years of age, eligible or not eligible for ASCT, and first-line or relapsed.

METHODS AND ANALYSIS

The proposed systematic review will be conducted in accordance with the JBI methodology for systematic reviews of effectiveness.[20] The protocol of this review has been registered with the PROSPERO database (registration number: CRD42020151142) and was developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[21]

Patient and Public Involvement

We did not directly include patient-level data in this study, but during the protocol development, priority of the research question, choice of outcome measures, and type of interventions were informed by the members of the Brazilian Health Ministry, which identified this research as a priority area for managing MM patients in Brazil.

Eligibility criteria

This study will meet the "PICO" structure described below:

Participants (P)

We will include studies on adults (regardless of sex) over 18 years of age meeting the International Myeloma Working Group diagnostic criteria for MM, eligible or not eligible for ASCT, undergoing first-line treatment, or relapse.

Intervention (I)/ Comparator (C)

This review will consider studies that evaluate the differences between:[19]

1. Similar backbone treatment regimens with or without bortezomib. For example, bortezomib/lenalidomide, dexamethasone (VRd)/lenalidomide, and dexamethasone (Rd).
2. Dissimilar backbone treatment regimens with or without bortezomib. For example, bortezomib/melphalan/prednisone (VMP) versus Rd.

Outcomes (O)

The primary outcomes will be the OS and progression-free survival (time from date of randomisation/allocation to date of death (from any cause)), according to the International Myeloma Working Group criteria. The secondary outcomes will include the overall response rate (the proportion of patients with the overall response), adherence, time to next treatment (time from randomisation/allocation to date of initiation of next treatment regimen or similar), adverse events (as defined by the National Cancer Institute Common Terminology Criteria for

Adverse Events), therapy-related deaths (death due to treatment-related toxicity, but not the disease progression), and quality of life (as defined by the validated quality of life measures or instruments used in each study). We will consider adherence to treatment of individuals who adhere to at least 80% of the proposed drug regimen. Individuals who were lost to follow-up, did not tolerate the treatment, and could not continue the proposed treatment will be included in this outcome.

Types of studies

This review will consider both the experimental and quasi-experimental study designs, including randomized/non-randomized controlled trials. In addition, analytical observational studies including prospective and retrospective cohort studies will be considered.

Exclusion criteria

We will exclude uncontrolled studies as well as those that did not evaluate any of the proposed outcomes.

Identification of studies

Electronic databases

Search strategies were applied to the following electronic health databases: Embase (by Elsevier, 1980–2022), Medline (by PubMed, 1966–2022), Latin American and Caribbean Health Sciences Literature (by Virtual Health Library, 1982–2022), and controlled clinical trials of the Cochrane Collaboration (Cochrane Central Register of Controlled Trials). We used the following index terms and their synonyms: multiple myeloma and bortezomib. Language or year restrictions were not considered in this study. References of relevant primary or secondary studies will be searched to identify additional eligible studies. Draft PubMed and Embase search strategies are included in supplementary file. References of relevant primary or secondary studies will be used in order to identify additional eligible studies.

Study selection

We will use EndNote 20 (Clarivate Analytics, PA, USA) to download all references and remove duplicates. Following a pilot test, titles and abstracts were screened by two independent reviewers for assessment against the inclusion criteria using the free web application Rayyan QCRI. [22]The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. The reasons for exclusion of full-text studies that did not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or by a third reviewer. The results of the search and study selection and inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[23]

Assessment of methodological quality

For the main outcomes from each selected trial, the risk of bias will be assessed independently and in pairs according to the standardized critical appraisal instruments from the JBI for experimental, quasi-experimental, and observational studies. Authors of papers will be contacted to request missing or additional data for clarification, wherever required. Any disagreements between the reviewers will be resolved through discussion or by a third reviewer. The results of the critical appraisal will be reported in a table with an accompanying narrative. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible). The judgement of the overall risk of bias will be made using one of three categories: low risk (if the criterion was adequately fulfilled in all domains), high risk (if the criterion was not fulfilled in at least one domain), unclear risk (if the report did not provide sufficient information to allow for a judgement and the risk of bias is

unknown in at least one domain). If possible, the results of the critical appraisal will be incorporated into the sensibility analysis using a meta-analysis approach.

Data extraction

Data will be extracted from studies included in the review by two independent reviewers using the standardized JBI data extraction tool. The data extracted will include specific details about the year of publication, country, sample size, follow-up time, eligibility criteria (inclusion and exclusion criteria), type of intervention and control, outcomes analyzed, and risk of bias. Patient characteristics (age, sex, staging, and cytogenetic risk) were also extracted. Authors of papers will be contacted to request missing or additional data, wherever required.

To ensure consistency between the reviewers, we will perform a calibration exercise before beginning the review. In the case of duplicate publications or multiple reports from the primary study, data extraction will be optimized using the best information available for all items in the same study. There will be a discussion between the reviewers and VSNN (guarantor of this proposed review) in case of disagreements.

Measurement of treatment effect

For the primary outcomes, we will extract the hazard ratios (HR) and their 95% confidence intervals (CI); we will calculate the overall odds ratio (OR) and 95% CI for the combined results using the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[24] For the other dichotomous data, the relative risk will be calculated with 95% CIs as the estimate of the intervention effect. Peto's one-step OR will be calculated for the event rates below 1%.[24] Continuous data will be expressed as mean ± standard deviation, and the differences between the mean values with 95% CIs will be used as estimates of the intervention effect.

Unit of analysis

The unit of analysis will be the data published in the included studies. For the studies that did not provide an intention-to-treat analysis, we will consider the number of patients randomized/allocated in each group, and for patients who missed the follow-up, we input as absent.

Lack of data

The authors of the original studies will be contacted, if necessary, to obtain missing data. We will use the data available in published articles provided by their authors or registration platforms. If available, we will preferentially use data from intention-to-treat analysis.

Evaluation of publication bias

If more than 10 trials are included in the meta-analysis of a specific outcome, we will use funnel plots to investigate the presence of publication bias.[25] An asymmetry may indicate the presence of such bias, in which case Egger regression tests will be applied.

Data synthesis

Similar outcomes will be plotted in the meta-analysis using Stata Statistical Software 17 (Stata Statistical Software: Release 17. College Station, TX, StataCorp LLC, USA). We will select the random effects model for the meta-analysis, and the studies will be evaluated separately according to their designs. If quantitative synthesis is not appropriate, narrative synthesis will be provided.

Sensitivity analysis

If possible, we plan to perform a sensitivity analysis by subgroup evaluation of studies with high, low, and unclear overall risk of bias.

Subgroup analysis

If enough data are available, subgroup analyses will be performed according to age (greater than or less than 65 years), staging (ISS I, II or III), cytogenetic risk (standard or high), and intervention scheme (1 and 2). We will use the instrument credibility of effect modification analyses (ICEMAN tool) to assess the credibility of the subgroups.[26]

Heterogeneity assessment

Inconsistencies between the results of the included studies will be ascertained by visual inspection of forest plots (no overlap of CIs around the effect estimates of the individual studies), by Higgins or I^2 statistic, in which I^2 >50% indicates a moderate probability of heterogeneity, and by chi-squared tests (Chi^2), where p <0.10 indicates heterogeneity. Meta-regression will be used to explore the causes of the inconsistencies. We will use age (greater than or less than 65 years), staging (ISS I, II, or III), cytogenetic risk (standard or high), and intervention scheme (1 and 2). The Knapp–Hartung correction was used to calculate the significance of the meta-regression coefficients. In the case of I^2 >30% (in more than five studies), the prediction interval (PI) from the random-effects meta-analyses was used because PI predicts the potential underlying effect in a new study, which is different from the average effect from the meta-analyses.[24]

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a summary of findings will be created using GRADEpro GDT (McMaster University, ON, Canada).[27] The summary of findings will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication

bias of the review results. For non-RCTs, ranking of the quality of the evidence will also be based on the presence of a large effect, plausible confounding, and dose response gradient. The outcomes reported in the summary of findings will be the OS, progression-free survival, overall response rate, adherence, time to next treatment, therapy-related deaths, and quality of life.

