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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 haematological 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 randomised and non-randomised 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 V.17. The relative risk will be calculated with a 95% CI as the effect size of bortezomib. For the OS and progression-free survival, we calculate the overall OR from the HRs 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.

PROSPERO registration number CRD42020151142.

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 randomised clinical trials (RCTs) and non-RCTs.
⇒ We will apply the Grading of Recommendations Assessment, Development and Evaluation 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 characterised 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 codependence and positive feedback. Neoplastic cells secrete varying amounts of monoclonal protein, a paraimmunoglobulin detectable in the blood and/or urine, and leads to the development of organic lesions characterised by anaemia, bone lysis (which may lead to pathological fractures), hypercalcaemia and renal failure. This is also associated with recurrent infections caused by tumour-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 haematological 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 months 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 (OS) 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 USA 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 1103 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 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 randomised 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 Joanna Briggs Institute (JBI) methodology for systematic reviews of effectiveness.[20] The protocol 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 randomisation/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 randomisation/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 randomised/non-randomised 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 online supplemental file. References of relevant primary or secondary studies will be used to identify additional eligible studies.

Study selection

We have used EndNote V.20 (Clarivate Analytics, Pennsylvania, 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 standardised 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 standardised 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 analysed, 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 optimised 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 vs 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 vs those with other therapeutic agents. For the primary outcomes, we will extract the HRs and their 95% CIs. We will calculate the overall 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±SD, 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 randomised/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 V.17 (Stata Statistical Software: Release 17., StataCorp). 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 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 χ^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.

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Contributors VdSN-N is the guarantor for this review. All authors developed the systematic review protocol, which was drafted by VdSN-N and LOC and revised by RDG. VdSN-N 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. VdSN-N has 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 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.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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