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Efficacy and safety of bortezomib, thalidomide, and lenalidomide in multiple myeloma: An overview of systematic reviews with meta-analyses

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ABSTRACT

This overview summarizes evidence for the efficacy and safety of bortezomib, thalidomide, and lenalidomide in patients with multiple myeloma. We searched the Medline, Scopus, and LILACS databases through August 2016, including systematic reviews with meta-analyses of randomized controlled trials assessing the efficacy and/or safety of bortezomib, thalidomide, or lenalidomide in patients with multiple myeloma. Two authors performed study selection, data extraction, and quality assessment using AMSTAR and GRADE instruments. Twenty-nine studies satisfied the inclusion criteria. All three drugs significantly improved overall response and progression-free survival; however, only bortezomib showed significantly greater overall survival compared with the control arm (induction therapy, continuous therapy, or at any phase of treatment). The main concerns on adverse events were thrombosis/embolism events, peripheral

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Thalidomide
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Systematic review
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neuropathy, and second primary malignancies. The most common problems detected in systematic reviews were non-registration of the study protocol and conflicts of interest not clearly acknowledged. Future research should adhere to quality assessment tools so that best evidence can be used in decision-making.
Protocol PROSPERO registration number: CRD42016036062.

1. Introduction

Multiple myeloma (MM) is a complex hematologic malignancy characterized by uncontrolled proliferation of plasma cells in the bone marrow (Kyle and Rajkumar, 2009). MM is the second-most common hematologic malignancy, accounted for approximately 1% of all cancer diagnoses and 2% of cancer-related deaths worldwide (Palumbo and Anderson, 2011). Unfortunately, this severe disease remains incurable. Therefore, the primary goal of therapy in patients with MM is to improve remission rates as much as possible and, ultimately, to prolong the length of survival (Röllig et al., 2015).

The introduction of novel therapeutic agents, such as immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib), over the past two decades has significantly improved the clinical response of patients with MM (Hostenkamp and Lichtenberg, 2015). These medications have been used as single agents or in combination regimens for newly diagnosed or relapsed/refractory MM, and their use varies across countries, depending on drug availability (Rajkumar and Kumar, 2016). Because the best treatment strategy for MM remains a challenge (Röllig et al., 2015), more evidence on the efficacy and safety of therapeutic options is required to support their process of diffusion and incorporation in healthcare.

In order to provide precise estimates of the true effect from these three drugs in MM, numerous systematic reviews with meta-analyses have been published. This type of study is less susceptible to bias, as it uses explicit, transparent, and replicable methods, and it is considered, therefore, as a golden standard for health care intervention evidence (Cook et al., 1997). Nevertheless, systematic reviews have presented varying quality in different health fields (Aguiar et al., 2014; Samargandi et al., 2016; Johal et al., 2015), which can lead to biased results and misleading clinical decision-making. In this regard, it is undoubtedly important to critically assess their methodological quality and conclusions.

Overviews are a relatively new approach to assessing and summarizing evidence from multiple systematic reviews into a single, usable document. This can be useful for practitioners, researchers, and policymakers by providing a comprehensive summary of the evidence about relevant clinical questions (Smith et al., 2011). However, to the best our knowledge, overviews of systematic reviews on efficacy and safety of novel agents for patients with MM are lacking in the current literature. Thus, the purpose of this overview was to summarize the evidence of the efficacy and safety of bortezomib, thalidomide, and lenalidomide in patients with MM from systematic reviews, to critically appraise the methodological quality of studies, and to identify gaps in the literature as a guide for future research in this area.

2. Methods

The protocol of this overview was registered on PROSPERO 2016- International Prospective Register of Systematic Reviews (registration number: CRD42016036062; http://www.crd.york.ac.uk/PROSPERO/).

2.1. Search strategy

A comprehensive literature search of systematic reviews with meta-analyses of randomized controlled trials (RCT) was performed in the Medline/PubMed, Scopus, and LILACS databases through August 2016. The search strategy included the use of MeSH terms or text words related to the health condition (multiple myeloma), to the medications (bortezomib, thalidomide, and lenalidomide, which are novel therapeutic agents usually used in chemotherapy regimens, according to the National Cancer Institute Thesaurus) (National Cancer Institute, 2016) and to study design (systematic review; systematic literature review; review; meta-analysis). The search strategy executed for the PubMed/Medline database can be found in Appendix 1 in the Supplementary material. Also, the grey literature (i.e., literature published in non-commercial form) was searched using the DOAJ (Directory of Open Access Journals) database, and we screened the reference lists of the appraised articles to identify any studies that might have been missed.

2.2. Study selection

To be included in this overview, the articles had to meet the following criteria: (1) be a systematic review with meta-analysis of RCT; (2) be published in English, Spanish or Portuguese; (3) have evaluated bortezomib, thalidomide, or lenalidomide as a single-agent or in combination regimens, in comparison with other drugs or placebo; (4) report efficacy and/or safety outcomes, such as overall survival (OS), progression-free survival (PFS), response rates (overall response – ORR, complete response – CR and very good partial response – VGPR), and adverse events; (5) include patients with newly diagnosed or previously treated MM. Articles were excluded if they were reviews without a clear search strategy, systematic reviews without a meta-analysis, a meta-analysis not from a systematic review, systematic reviews including non-RCT studies, or systematic reviews including various drugs where the results of the examined drugs could not be separately extracted.

2.3. Review methods

Two authors (P.M.A. and T.M.L.) independently screened the title and abstract of citations to identify potentially relevant studies. Full-text articles were obtained and reviewed for further assessment according to the inclusion and exclusion criteria. Any disagreements were resolved by consensus through discussion.

2.4. Data extraction

Data from included studies were extracted using a spreadsheet preformatted in Microsoft Excel by two researchers (P.M.A. and T.M.L.) independently. The following information was collected: year of publication, literature search, target population, number of included RCTs and patients, interventions, comparators, outcomes reported, approaches for data pooling, estimates of effect