ACKNOWLEDGEMENT

We thank Dr. Lehana Thabane for motivating us to publish this systematic review protocol, and we thank Editage for reviewing the language of our manuscript.

ETHICS DISSEMINATION

As no primary data collection will be undertaken, no formal ethical assessment is required by our institution. We plan to present the results of this systematic review in a peer-reviewed scientific journal. We also intend to present this, including preliminary findings, at appropriate conferences.

AUTHOR CONTRIBUTIONS

VSNN is the guarantor for this review. All authors developed the systematic review protocol, which was drafted by VSNN and LOC and revised by RDG. VSNN has developed the search strategies. LOC and RDG will independently screen eligible studies, extract data from included studies, and assess the risk of bias. LOC will elaborate on the standard extract form. VSNN will supervise all phases of this review and referee any disagreement to avoid any errors. All authors participated in data synthesis and quality of evidence. All authors critically revised the manuscript and approved the final version.

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COMPETING INTERESTS STATEMENT

LOC reports advisory board consultancy for Janssen, conference meeting support from Janssen and Amgen, speaker honoraria from Janssen, Bristol Myers Squibb, and Amgen.

RDG reports advisory board consultancy for Janssen and Abbvie, conference meeting support from Janssen, Roche, and Takeda; speaker honoraria from Janssen, Takeda, Bristol Myers Squibb, and Abbvie.

VSNN, none to declare.

REFERENCES

1. Palumbo A, Anderson K. Multiple myeloma. *The New England journal of medicine* 2011;364(11):1046-60. doi: 10.1056/NEJMra1011442 [published Online First: 2011/03/18]
2. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology* 2014;15(12):e538-48. doi: 10.1016/S1470-2045(14)70442-5 [published Online First: 2014/12/03]
3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424. doi: 10.3322/caac.21492 [published Online First: 2018/09/13]
4. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic proceedings* 2003;78(1):21-33. doi: 10.4065/78.1.21 [published Online First: 2003/01/17]
5. Kurtin S. Relapsed or Relapsed/Refractory Multiple Myeloma. *J Adv Pract Oncol* 2013;4(6):10.
6. Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2018;93(8):981-1114. doi: 10.1002/ajh.25117 [published Online First: 2018/11/08]
7. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;111(5):2516-20. doi: 10.1182/blood-2007-10-116129 [published Online First: 2007/11/03]
8. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014;28(5):1122-8. doi: 10.1038/leu.2013.313 [published Online First: 2013/10/26]
9. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood* 2008;111(5):2521-6. doi: 10.1182/blood-2007-08-104984 [published Online First: 2007/09/29]
10. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *The New England journal of medicine* 1999;341(21):1565-71. doi: 10.1056/NEJM199911183412102 [published Online First: 1999/11/24]

11. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *The New England journal of medicine* 2005;352(24):2487-98. doi: 10.1056/NEJMoa043445 [published Online First: 2005/06/17]
12. Richardson PG, Blood E, Mitsiades CS, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood* 2006;108(10):3458-64. doi: 10.1182/blood-2006-04-015909 [published Online First: 2006/07/15]
13. Saúde Md. Bortezomibe para o tratamento de pacientes adultos com mieloma múltiplo previamente tratados. In: Conitec, ed., 2020:28.
14. Saúde Md. Bortezomibe para o tratamento de pacientes adultos com mieloma múltiplo, não previamente tratados, elegíveis ao transplante autólogo de célulastronco hematopoiéticas. In: Conitec, ed., 2020:29.
15. Fujisawa M, Suehara Y, Fukumoto K, et al. Changes in survival rate of multiple myeloma after the introduction of bortezomib: a single institutional experience over 20 years. *Ann Hematol* 2016;95(1):63-72. doi: 10.1007/s00277-015-2522-9 [published Online First: 2015/10/27]
16. Hungria VTM, Lee JH, Maiolino A, et al. Survival differences in multiple myeloma in Latin America and Asia: a comparison involving 3664 patients from regional registries. *Ann Hematol* 2019;98(4):941-49. doi: 10.1007/s00277-019-03602-4 [published Online First: 2019/02/08]
17. de Moraes Hungria VT, Martinez-Banos DM, Penafiel CR, et al. Multiple myeloma treatment patterns and clinical outcomes in the Latin America Haemato-Oncology (HOLA) Observational Study, 2008-2016. *Br J Haematol* 2020;188(3):383-93. doi: 10.1111/bjh.16124 [published Online First: 2019/08/09]
18. Djebbari F, Srinivasan A, Vallance G, et al. Clinical outcomes of bortezomib-based therapy in myeloma. *PloS one* 2018;13(12):e0208920. doi: 10.1371/journal.pone.0208920 [published Online First: 2018/12/13]
19. Scott K, Hayden PJ, Will A, et al. Bortezomib for the treatment of multiple myeloma. *Cochrane Database Syst Rev* 2016;4:CD010816. doi: 10.1002/14651858.CD010816.pub2 [published Online First: 2016/04/21]
20. Tufanaru C MZ, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis: JBI, 2020, 2020.
21. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)* 2015;350:g7647. doi: 10.1136/bmj.g7647 [published Online First: 2015/01/04]
22. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4 [published Online First: 2016/12/07]
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151(4):W65-94. doi: 10.7326/0003-4819-151-4-200908180-00136 [published Online First: 2009/07/23]
24. Higgins JPTT, J., editor. *Cochrane Handbook for Systematic Reviews of Interventions*. Second ed. Oxford: The Cochrane Collaboration and John Wiley & Sons Ltd., 2019.
25. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629 [published Online First: 1997/10/06]
26. Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ : Canadian Medical Association journal = journal de l'Association*

medicale canadienne 2020;192(32):E901-E06. doi: 10.1503/cmaj.200077 [published Online First: 2020/08/12]

27. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ (Clinical research ed)* 2016;353:i2089. doi: 10.1136/bmj.i2089 [published Online First: 2016/07/02]

SUPPLEMENTARY FILE

Search Strategy

PubMed

#1"Multiple Myeloma"[Mesh] OR (Myeloma)

#2"Bortezomib"[Mesh] OR (Velcade)

*#3 ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

** # 4 (cohort[all] OR (control[all] AND study[all]) OR (control[tw] AND group*[tw]) OR epidemiologic studies[mh] OR program[tw] OR clinical trial[pt] OR comparative stud*[all] OR evaluation studies[all] OR statistics as topic[mh] OR survey*[tw] OR follow-up*[all] OR time factors[all] OR ci[tw]) NOT ((animals[mh:noexp] NOT humans[mh:noexp]) OR comment[pt] OR editorial[pt] OR review[pt] OR meta analysis[pt] OR case report[tw] OR consensus[mh] OR guideline[pt] OR history[sh])

*Filter for RCT PubMed. sensitivity- and precision-maximizing version (2008 revision); PubMed format. https://work.cochrane.org/pubmed

** Waffenschmidt S et al. Development and validation of study filters for identifying controlled non-randomized studies in PubMed and Ovid MEDLINE. Search filter with best sensitivity for controlled NRS (PubMed)
https://doi.org/10.1002/jrsm.1425

#1 AND #2 AND (#3 OR #4)

