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Efficacy and safety of bendamustine combined with chemotherapy for relapsed/refractory multiple myeloma: A protocol for systematic review and meta-analysis

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Review question / Objective: Multiple myeloma (MM) is a plasma cell malignancy that ranks second among haematological malignancies. Despite encouraging results with the use of drugs such as proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies, many MM patients still develop resistance and relapse, eventually become relapsed refractory multiple myeloma (RRMM). The current treatment of RRMM remains a challenge. Bendamustine is a unique cytotoxic agent. Clinical studies have shown that bendamustine in combination with chemotherapy has therapeutic advantages for RRMM, but evidence from evidence-based medicine is lacking. Therefore, we conducted a systematic review and meta-analysis protocol to assess the efficacy and safety of bendamustine combined with chemotherapy for RRMM.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 April 2022 and was last updated on 07 April 2022 (registration number INPLASY202240038).

INTRODUCTION

Review question / Objective: Multiple myeloma (MM) is a plasma cell malignancy that ranks second among haematological malignancies. Despite encouraging results with the use of drugs such as proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies, many MM patients still develop resistance and relapse, eventually become relapsed refractory multiple myeloma (RRMM). The current
treatment of RRMM remains a challenge. Bendamustine is a unique cytotoxic agent. Clinical studies have shown that bendamustine in combination with chemotherapy has therapeutic advantages for RRMM, but evidence from evidence-based medicine is lacking. Therefore, we conducted a systematic review and meta-analysis protocol to assess the efficacy and safety of bendamustine combined with chemotherapy for RRMM.

**Condition being studied:** relapsed/refractory multiple myeloma. Use Endnote X9.0 software to manage literature. After searching literature based on the above steps, import them into endnote software for literature screening. First, 2 independent researchers will conduct a preliminary literature screening based on the titles and abstracts of the included literature to eliminate duplicate and non-RCTs. Then read the full text of the remaining literature according to the previously designed principles of eligibility criteria, and finally determine the appropriate literature. When 2 researchers disagree, a third researcher will resolve it. The specific screening process is shown in Figure 1. According to the Cochrane Handbook for Systematic Reviews of Interventions, 2 researchers independently extracted and recorded the required information from all the included literature. When 2 researchers disagree, they will discuss to reach an agreement, otherwise they will work with the third researcher to resolve. The required information mainly includes the author, publication time, study design, participants number and demographic characteristics (age, sex, etc), treatment status (e.g., the initial dose and treatment period of Bendamustine), and outcomes. If any of the above information in the included literature is incomplete, we will contact the corresponding author via email to obtain the required data.

**METHODS**

**Participant or population:** Patients with RRMM, whether diagnosed by a clinician, or by any recognized criteria diagnosis of RRMM, will be included. There are no restrictions on nationality, age, sex, or race. Patients with severe liver and kidney, or other uncontrolled systemic diseases are excluded.

**Intervention:** The treatment group was given Bendamustine (5–10 mg) on the basis of routine chemotherapy. The control group was only given routine chemotherapy, or the same dose of placebo was given on the basis of routine chemotherapy.

**Comparator:** There are no restrictions on the type, dose and use of drugs. Routine chemotherapy regimens mainly include proteasome inhibitors (PIs), such as bortezomib, carfilzomib, and ixazomib; immunomodulatory drugs (IMiDs) such as lenalidomide and pomalidomide; monoclonal antibodies (mAbs) namely daratumumab and elotuzumab; and other treatments in development including CAR-T-cell therapy. The course of chemotherapy, follow-up time and the number of patients are unlimited.

**Study designs to be included:** The study will contain all relevant RCTs and systematic review/meta-analysis of Bendamustine combined with chemotherapy therapy for RRMM. Case reports, conference papers, overview, animal study, non-RCT, or semi-RCT trials, will not be included in the study, and the language will be confined to Chinese or English.

**Eligibility criteria:** We will formulate the inclusion and exclusion criteria for this study based on the PICOS principles.

**Information sources:** We will carefully discuss the retrieval skills and precautions of the literature retrieval, and formulate the final retrieval strategy after multiple pre-searches. The search databases are as follows: Cochrane Library, PubMed, Cochrane Controlled Trial Center Registration, Chinese Biomedical Literature Database, Embase, CNKI, Chinese Journal Full-text Data-base, Wan-fang Database, Chinese Science and Technology Journal Database, Web of Science, and Allied and
Complementary Medicine Database. In addition, the references listed in each included article are also manually searched. Retrieve the databases by combining subject words with random words. Appropriate adjustments will be made according to the grammatical rules of different databases to ensure the completeness and comprehensiveness of the search. The retrieval time was from establishment of the databases to March 2022, and the languages are limited to Chinese and English.

Main outcome(s): The primary outcomes include Progression-free survival, (PFS), Overall survival, (OS); the secondary outcomes include Overall response rate (ORR), Stringent complete remission (sCR), Complete remission (CR), Very good partial response (VGPR), Partial response (PR), etc; the safety indicators include neutropenia, thrombocytopenia, lymphopenia, anemia, constipation, fatigue, nausea, decreased appetite, pneumonia, diarrhea, vomiting, and other adverse events.

Quality assessment / Risk of bias analysis: Two reviewers will independently assess the quality of the included literature according to the Cochrane Collaboration's tool for RCTs. If there is a disagreement between 2 reviewers, the third reviewer resolves the issue. According to Cochrane Handbook V.5.2.0, characteristics of each item will be evaluated in 3 categories: low, unclear, and high. The results of the quality assessment will be completed using software Review Manager 5.3.

Strategy of data synthesis: We will execute Rev Man 5.3 and STATA 16 software for traditional meta-analysis. For dichotomous data, we will calculate a summary estimate with 95% confidence interval odds ratio value; for continuous data, we will calculate a summary estimate of standardized mean difference with 95% confidence interval, and P50%, it indicates that there is heterogeneity among the included literature, and assess the effect size by the random effect; on the contrary, a fixed effect model is used.

Subgroup analysis: Taking into account the issue of heterogeneity, we will conduct a subgroup analysis based on the specific circumstances of the included literature. If there is a problem of heterogeneity, we will conduct a subgroup analysis of age, sex, interventions, treatment type, disease course, country, publication year, onset time, and duration.

Sensitivity analysis: This systematic review will use the method of eliminating each study one by one for sensitivity analysis. If the effective indicators of Bendamustine combined with chemotherapy in the treatment of RRMM have not changed significantly, it indicates that the study is robustness. On the contrary, it is not robustness. According to the specific situation, low-quality research is excluded.

Country(ies) involved: China.

Keywords: bendamustine, chemotherapy, meta-analysis, relapsed refractory multiple myeloma.

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