INTRODUCTION

Review question / Objective: The present study aimed to comprehensively evaluate the efficacy and safety of tandem AHSCT in the treatment of multiple myeloma through systematic review and meta-analysis.

Condition being studied: Multiple myeloma (MM) is a malignant clonal disease with abnormal proliferation of plasma cells in bone marrow. Although autologous hematopoietic stem cell transplantation (AHSCT) can improve the progression-free survival (PFS) of most MM patients, recurrence is inevitable. However, the...
related factors of the efficacy of AHSCT for MM patients in different treatment centers are inconsistent. In recent years, with the extensive development of AHSCT and the application of new drugs, the overall quality of life and treatment efficiency of patients with multiple myeloma have been significantly improved. The better the degree of remission of patients with MM before transplantation, the more obvious the improvement of overall survival and progression free survival after transplantation, and the patients will have a longer survival after AHSCT. At present, AHSCT is still the first-line treatment option for transplant patients, but patients still face the risk of recurrence after transplantation. Tandem AHSCT refers to two times of transplantation within 6 months, especially for newly diagnosed patients with high-risk genetic factors, or patients who have not achieved sufficient deep remission after the first transplantation, tandem AHSCT is preferred. Lee et al. showed that early recurrence after transplantation and high-risk cytogenetics were prognostic factors affecting the survival of MM patients, and the risk ratio of early recurrence was the highest. There are different reports about the predictors of early recurrence. Gopalakrishnan et al. reported that r-ISS staging can predict the early recurrence of MM patients after AHSCT, while post-transplant maintenance therapy is not related to the early recurrence. In conclusion, early recurrence after AHSCT is the most important prognostic factor for the survival of MM patients. Therefore, how to further improve the depth of remission of patients to achieve long-term survival is the main problem. However, due to the small sample size and low efficiency of various studies, there is still a lack of large-scale, multi center randomized controlled trials to verify its effectiveness and safety. In this study, evidence-based medicine will be used to comprehensively search the scientific and technological literature database to obtain relevant research literature, and the quality of literature will be screened and evaluated according to the established standards. Analysis and evaluation of the efficacy and safety of tandem AHSCT in the treatment of MM can provide an objective basis for clinical diagnosis and treatment.

METHODS

Participant or population: (1) It is consistent with the clinical diagnostic criteria of MM; (2) The diagnosis of each study group is clear, all of them are primary patients; (3) The data included in the research is reliable and the sample size was clear; (4) Select one of the duplicate documents or reports on the same population; (5) There are no restrictions on race, nationality, gender, age, or region; (6) Patients with other complex and serious diseases are not included.

Intervention: The intervention group was treated with tandem autologous hematopoietic cell transplantation, and the control group was treated with single autologous hematopoietic cell transplantation.

Comparator: Interventions and comparisons The intervention group was treated with tandem autologous hematopoietic cell transplantation, and the control group was treated with single autologous hematopoietic cell transplantation. In the actual treatment, in order to ensure the normal vital signs of patients, the control group and the intervention group need to take the drugs to protect organs and provide nutrition according to the conventional treatment, and at the same time, the blood examination should be carried out regularly. The number of blood tests was more than or equal to twice a week, and the patients were observed to take drugs according to the clinical symptoms.

Study designs to be included: The study will contain all relevant randomized controlled trials (RCT) and systematic review/meta-analysis of different doses of tandem AHSCT for the treatment of MM. Case reports, overview, 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:** Exclusion criteria(1) The identification of MM does not meet the criteria of this article; (2) The patients with MM who have been diagnosed and treated or experienced radiotherapy and chemotherapy, secondary MM; (3) Lack of literature on main research indicators; (4) A history of other malignant tumors in the past 3 years; (5) Literature review without control study; (6) Literature with incomplete or false clinical data; (7) No support for follow-up treatment.

**Information sources:** We will conduct several pre-searches, carefully discuss the matters needing attention in literature retrieval, and finally formulate the retrieval strategy. The search databases are as follows: PubMed, Cochrane Library, CNKI, Cochrane Controlled Trial Center Registration, VIP Database, EMBASE, Wanfang Database, ScienceNet. The search strategy consists of grid and keywords. The specific retrieval scheme of PubMed database is shown in Table 1.

**Main outcome(s):** Primary outcomes: overall survival (OS) and progression-free survival (PFS).

**Additional outcome(s):** Secondary outcomes: including stringent complete response (sCR), complete remission (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD), clinical recurrence, recurrence after CR.

**Quality assessment / Risk of bias analysis:** Two independent reviewers will evaluate the quality of the included articles based on the Cochrane Collaboration randomized controlled trial tool. According to Cochrane manual v.5.2.0, the characteristics of each project will be divided into three categories: low, unclear and high. The results of the quality assessment will be completed using software Review Manager 5.3.

**Strategy of data synthesis:** Use endnoteX9.0 software to manage literature, and all duplicate references will be deleted. First, two independent researchers will conduct a preliminary literature screening. When the two researchers disagreed, the controversial literatures were discussed to decide whether they should be included. If necessary, a third-party researcher can help solve the problem and explain why. The specific screening process is shown in Figure 1. If any information in the attached literature is incomplete, we will contact the author by email to obtain the corresponding data.

**Subgroup analysis:** Taking into account the issue of heterogeneity, we will conduct a subgroup analysis of the reasons for the heterogeneity according to the source of the heterogeneity. If there is a problem of heterogeneity, we will use several aspects such as gender, age, treatment type, disease course, country, publication year, onset time, and duration for group analysis in different design schemes.

**Sensitivity analysis:** This systematic review will use the exclusion method to analyze the sensitivity of all outcome indicators to disease. We followed the methods of Yin et al. If the heterogeneity changes after changing some important factors that may affect the results, it is the cause of heterogeneity. On the contrary, if the quality does not change, the sensitivity is low and the result is stable and reliable.

**Country(ies) involved:** China.

**Keywords:** multiple myeloma, tandem autologous hematopoietic stem cell transplantation, protocol, systematic review.

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