Embase

#1 ('bortezomib'/exp OR 'velcade'/exp) AND [embase]/lim

#2 ('mieloma múltiplo'/exp OU 'mieloma'/exp) AND [embase]/lim

#3 random:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti

#4 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp

*Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association: JMLA. 2006 Jan;94(1):41-7

#1 AND #2 AND (#3 OR #4)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Sources	#5a	Indicate sources of financial or other support for the review	14-15
Sponsor	#5b	Provide name for the review funder and / or sponsor	14-15
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-8
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such	7-9

		as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-12
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp. Data
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9-10
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-12

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-12
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11-12
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	11-13
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13-14

BMJ Open

Title: Effectiveness of bortezomib in the treatment of multiple myeloma: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061808.R1
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Title: Effectiveness of bortezomib in the treatment of multiple myeloma: a systematic review protocol

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Abstract

Introduction: Multiple myeloma (MM) is an incurable malignant neoplasm that accounts for approximately 1% of all cancers and 10% of hematological malignancies. Bortezomib is one of the most commonly used medications in first-line treatment and subsequent relapses, either as a single agent or in combination with other therapies. We aim to assess the effects of bortezomib on the overall survival (OS), progression-free survival, overall response rate, time to next treatment, health-related quality of life, compliance, adverse events, and treatment-related death in MM patients.

Methods and Analysis: We have performed a systematic review and meta-analysis and will include both randomized and non-randomized controlled studies where the efficacy of bortezomib was compared in similar or dissimilar background therapies in each arm. General and adaptive search strategies were created for the following electronic health databases: Embase, Medline, LILACS, and CENTRAL. Two reviewers have independently selected eligible studies, and will assess the risk of bias, and extract data from the included studies. Similar outcomes will be plotted in the meta-analysis using the Stata Statistical Software 17. The relative risk will be calculated with a 95% confidence interval as the effect size of bortezomib. For the OS and PFS, we calculate the overall odds ratio (OR) from the hazard ratios of each included study. Peto's one-step OR will be calculated for event rates below 1%. We will use the Grading of Recommendations Assessment, Development, and Evaluation system to evaluate the certainty of evidence.

Ethics and Dissemination: As no primary data collection will be undertaken, formal ethical assessment is not required. We plan to present the results of this systematic review in a peer-reviewed scientific journal, conferences, and popular press.

Registration Number: Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on April 24, 2020 (registration number CRD42020151142).

Keywords: Myeloma, Multiple Myeloma, Bortezomib, Systematic Review, Meta-Analysis

Strengths and Limitations of this study

- Trial eligibility evaluation, risk of bias assessment, and data extraction will be performed by teams of reviewers, independently and in pairs.
- We will include randomized clinical trials (RCTs) and non-RCTs.
- We will apply the GRADE approach to evaluate our confidence in the effect estimates of each intervention.
- The potential causes of heterogeneity between studies are anticipated and will be evaluated by subgroup analysis.
- We expect variability in effect estimates among the different treatment interventions.

Introduction

Multiple myeloma (MM) is a malignant neoplasm characterized by clonal proliferation of plasmocytes; it is the neoplastic counterpart of terminally differentiated B cells that suffered oncogenic events during their development. Neoplastic plasmocytes establish firm and precise relationships with the microenvironment of the bone marrow stroma, with a bond of co-dependence and positive feedback. The neoplastic cells secrete varying amounts of a para-immunoglobulin called monoclonal protein (detectable in the blood and/or urine), and leads to the development of organic lesions characterized by anemia, bone lysis (which may lead to pathological fractures), hypercalcemia, and renal failure. Further, this is also associated with recurrent infections due to tumor-induced immunosuppression, and the inability of the immune system to adequately produce physiologically functioning immunoglobulins.[1]

MM accounts for approximately 1% of all cancers and 10% of hematological neoplasms, the second most common in this category.[2] According to the Global Cancer Observatory statistics, there were an estimated 160,000 cases of MM globally in 2018.[3] The frequency is slightly higher in men, the occurrence is twice high in blacks than in Caucasians, and the average age at diagnosis is around 65 years.[4]

MM is considered an incurable disease, with periods of remission interspersed with recurrences and retreatment. With each new treatment, the disease tends to respond less, and therefore, remains controlled for decreased duration.[5] The principles of antineoplastic therapy are currently based on the induction period (4–6 month cycles), followed by autologous stem cell transplantation (ASCT) in eligible patients, and subsequent maintenance until disease progression (relapse) or toxicity. Patients not eligible for transplantation are typically treated with 2–4 consolidation cycles with the same chemotherapy regimen of induction cycles followed by maintenance.[6]

Treatment paradigms have changed dramatically over the last two decades. By the end of 1990, the therapy was based on corticosteroids, alkylating agents, and anthracyclines (cyclophosphamide, cisplatin, dexamethasone/prednisone, doxorubicin, etoposide, and melphalan), resulting in a median overall survival of approximately 30 months, with a 5-year survival rate of 30–35%.[7] However, new therapies have emerged in the last 20 years and resulted in a significant improvement in survival, especially in developed countries. In the United States and Europe, the 5-year survival rate was increased to 50–55% in this period.[8 9] The initial impact of this transformation was observed after the introduction of thalidomide, bortezomib, and lenalidomide into the therapeutic arsenal.[10-12] In an observational study evaluating 387 patients who relapsed after ASCT, an increased median survival (2 years) was noticed in patients treated with one or more of these three therapies.[7] Additionally, in the last 8 years, several therapeutic options have been made available for relapsed patients, including carfilzomib, ixazomib, panobinostat, elotuzumab, pomalidomide, daratumumab, belantamab mofadotin and selinexor. This has allowed generating a large number of treatment combinations capable of prolonging the patient's survival.[6]

In Brazil, immunomodulatory imides (thalidomide/Lenalidomide), bortezomib, carfilzomib, elotuzumab, ixazomib, and daratumumab have been approved by the National Health Surveillance Agency (ANVISA) and are available for use. However, the vast majority of these therapies are not available in public health system, and restricted only to private clinic patients, which comprise only 25% of the Brazilian population. The Brazilian health ministry by its "Diagnostic and Therapeutic Guidelines for Multiple Myeloma" has incorporated bortezomib as the first-line MM therapy; however, real-world studies (especially in Latin America) demonstrating the efficacy of bortezomib was missing.[13 14] After the official Brazilian government guidelines, a few studies have shown the benefits of bortezomib in

different scenarios in Europe, Asia, and Latin America. [15-18] A retrospective study of a cohort of 1,103 patients from Latin America (287 from Brazil) showed that the bortezomib treatments were mostly restricted to private clinic patients and yielded better outcomes, regardless of ASCT eligibility.[17] After the recent incorporation that bortezomib is an important addition to the limited therapeutic arsenal for individuals with MM in Brazil and other countries, there is an expectation of the overall survival (OS) gain in patients who previously did not have access to new drugs.

In 2016, a systematic review published in the Cochrane database on the use of bortezomib for the treatment of MM highlighted a statistically significant improvement in important clinical outcomes (such as the OS), reinforcing its indication as a standard therapy for the disease.[19] However, this review included only randomized clinical trials (RCTs) published until 2016 and did not include observational studies, therefore lacking real-world data and more recent RCTs.

The objective of this review is to evaluate the efficacy, effectiveness, and safety of bortezomib in the treatment of MM in patients over 18 years of age, regardless of treatment setting and ASCT eligibility.

METHODS AND ANALYSIS

The proposed systematic review has been conducted in accordance with the JBI methodology for systematic reviews of effectiveness.[20] The protocol of this review has been registered with the PROSPERO database (registration number: CRD42020151142) and was developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[21]

Patient and Public Involvement

We did not directly include patient-level data in this study, but during the protocol development, priority of the research question, choice of outcome measures, and type of interventions were informed by the members of the Brazilian Health Ministry, which identified this research as a priority area for managing MM patients in Brazil.

