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Bortezomib for the treatment of Multiple Myeloma: A Systematic Review and Meta-Analysis

EIXO 1: SUSTENTABILIDADE NOS SISTEMAS DE SAÚDE

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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. Objective: To assess the effects of bortezomib on progression-free survival (PFS), overall response rate (ORR), adverse events in patients with MM.

Methods: We have performed a systematic review and included randomized (RCT) and non- -randomized controlled studies where bortezomib was compared in similar or dissimilar background therapies in each arm. Embase, Medline, LILACS, and CENTRAL were our data source. Two reviewers independently selected studies, assessed the risk of bias, and extract data from the included studies. Similar outcomes were plotted in the meta-analysis using the Stata Statistical Software 18. The relative risk (RR) was 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. We used the Grading of Recommendations Assessment, Development, and Evaluation system to evaluate the certainty of evidence.

Results: We identified 7,996 references, and 28 studies fulfilled our eligibility criteria. Sixteen studies were randomized, and 12 were non-randomized (retrospective studies). In the studies with similar background therapies in each arm, bortezomibe improves PFS (Peto OR 0.71, 95% CI 0.64 to 0.78, , 7 RCTs, 2572 participants, moderate-quality evidence), , and there was no difference in ORR between the groups. In studies with different background therapies in each arm, bortezomib continued to improve PFS (Peto OR 0.86, 95% CI 0.80 to 0.93, , 8 RCTs, 4209 participants, moderate-quality evidence), but not in studies where participants had previously used bortezomib (Peto OR 1.7, 95% CI 1.46 to 1.97 , 2 RCTs, 1084 participants), the same occurred in ORR (RR 1.14, 95% CI 1.01 to 1.29 and RR 0.81, 95% CI 0.75 to 0.89, respectively). In both similar and dissimilar background therapies bortezomibe increases the risk of neuropathy adverse events (RR 2.9, 95% CI 2.18 to 3.87, 5 RCTs, 1901 participants, and RR 4.57, 95% CI 2.50 to 8.35, 9 RCTs, 1901 participants, respectively). In all non-RCT studies bortezomibe was compared with active control. The meta-analysis of PFS was not performed due to study design (retrospective studies), from the 5 studies that evaluated this outcome, in 2 studies patients had a significantly longer PFS, and in 3 studies although bortezomib had better PFS, there was no statistically significant difference between groups.

Discussion and conclusions: Regarding PFS in the studies with dissimilar background therapies, bortezomib has often been compared with newer therapies. Even though we were unable to isolate the effect of bortezomib, when we performed subgroup analysis according to previous use of bortezomib, it is clear that for those patients without previous use, there is a better intervention effect. Patients who had previous contact with the drug, and were later re-exposed to it, clearly did not benefit from this re-exposure. Conclusion:Bortezomib has been approved by the FDA and other regulatory agencies for about 20 years. Thus, we have data from RCT and retrospective studies that highlight their effectiveness and long-term safety profile. This project was funded by the Call for Financial Support for Studies in Health Technology Assessment of the National Council for Scientific and Technological Development (CNPq) in partnership with the Brazilian Health Ministry through the DGITIS/SCTIE, grant number: 423641/2021-2.

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