INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None.

Efficacy of ixazomib for the treatment of relapsed/refractory multiple myeloma: A protocol of systematic review and meta-analysis

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Review question / Objective: **Can ixazomib effectively and safety treat relapsed/refractory multiple myeloma (RRMM)?**
Condition being studied: **Relapsed/refractory multiple myeloma; AND ixazomib.**
Information sources: **We will check the electronic databases of Cochrane Library, PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature, the Allied and Complementary Medicine Database, PsycINFO, WANGFANG and China National Knowledge Infrastructure to identify any potential randomized controlled trials on investigating the efficacy and safety of ixazomib for the treatment of patients with RRMM from their origin to the March 31, 2020. We will not implement any limitations of language and publication status. The sample of detailed search strategy for Cochrane Library will be built. Similar search strategies will be adapted to any other electronic databases. Additionally, we will also search other sources, such as abstracts of scientific conferences/ symposia, and reference lists of associated reviews.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 April 2020 and was last updated on 05 April 2020 (registration number INPLASY202040027).

INTRODUCTION

Review question / Objective: **Can ixazomib effectively and safety treat relapsed/ refractory multiple myeloma (RRMM)?**

Condition being studied: **Relapsed/ refractory multiple myeloma; AND ixazomib.**

METHODS

Participant or population: **All participants who were diagnosed as RRMM will be included in this study. We will not employ any restrictions of ethnicity, gender, and age.**

Intervention: **In the experimental group, all patients received ixazomib with any deliver types. However, we will exclude patients who also taken other medications.**

Comparator: In the control group, patients underwent any treatments will be considered for inclusion in this study. However, we will not consider patients who also received ixazomib.

Study designs to be included: Only randomized controlled trials (RCTs) which explored the efficacy and safety of ixazomib for the treatment of patients with RRMM will be included.

Eligibility criteria: This study includes RCTs that compared the efficacy and safety of ixazomib to any management for the treatment of RRMM.

Information sources: We will check the electronic databases of Cochrane Library, PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature, the Allied and Complementary Medicine Database, PsycINFO, WANGFANG and China National Knowledge Infrastructure to identify any potential randomized controlled trials on investigating the efficacy and safety of ixazomib for the treatment of patients with RRMM from their origin to the March 31, 2020. We will not implement any limitations of language and publication status. The sample of detailed search strategy for Cochrane Library will be built. Similar search strategies will be adapted to any other electronic databases. Additionally, we will also search other sources, such as abstracts of scientific conferences/ symposia, and reference lists of associated reviews.

Main outcome(s): Overall survival (defined as the time from randomization to death from any causes); Progression-free survival (defined as the time from random assignment to disease progression or death from any cause).

Additional outcome(s): Pathological complete response (defined as the complete disappearance of the invasive cancer and no tumor in the axillary lymph nodes); Recurrence-free survival (defined as the time from randomization to the first of either recurrence or relapse, second cancer, or death); Disease-free survival (length of time after treatment during which no disease is found); Quality of life (as measured by any relevant scales, such as 36-Item Short Form Survey); Any adverse events.

Data management: Before data collection, a standardized data extraction sheet will be designed by the review team and will be piloted calibration using at least three eligible studies. Information will be extracted by two authors independently. Any different views will be discussed by two authors. If no resolution can be made, a third author will be invited to solve them via discussion or consultation. We mainly collect the below data: Study characteristics: title, authors, time of publication, et al; Participant characteristics: sex, age, diagnostic criteria, eligibility criteria, et al; Study methods: trial setting, trial design, sample size, randomization, blind, et al; Interventions and controls: delivery types, dosage, duration, et al; Outcomes: primary, secondary, and safety outcome measurements, et al; Others: funding information, et al.

Quality assessment / Risk of bias analysis: For each qualified trial, risk of bias evaluation will be appraised by two independent authors using Cochrane risk of bias tool. It will judge each study through seven items, and each parameter of bias will be scored as having high, unclear or low risk of bias. Any divergences between the two authors will be solved through discussion with a third author.

Strategy of data synthesis: RevMan 5.3 Software will be used for statistical analysis. Continuous data (such as such as overall survival and progression-free survival) will be pooled and described as standardized mean difference or mean difference and 95% confidence intervals (CIs). Dichotomous data (such as the incidence of adverse events) will be synthesized and presented as risk ratio and 95% CIs. Statistical heterogeneity of effect sizes will be identified using I^2 statistic test. It is interpreted as follows: 0–50%

indicating low heterogeneity, and 51–100% showing substantial heterogeneity. When I^2 ≤50%, a fixed effects model will be utilized for data pooling; when I^2 >50%, a random-effects model will be chosen. When significant clinical heterogeneity is identified, we will perform subgroup and sensitivity analysis to check the possible reasons for such high heterogeneity. If there is sufficient homogeneity among included studies, we will perform a quantitative analysis in the form of a meta-analysis. Otherwise, we will carry out a descriptive analysis. We will summarize outcome results with narrative approaches by using detailed written commentary to demonstrate the findings, participants, interventions, and comparators. The outcomes of overall survival, progression-free survival, recurrence-free survival, disease-free survival, and quality of life will be summarized as mean or standardized mean and standard deviation. The outcomes of pathological complete response and incidence of adverse events will be presented as rates, ranges and median.

Subgroup analysis: We will perform subgroup analysis in accordance with different study characteristics, interventions, controls, and outcome indicators.

Sensibility analysis: When sufficient trials are included, we will operate sensitivity analysis to test the robustness of outcome results by removing low quality trials.

Countries involved: China

Keywords: Relapsed/refractory multiple myeloma; ixazomib; efficacy; safety.