Eligibility criteria

This study will meet the "PICO" structure described below:

Participants (P)

We will include studies on adults (regardless of sex) over 18 years of age meeting the International Myeloma Working Group diagnostic criteria for MM, eligible or not eligible for ASCT, undergoing first-line treatment, or relapse.

Intervention (I)/ Comparator (C)

This review will consider studies that evaluate the differences between:[19]

1. Similar backbone treatment regimens with or without bortezomib. For example, bortezomib/lenalidomide, dexamethasone (VRd)/lenalidomide, and dexamethasone (Rd).
2. Dissimilar backbone treatment regimens with or without bortezomib or bortezomib compared to other agents. For example, bortezomib/melphalan/prednisone (VMP) versus Rd.

Outcomes (O)

The primary outcome will be progression-free survival (time from date of randomisation/allocation to date of death (from any cause)), according to the International Myeloma Working Group criteria. The secondary outcomes will include OS, overall response rate (the proportion of patients with the overall response), adherence, time to next treatment

(time from randomisation/allocation to date of initiation of next treatment regimen or similar), adverse events (as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events), therapy-related deaths (death due to treatment-related toxicity, but not the disease progression), and quality of life (as defined by the validated quality of life measures or instruments used in each study). We will consider adherence to treatment of individuals who adhere to at least 80% of the proposed drug regimen. Individuals who were lost to follow-up, did not tolerate the treatment, and could not continue the proposed treatment will be included in this outcome.

Types of studies

This review will consider both the experimental and quasi-experimental study designs, including randomized/non-randomized controlled trials. In addition, analytical observational studies including prospective and retrospective cohort studies will be considered.

Exclusion criteria

We will exclude uncontrolled studies as well as those that did not evaluate any of the proposed outcomes.

Identification of studies

Electronic databases

Search strategies were applied to the following electronic health databases: Embase (by Elsevier, 1980–2022), Medline (by PubMed, 1966–2022), Latin American and Caribbean Health Sciences Literature (by Virtual Health Library, 1982–2022), and controlled clinical trials of the Cochrane Collaboration (Cochrane Central Register of Controlled Trials). We used the following index terms and their synonyms: multiple myeloma and bortezomib. Language or year restrictions were not considered in this study. References of relevant primary or secondary studies will be searched to identify additional eligible studies. Draft PubMed and

Embase search strategies are included in supplementary file. References of relevant primary or secondary studies will be used in order to identify additional eligible studies.

Study selection

We used EndNote 20 (Clarivate Analytics, PA, USA) to download all references and remove duplicates. Following a pilot test, titles and abstracts have been screened by two independent reviewers for assessment against the inclusion criteria using the free web application Rayyan QCRI. [22]The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. The reasons for exclusion of full-text studies that did not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or by a third reviewer. The results of the search and study selection and inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[23]

Assessment of methodological quality

For the main outcomes from each selected trial, the risk of bias will be assessed independently and in pairs according to the standardized critical appraisal instruments from the JBI for experimental, quasi-experimental, and observational studies. Authors of papers will be contacted to request missing or additional data for clarification, wherever required. Any disagreements between the reviewers will be resolved through discussion or by a third reviewer. The results of the critical appraisal will be reported in a table with an accompanying narrative. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible). The judgement of the overall risk of bias will be made using one of three categories: low risk (if the criterion was adequately fulfilled in all

domains), high risk (if the criterion was not fulfilled in at least one domain), unclear risk (if the report did not provide sufficient information to allow for a judgement and the risk of bias is unknown in at least one domain). If possible, the results of the critical appraisal will be incorporated into the sensibility analysis using a meta-analysis approach.

Data extraction

Data will be extracted from studies included in the review by two independent reviewers using the standardized JBI data extraction tool. The data extracted will include specific details about the year of publication, country, sample size, follow-up time, eligibility criteria (inclusion and exclusion criteria), type of intervention and control, outcomes analysed, and risk of bias. Patient characteristics (age, sex, staging, and cytogenetic risk) will be also extracted. Authors of papers will be contacted to request missing or additional data, wherever required.

To ensure consistency between the reviewers, we will perform a calibration exercise before beginning the review. In the case of duplicate publications or multiple reports from the primary study, data extraction will be optimized using the best information available for all items in the same study. There will be a discussion between the reviewers and VSNN (guarantor of this proposed review) in case of disagreements.

Measurement of treatment effect

For the primary outcomes, we will extract the hazard ratios (HR) and their 95% confidence intervals (CI); we will calculate the overall odds ratio (OR) and 95% CI for the combined results using the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[24] For the other dichotomous data, the relative risk will be calculated with 95% CIs as the estimate of the intervention effect. Peto's one-step OR will be calculated for the event rates below 1%.[24] Continuous data will be expressed as mean ± standard deviation,

and the differences between the mean values with 95% CIs will be used as estimates of the intervention effect.

Unit of analysis

The unit of analysis will be the data published in the included studies. For the studies that did not provide an intention-to-treat analysis, we will consider the number of patients randomized/allocated in each group, and for patients who missed the follow-up, we input as absent.

Lack of data

The authors of the original studies will be contacted, if necessary, to obtain missing data. We will use the data available in published articles provided by their authors or registration platforms. If available, we will preferentially use data from intention-to-treat analysis.

Evaluation of publication bias

If more than 10 trials are included in the meta-analysis of a specific outcome, we will use funnel plots to investigate the presence of publication bias.[25] An asymmetry may indicate the presence of such bias, in which case Egger regression tests will be applied.

Data synthesis

Similar outcomes will be plotted in the meta-analysis using Stata Statistical Software 17 (Stata Statistical Software: Release 17. College Station, TX, StataCorp LLC, USA). We will select the random effects model for the meta-analysis, and the studies will be evaluated separately according to their designs. If quantitative synthesis is not appropriate, narrative synthesis will be provided.

Sensitivity analysis

If possible, we plan to perform a sensitivity analysis by subgroup evaluation of studies with high, low, and unclear overall risk of bias.

Subgroup analysis

If enough data are available, subgroup analyses will be performed according to age (greater than or less than 65 years), staging (ISS I, II or III), cytogenetic risk (standard or high), and intervention scheme (1 and 2). We will use the instrument credibility of effect modification analyses (ICEMAN tool) to assess the credibility of the subgroups.[26]

Heterogeneity assessment

Inconsistencies between the results of the included studies will be ascertained by visual inspection of forest plots (no overlap of CIs around the effect estimates of the individual studies), by Higgins or I^2 statistic, in which I^2 >50% indicates a moderate probability of heterogeneity, and by chi-squared tests (Chi^2), where p <0.10 indicates heterogeneity. Meta-regression will be used to explore the causes of the inconsistencies. We will use age (greater than or less than 65 years), staging (ISS I, II, or III), cytogenetic risk (standard or high), and intervention scheme (1 and 2). The Knapp–Hartung correction will be used to calculate the significance of the meta-regression coefficients. In the case of I^2 >30% (in more than five studies), the prediction interval (PI) from the random-effects meta-analyses will be used because PI predicts the potential underlying effect in a new study, which is different from the average effect from the meta-analyses.[24]

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a summary of

findings will be created using GRADEpro GDT (McMaster University, ON, Canada).[27] The summary of findings will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. For non-RCTs, ranking of the quality of the evidence will also be based on the presence of a large effect, plausible confounding, and dose response gradient. The outcomes reported in the summary of findings will be the OS, progression-free survival, overall response rate, adherence, time to next treatment, therapy-related deaths, and quality of life.

ACKNOWLEDGEMENT

We thank Dr. Lehana Thabane for motivating us to publish systematic review protocols, and we thank Editage for reviewing the language of our manuscript.

ETHICS DISSEMINATION

As no primary data collection will be undertaken, no formal ethical assessment is required by our institution. We plan to present the results of this systematic review in a peer-reviewed scientific journal. We also intend to present this, including preliminary findings, at appropriate conferences.

AUTHOR CONTRIBUTIONS

VSNN is the guarantor for this review. All authors developed the systematic review protocol, which was drafted by VSNN and LOC and revised by RDG. VSNN has developed the search strategies. LOC and RDG have independently screened eligible studies, they will extract data from included studies, and assess the risk of bias. LOC will elaborate on the standard extract form. VSNN have supervised all phases of this review and refereed any disagreement to avoid any errors. All authors will participate in data synthesis and quality of evidence. All authors critically revised the manuscript and approved the final version.

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COMPETING INTERESTS STATEMENT

LOC reports advisory board consultancy for Janssen, conference meeting support from Janssen and Amgen, speaker honoraria from Janssen, Bristol Myers Squibb, and Amgen.

RDG reports advisory board consultancy for Janssen and Abbvie, conference meeting support from Janssen, Roche, and Takeda; speaker honoraria from Janssen, Takeda, Bristol Myers Squibb, and Abbvie.

VSNN, none to declare.

REFERENCES

1. Palumbo A, Anderson K. Multiple myeloma. *The New England journal of medicine* 2011;364(11):1046-60. doi: 10.1056/NEJMra1011442 [published Online First: 2011/03/18]
2. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology* 2014;15(12):e538-48. doi: 10.1016/S1470-2045(14)70442-5 [published Online First: 2014/12/03]
3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424. doi: 10.3322/caac.21492 [published Online First: 2018/09/13]
4. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic proceedings* 2003;78(1):21-33. doi: 10.4065/78.1.21 [published Online First: 2003/01/17]
5. Kurtin S. Relapsed or Relapsed/Refractory Multiple Myeloma. *J Adv Pract Oncol* 2013;4(6):10.
6. Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2018;93(8):981-1114. doi: 10.1002/ajh.25117 [published Online First: 2018/11/08]
7. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;111(5):2516-20. doi: 10.1182/blood-2007-10-116129 [published Online First: 2007/11/03]

8. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014;28(5):1122-8. doi: 10.1038/leu.2013.313 [published Online First: 2013/10/26]
9. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood* 2008;111(5):2521-6. doi: 10.1182/blood-2007-08-104984 [published Online First: 2007/09/29]
10. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *The New England journal of medicine* 1999;341(21):1565-71. doi: 10.1056/NEJM199911183412102 [published Online First: 1999/11/24]
11. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *The New England journal of medicine* 2005;352(24):2487-98. doi: 10.1056/NEJMoa043445 [published Online First: 2005/06/17]
12. Richardson PG, Blood E, Mitsiades CS, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood* 2006;108(10):3458-64. doi: 10.1182/blood-2006-04-015909 [published Online First: 2006/07/15]
13. Saúde Md. Bortezomibe para o tratamento de pacientes adultos com mieloma múltiplo previamente tratados. In: Conitec, ed., 2020:28.
14. Saúde Md. Bortezomibe para o tratamento de pacientes adultos com mieloma múltiplo, não previamente tratados, elegíveis ao transplante autólogo de célulastronco hematopoiéticas. In: Conitec, ed., 2020:29.
15. Fujisawa M, Suehara Y, Fukumoto K, et al. Changes in survival rate of multiple myeloma after the introduction of bortezomib: a single institutional experience over 20 years. *Ann Hematol* 2016;95(1):63-72. doi: 10.1007/s00277-015-2522-9 [published Online First: 2015/10/27]
16. Hungria VTM, Lee JH, Maiolino A, et al. Survival differences in multiple myeloma in Latin America and Asia: a comparison involving 3664 patients from regional registries. *Ann Hematol* 2019;98(4):941-49. doi: 10.1007/s00277-019-03602-4 [published Online First: 2019/02/08]
17. de Moraes Hungria VT, Martinez-Banos DM, Penafiel CR, et al. Multiple myeloma treatment patterns and clinical outcomes in the Latin America Haemato-Oncology (HOLA) Observational Study, 2008-2016. *Br J Haematol* 2020;188(3):383-93. doi: 10.1111/bjh.16124 [published Online First: 2019/08/09]
18. Djebbari F, Srinivasan A, Vallance G, et al. Clinical outcomes of bortezomib-based therapy in myeloma. *PloS one* 2018;13(12):e0208920. doi: 10.1371/journal.pone.0208920 [published Online First: 2018/12/13]
19. Scott K, Hayden PJ, Will A, et al. Bortezomib for the treatment of multiple myeloma. *Cochrane Database Syst Rev* 2016;4:CD010816. doi: 10.1002/14651858.CD010816.pub2 [published Online First: 2016/04/21]
20. Tufanaru C MZ, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis: JBI, 2020, 2020.
21. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)* 2015;350:g7647. doi: 10.1136/bmj.g7647 [published Online First: 2015/01/04]
22. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4 [published Online First: 2016/12/07]
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151(4):W65-94. doi: 10.7326/0003-4819-151-4-200908180-00136 [published Online First: 2009/07/23]

24. Higgins JPTT, J., editor. *Cochrane Handbook for Systematic Reviews of Interventions*. Second ed. Oxford: The Cochrane Collaboration and John Wiley & Sons Ltd., 2019.
25. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629 [published Online First: 1997/10/06]
26. Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2020;192(32):E901-E06. doi: 10.1503/cmaj.200077 [published Online First: 2020/08/12]
27. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ (Clinical research ed)* 2016;353:i2089. doi: 10.1136/bmj.i2089 [published Online First: 2016/07/02]

SUPPLEMENTARY FILE

Search Strategy

PubMed

#1"Multiple Myeloma"[Mesh] OR (Myeloma)

#2"Bortezomib"[Mesh] OR (Velcade)

*#3 ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

** # 4 (cohort[all] OR (control[all] AND study[all]) OR (control[tw] AND group*[tw]) OR epidemiologic studies[mh] OR program[tw] OR clinical trial[pt] OR comparative stud*[all] OR evaluation studies[all] OR statistics as topic[mh] OR survey*[tw] OR follow-up*[all] OR time factors[all] OR ci[tw]) NOT ((animals[mh:noexp] NOT humans[mh:noexp]) OR comment[pt] OR editorial[pt] OR review[pt] OR meta analysis[pt] OR case report[tw] OR consensus[mh] OR guideline[pt] OR history[sh])

*Filter for RCT PubMed. sensitivity- and precision-maximizing version (2008 revision); PubMed format. https://work.cochrane.org/pubmed

** Waffenschmidt S et al. Development and validation of study filters for identifying controlled non-randomized studies in PubMed and Ovid MEDLINE. Search filter with best sensitivity for controlled NRS (PubMed)
https://doi.org/10.1002/jrsm.1425

#1 AND #2 AND (#3 OR #4)

Embase

#1 ('bortezomib'/exp OR 'velcade'/exp) AND [embase]/lim

#2 ('mieloma múltiplo'/exp OU 'mieloma'/exp) AND [embase]/lim

#3 random:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti

#4 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp

*Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association: JMLA. 2006 Jan;94(1):41-7

#1 AND #2 AND (#3 OR #4)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Sources	#5a	Indicate sources of financial or other support for the review	14-15
Sponsor	#5b	Provide name for the review funder and / or sponsor	14-15
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-8
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such	7-9

		as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-12
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp. Data
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9-10
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-12

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-12
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11-12
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	11-13
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13-14

BMJ Open

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Effect of bortezomib on the treatment of multiple myeloma: A systematic review protocol

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Abstract

Introduction: Multiple myeloma (MM) is an incurable malignant neoplasm that accounts for approximately 1% of all cancers and 10% of hematological malignancies. Bortezomib is one of the most commonly used medications in first-line treatment and subsequent relapses, either as a single agent or in combination with other therapies. This study aims to assess the effects of bortezomib on the overall survival (OS), progression-free survival, overall response rate, time to next treatment, health-related quality of life, compliance, adverse events, and treatment-related death in patients with MM.

Methods and Analysis: We have performed a systematic review and meta-analysis and will include both randomized and nonrandomized controlled studies where the effect of bortezomib was compared in similar or dissimilar background therapies in each arm. General and adaptive search strategies have been created for the following electronic health databases: Embase, Medline, LILACS, and CENTRAL. Two reviewers have independently selected eligible studies, will assess the risk of bias, and will extract data from the included studies. Similar outcomes will be plotted in the meta-analysis using the Stata Statistical Software 17. The relative risk will be calculated with a 95% confidence interval as the effect size of bortezomib. For the OS and progression-free survival, we calculate the overall odds ratio (OR) from the hazard ratios of each included study. Peto's one-step OR will be calculated for event rates below 1%. We will use the Grading of Recommendations Assessment, Development, and Evaluation system to evaluate the certainty of evidence.

Ethics and Dissemination: As no primary data collection will be undertaken, formal ethical assessment is not required. We plan to present the results of this systematic review in a peer-reviewed scientific journal, conferences, and popular press.

Registration Number: Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on April 24, 2020 (registration number CRD42020151142).

Keywords: Myeloma, Multiple Myeloma, Bortezomib, Systematic Review, Meta-Analysis

Strengths and Limitations of this study

- Trial eligibility evaluation, risk-of-bias assessment, and data extraction will be performed by teams of reviewers, independently and in pairs.
- We will include randomized clinical trials (RCTs) and non-RCTs.
- We will apply the GRADE approach to evaluate our confidence in the effect estimates of each intervention.
- The potential causes of heterogeneity between studies are anticipated and will be evaluated by subgroup analysis or meta-regression.
- We expect variability in effect estimates among the treatment interventions.

Introduction

Multiple myeloma (MM) is a malignant neoplasm characterized by clonal proliferation of plasmocytes; it is the neoplastic counterpart of terminally differentiated B cells that encountered oncogenic events during their development. Neoplastic plasmocytes establish firm and precise relationships with the microenvironment of the bone marrow stroma, with a bond of co-dependence and positive feedback. Neoplastic cells secrete varying amounts of monoclonal protein, a para-immunoglobulin detectable in the blood and/or urine, and leads to the development of organic lesions characterized by anemia, bone lysis (which may lead to pathological fractures), hypercalcemia, and renal failure. This is also associated with recurrent infections caused by tumor-induced immunosuppression and the inability of the immune system to adequately produce physiologically functioning immunoglobulins.[1]

MM accounts for approximately 1% of all cancers and 10% of hematological neoplasms, the second most common in this category.[2] According to the Global Cancer Observatory statistics, there were approximately 160,000 cases of MM globally in 2018.[3] The frequency is slightly higher in men, the occurrence is twice high in blacks than in whites, and the average age at diagnosis is approximately 65 years.[4]

MM is considered an incurable disease, with periods of remission interspersed with recurrences and retreatment. With each new treatment, the disease tends to respond less and, therefore, remains controlled for a decreased duration.[5] The principles of antineoplastic therapy are currently based on the induction period (4–6 month cycles), followed by autologous stem cell transplantation (ASCT) in eligible patients, and subsequent maintenance until disease progression (relapse) or toxicity. Patients unfit for transplantation are typically treated with 2–4 consolidation cycles, with the same chemotherapy regimen of induction cycles followed by maintenance.[6]

Treatment paradigms have changed dramatically over the last two decades. At the end of 1990, the therapy was based on corticosteroids, alkylating agents, and anthracyclines (such as cyclophosphamide, cisplatin, dexamethasone/prednisone, doxorubicin, etoposide, and melphalan), resulting in median overall survival of approximately 30 months, with a 5-year survival rate of 30%–35%.[7] However, new therapies have emerged in the last 20 years and led to a significant improvement in survival, especially in developed countries. In the United States and Europe, the 5-year survival rate increased to 50%–55% in this period.[8 9] The initial effect of this transformation was observed after the introduction of thalidomide, bortezomib, and lenalidomide into the therapeutic arsenal.[10-12] In an observational study of 387 patients who relapsed after ASCT, an increased median survival (2 years) was noticed in patients who received one or more of these three therapies.[7] Moreover, in the last 8 years, several therapeutic options have been made available for patients on relapse, including carfilzomib, ixazomib, panobinostat, elotuzumab, pomalidomide, daratumumab, belantamab mofodotin, and selinexor. This has allowed generating various treatment combinations capable of prolonging the patient's survival.[6]

In Brazil, immunomodulatory imides (thalidomide/lenalidomide), bortezomib, carfilzomib, elotuzumab, ixazomib, and daratumumab have been approved by the National Health Surveillance Agency and are available for use. However, these therapies are not available in the public health system and are restricted only to patients in private clinics, which comprise only 25% of the Brazilian population. The Brazilian health ministry by its "Diagnostic and Therapeutic Guidelines for Multiple Myeloma" has incorporated bortezomib as the first-line MM therapy; however, no real-world studies (especially in Latin America) have demonstrated the efficacy of bortezomib.[13 14] Following the introduction of the official Brazilian government guidelines, a few studies have revealed the benefits of bortezomib in

different scenarios in Europe, Asia, and Latin America.[15-18] A retrospective study of 1,103 patients from Latin America (287 from Brazil) reported that bortezomib treatments were mostly restricted to patients receiving treatment in private clinic and yielded better outcomes, regardless of ASCT eligibility.[17] After the recent incorporation that bortezomib is an important addition to the limited therapeutic arsenal for individuals with MM in Brazil and other countries, the overall survival (OS) gain is expected in patients who previously did not have access to new drugs.

In 2016, a systematic review published in the Cochrane database on the use of bortezomib for the treatment of MM highlighted a significant improvement in important clinical outcomes (such as the OS), reinforcing its indication as standard therapy for the disease.[19] However, this review included only randomized clinical trials (RCTs) published until 2016 and did not include observational studies; therefore, it lacks real-world data and more recent RCTs.

This study aims to assess the effect of bortezomib on the OS, progression-free survival (PFS), overall response rate, time to next treatment, health-related quality of life, compliance, adverse events, and treatment-related death in patients with MM by comparing bortezomib treatment with the treatment without bortezomib in patients with the same background therapies, different background therapies, or other therapeutic agents.

METHODS AND ANALYSIS

The proposed systematic review has been conducted in accordance with the JBI methodology for systematic reviews of effectiveness.[20] The protocol of this review has been registered with the PROSPERO database (Registration no. CRD42020151142) and was

developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[21]

Patient and Public Involvement

We did not directly include patient-level data in this study, but during the protocol development, priority of the research question, choice of outcome measures, and type of interventions were informed by the members of the Brazilian Health Ministry, which identified this research as a priority area for managing patients with MM in Brazil.

Eligibility criteria

This study will meet the "PICO" structure described below:

Participants (P)

We will include studies on adults (regardless of sex) aged >18 years who meet the International Myeloma Working Group diagnostic criteria for MM, eligible or not eligible for ASCT, undergo first-line treatment, or have a relapse.

Intervention (I)/ Comparator (C)

This review will consider studies that evaluate the differences between[19]:

1. Bortezomib treatment was compared with treatment without bortezomib under the same background therapy in the intervention and control groups, for example, bortezomib plus lenalidomide plus dexamethasone (VRd) versus lenalidomide plus dexamethasone (Rd).
2. Bortezomib treatment was compared with treatment without bortezomib under different background therapies in the intervention and control groups, or bortezomib was compared with other therapeutic agents, for example, bortezomib plus melphalan plus prednisone (VMP) versus Rd, or bortezomib versus dexamethasone, respectively.

Outcomes (O)

The primary outcome will be PFS (time from the date of randomization/allocation to the date of death (from any cause)) according to the International Myeloma Working Group criteria. The secondary outcomes will include OS, overall response rate (the proportion of patients with the overall response), adherence, time to next treatment (time from randomization/allocation to the date of the initiation of the next treatment regimen or similar), adverse events (as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events), therapy-related deaths (death due to treatment-related toxicity, but not disease progression), and quality of life (as defined by the validated quality-of-life measures or instruments used in each study). We will consider adherence to treatment of individuals who adhere to at least 80% of the proposed drug regimen. Individuals who were lost to follow-up, did not tolerate the treatment, and could not continue the proposed treatment will be included in this outcome.

Types of studies

This review will consider both experimental and quasi-experimental study designs, including randomized/nonrandomized controlled trials. In addition, analytical observational studies including prospective and retrospective cohort studies will be considered.

Exclusion criteria

We will exclude uncontrolled studies and those that did not evaluate any of the proposed outcomes.

Identification of studies

Electronic databases

Search strategies have been applied to the following electronic health databases: Embase (by Elsevier, 1980–2022), Medline (by PubMed, 1966–2022), Latin American and

Caribbean Health Sciences Literature (by Virtual Health Library, 1982–2022), and controlled clinical trials of the Cochrane Collaboration (Cochrane Central Register of Controlled Trials). We have used the following index terms and their synonyms: multiple myeloma and bortezomib. Language or year restrictions will not be considered in this study. References of relevant primary or secondary studies will be searched to identify additional eligible studies. Draft PubMed and Embase search strategies are included in the supplementary file. References of relevant primary or secondary studies will be used to identify additional eligible studies.

Study selection

We have used EndNote 20 (Clarivate Analytics, PA, USA) to download all references and remove duplicates. Following a pilot test, titles and abstracts have been screened by two independent reviewers for assessment against the inclusion criteria using the free web application Rayyan QCRI.[22] The full text of selected articles will be assessed in detail against the inclusion criteria by two independent reviewers. The reasons for the exclusion of full-text studies that did not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or by a third reviewer. The results of the search and study selection and inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram.[23]

Assessment of methodological quality

For the main outcomes from each selected trial, the risk of bias will be assessed independently and in pairs according to the standardized critical appraisal instruments from the JBI for experimental, quasi-experimental, and observational studies. Authors of papers will be contacted to request missing or additional data for clarification, wherever required. Any

disagreements between the reviewers will be resolved through discussion or by a third reviewer. The results of the critical appraisal will be reported in a table with an accompanying narrative. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible). The judgment of the overall risk of bias will be made using one of three categories: low risk (if the criterion was adequately fulfilled in all domains), high risk (if the criterion was not fulfilled in at least one domain), unclear risk (if the report did not provide sufficient information to allow for a judgment and the risk of bias is unknown in at least one domain). If possible, the results of the critical appraisal will be incorporated into the sensibility analysis using a meta-analysis approach.

Data extraction

Data will be extracted from studies included in the review by two independent reviewers using the standardized JBI data extraction tool. Data extracted will include specific details about the year of publication, country, study design, sample size, follow-up time, eligibility criteria (inclusion and exclusion criteria), type of intervention and control, outcomes analyzed, and risk of bias. Patient characteristics (such as age, sex, staging, and cytogenetic risk) will be extracted as well. Authors of papers will be contacted to request missing or additional data, wherever required.

To ensure consistency between the reviewers, we will perform a calibration exercise before beginning the review. In the case of duplicate publications or multiple reports from the primary study, data extraction will be optimized using the best information available for all items in the same study. A discussion will ensue between the reviewers and VSNN (guarantor of this proposed review) in case of disagreements.

Measurement of treatment effect

We will measure the effect of bortezomib in the treatment of MM in two analyses: (1) combining studies of bortezomib versus those without bortezomib in individuals with the same background therapy in each arm, and (2) combining studies of bortezomib versus those without bortezomib in individuals with different background therapies in each arm and studies of bortezomib versus those with other therapeutic agents. For the primary outcomes, we will extract the hazard ratios (HR) and their 95% confidence intervals (CI). We will calculate the overall odds ratio (OR) and 95% CI for the combined results using the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[24] For other dichotomous data, the relative risk will be calculated with 95% CIs as the estimate of the intervention effect. Peto's one-step OR will be calculated for the event rates below 1%.[24] Continuous data will be expressed as mean ± standard deviation, and the differences between the mean values with 95% CIs will be used as estimates of the intervention effect.

Unit of analysis

The unit of analysis will be the data published in the included studies. For the studies that did not provide an intention-to-treat analysis, we will consider the number of patients randomized/allocated in each group, and for patients who missed the follow-up, we input them as absent.

Lack of data

The authors of the original studies will be contacted, if necessary, to obtain missing data. We will use the data available in published articles provided by their authors or registration platforms. If available, we will preferentially use data from the intention-to-treat analysis.

Evaluation of publication bias

If more than 10 trials are included in the meta-analysis of a specific outcome, we will use funnel plots to investigate the presence of publication bias.[25] An asymmetry may indicate the presence of such bias, in which case Egger regression tests will be applied.

Data synthesis

Similar outcomes will be plotted in the meta-analysis using Stata Statistical Software 17 (Stata Statistical Software: Release 17. College Station, TX, StataCorp LLC, USA). We will select the random-effects model for the meta-analysis, and the studies will be evaluated separately according to their designs. If quantitative synthesis is not appropriate, a narrative synthesis will be provided.

Sensitivity analysis

If possible, we plan to perform a sensitivity analysis by subgroup evaluation of studies with high, low, and unclear overall risk of bias.

Subgroup analysis

For a meta-analysis of a specific outcome, if sufficient data are available, subgroup analyses will be performed according to age (>65 years or <65 years), staging (ISS I, II, or III), and cytogenetic risk (standard or high). We will use the instrument credibility of effect modification analyses (ICEMAN tool) to assess the credibility of the subgroups.[26]

Heterogeneity assessment

Inconsistencies between the results of the included studies will be ascertained by visual inspection of forest plots (no overlap of CIs around the effect estimates of the individual studies), by Higgins or I^2 statistic, in which I^2 >50% indicates a moderate probability of

heterogeneity, and by chi-squared tests (Chi^2), where $p < 0.10$ indicates heterogeneity. Meta-regression will be used to explore the causes of the inconsistencies. We will use age ((>65 years or <65 years), staging (ISS I, II, or III), and cytogenetic risk (standard or high). The Knapp–Hartung correction will be used to calculate the significance of the meta-regression coefficients. In the case of $I^2 > 30\%$ (>5 studies), the prediction interval (PI) from the random-effects meta-analyses will be used because PI predicts the potential underlying effect in a new study, which is different from the average effect from the meta-analyses.[24]

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed, and a summary of findings will be created using GRADEpro GDT (McMaster University, ON, Canada).[27] The summary of findings will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. For non-RCTs, ranking of the quality of the evidence will also be based on the presence of a large effect, plausible confounding, and dose–response gradient. The outcomes reported in the summary of findings will be the OS, PFS, overall response rate, adherence, time to next treatment, therapy-related deaths, and quality of life.

ETHICS DISSEMINATION

As no primary data collection will be undertaken, no formal ethical assessment is required by our institution. We plan to present the results of this systematic review in a peer-reviewed scientific journal. We also intend to present this, including preliminary findings, at appropriate conferences.

REFERENCES

1. Palumbo A, Anderson K. Multiple myeloma. *The New England journal of medicine* 2011;364(11):1046-60. doi: 10.1056/NEJMra1011442 [published Online First: 2011/03/18]
2. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology* 2014;15(12):e538-48. doi: 10.1016/S1470-2045(14)70442-5 [published Online First: 2014/12/03]
3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394-424. doi: 10.3322/caac.21492 [published Online First: 2018/09/13]
4. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic proceedings* 2003;78(1):21-33. doi: 10.4065/78.1.21 [published Online First: 2003/01/17]
5. Kurtin S. Relapsed or Relapsed/Refractory Multiple Myeloma. *J Adv Pract Oncol* 2013;4(6):10.
6. Multiple myeloma: 2018 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2018;93(8):981-1114. doi: 10.1002/ajh.25117 [published Online First: 2018/11/08]
7. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;111(5):2516-20. doi: 10.1182/blood-2007-10-116129 [published Online First: 2007/11/03]
8. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014;28(5):1122-8. doi: 10.1038/leu.2013.313 [published Online First: 2013/10/26]
9. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood* 2008;111(5):2521-6. doi: 10.1182/blood-2007-08-104984 [published Online First: 2007/09/29]
10. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *The New England journal of medicine* 1999;341(21):1565-71. doi: 10.1056/NEJM199911183412102 [published Online First: 1999/11/24]
11. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *The New England journal of medicine* 2005;352(24):2487-98. doi: 10.1056/NEJMoa043445 [published Online First: 2005/06/17]
12. Richardson PG, Blood E, Mitsiades CS, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood* 2006;108(10):3458-64. doi: 10.1182/blood-2006-04-015909 [published Online First: 2006/07/15]
13. Saúde Md. Bortezomibe para o tratamento de pacientes adultos com mieloma múltiplo previamente tratados. In: Conitec, ed., 2020:28.
14. Saúde Md. Bortezomibe para o tratamento de pacientes adultos com mieloma múltiplo, não previamente tratados, elegíveis ao transplante autólogo de célulastronco hematopoiéticas. In: Conitec, ed., 2020:29.
15. Fujisawa M, Suehara Y, Fukumoto K, et al. Changes in survival rate of multiple myeloma after the introduction of bortezomib: a single institutional experience over 20 years. *Ann Hematol* 2016;95(1):63-72. doi: 10.1007/s00277-015-2522-9 [published Online First: 2015/10/27]
16. Hungria VTM, Lee JH, Maiolino A, et al. Survival differences in multiple myeloma in Latin America and Asia: a comparison involving 3664 patients from regional registries. *Ann Hematol* 2019;98(4):941-49. doi: 10.1007/s00277-019-03602-4 [published Online First: 2019/02/08]
17. de Moraes Hungria VT, Martinez-Banos DM, Penafiel CR, et al. Multiple myeloma treatment patterns and clinical outcomes in the Latin America Haemato-Oncology (HOLA)

Observational Study, 2008-2016. *Br J Haematol* 2020;188(3):383-93. doi: 10.1111/bjh.16124 [published Online First: 2019/08/09]

18. Djebbari F, Srinivasan A, Vallance G, et al. Clinical outcomes of bortezomib-based therapy in myeloma. *PloS one* 2018;13(12):e0208920. doi: 10.1371/journal.pone.0208920 [published Online First: 2018/12/13]
19. Scott K, Hayden PJ, Will A, et al. Bortezomib for the treatment of multiple myeloma. *Cochrane Database Syst Rev* 2016;4:CD010816. doi: 10.1002/14651858.CD010816.pub2 [published Online First: 2016/04/21]
20. Tufanaru C MZ, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis: JBI, 2020, 2020.
21. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)* 2015;350:g7647. doi: 10.1136/bmj.g7647 [published Online First: 2015/01/04]
22. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4 [published Online First: 2016/12/07]
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151(4):W65-94. doi: 10.7326/0003-4819-151-4-200908180-00136 [published Online First: 2009/07/23]
24. Higgins JPTT, J., editor. *Cochrane Handbook for Systematic Reviews of Interventions*. Second ed. Oxford: The Cochrane Collaboration and John Wiley & Sons Ltd., 2019.
25. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629 [published Online First: 1997/10/06]
26. Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2020;192(32):E901-E06. doi: 10.1503/cmaj.200077 [published Online First: 2020/08/12]
27. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ (Clinical research ed)* 2016;353:i2089. doi: 10.1136/bmj.i2089 [published Online First: 2016/07/02]

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AUTHOR CONTRIBUTIONS

VSNN is the guarantor for this review. All authors developed the systematic review protocol, which was drafted by VSNN and LOC and revised by RDG. VSNN has developed the search strategies. LOC and RDG have independently screened eligible studies, and they will extract data from included studies and assess the risk of bias. LOC will elaborate on the standard extract form. VSNN has supervised all phases of this review and refereed any disagreement to avoid any errors. All authors will participate in the data synthesis and quality of evidence. All authors critically revised the manuscript and approved the final version.

FUNDING STATEMENT

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COMPETING INTERESTS STATEMENT

LOC reports advisory board consultancy for Janssen, conference meeting support from Janssen and Amgen, and speaker honoraria from Janssen, Bristol Myers Squibb, and Amgen.

RDG reports advisory board consultancy for Janssen and Abbvie; conference meeting support from Janssen, Roche, and Takeda; and speaker honoraria from Janssen, Takeda, Bristol Myers Squibb, and Abbvie.

VSNN, none to declare.

STUDY STATUS

Titles and abstracts have been screened by two independent reviewers for the assessment against the inclusion criteria using the free web application Rayyan QCRI.

SUPPLEMENTARY FILE

Search Strategy

PubMed

#1"Multiple Myeloma"[Mesh] OR (Myeloma)

#2"Bortezomib"[Mesh] OR (Velcade)

*#3 ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

** # 4 (cohort[all] OR (control[all] AND study[all]) OR (control[tw] AND group*[tw]) OR epidemiologic studies[mh] OR program[tw] OR clinical trial[pt] OR comparative stud*[all] OR evaluation studies[all] OR statistics as topic[mh] OR survey*[tw] OR follow-up*[all] OR time factors[all] OR ci[tw]) NOT ((animals[mh:noexp] NOT humans[mh:noexp]) OR comment[pt] OR editorial[pt] OR review[pt] OR meta analysis[pt] OR case report[tw] OR consensus[mh] OR guideline[pt] OR history[sh])

*Filter for RCT PubMed. sensitivity- and precision-maximizing version (2008 revision); PubMed format. https://work.cochrane.org/pubmed

** Waffenschmidt S et al. Development and validation of study filters for identifying controlled non-randomized studies in PubMed and Ovid MEDLINE. Search filter with best sensitivity for controlled NRS (PubMed)
https://doi.org/10.1002/jrsm.1425

#1 AND #2 AND (#3 OR #4)

Embase

#1 ('bortezomib'/exp OR 'velcade'/exp) AND [embase]/lim

#2 ('mieloma múltiplo'/exp OU 'mieloma'/exp) AND [embase]/lim

#3 random:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti

#4 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp

*Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association: JMLA. 2006 Jan;94(1):41-7

#1 AND #2 AND (#3 OR #4)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Sources	#5a	Indicate sources of financial or other support for the review	14-15
Sponsor	#5b	Provide name for the review funder and / or sponsor	14-15
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Rationale	#6	Describe the rationale for the review in the context of what is already known	4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-8
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such	7-9

		as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-12
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supp. Data
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9-10
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-12

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-12
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11-12
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	11-13
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13-14