INPLASY PROTOCOL

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Corresponding author:
Yan Huo

yan-huo@review-solutions.ltd

Author Affiliation:
Department of Hematology, School of Medicine, Shanghai Fourth People's Hospital, Tongji University, Shanghai, China.

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None declared.

Evaluation of Daratumumab for Multiple Myeloma in Patients with Renal Insufficiency: evidence map and Meta-analysis

Jiang, H[1]; Li, L[2]; Guo MY[3]; Li, MZ[4]; Wu, H[5]; Chen, XM[6]; Gao, MZ[7]; Xu, QQ[8]; Mi, J[9]; Cui, CC[10]; Fu, WJ[11].

Review question / Objective: **To summarize the evidence of current treatment regimens for patients with MM concomitant RI and identify potential research gaps in the field of multiple myeloma. To explore the efficacy of Daratumumab add on therapy for patients with MM concomitant RI.**
Information sources: **A systematic search in the databases of PubMed, EMBASE and Cochrane Library will be conducted from inception without limitations on language, time and document type, using indexing and free-text terms on "multiple myeloma", "medication". Reference lists of included studies will be checked for relevant studies to identify any additional published or unpublished material (grey literature) not retrieved by the electronic search. Search strategies for all databases will be described in detail.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 February 2023 and was last updated on 26 February 2023 (registration number INPLASY202320115).

INTRODUCTION

Review question / Objective: **To summarize the evidence of current treatment regimens for patients with MM concomitant RI and identify potential research gaps in the field of multiple myeloma. To explore the efficacy of Daratumumab add on therapy for patients with MM concomitant RI.**

Rationale: **Multiple myeloma (MM) constitutes the second most common hematological malignancy and is associated with significant mortality and**

morbidity. The incidence of renal insufficiency (RI) in patients with MM ranges from 20% to 50%. RI in patients with MM was resulted primarily from the toxic effects of monoclonal light chains on kidneys.

Renal insufficiency is a common feature of MM, several studies of conventional chemotherapy have confirmed that RI was associated with poor prognosis in MM, with a median survival of shorter than 2 years. The introduction of novel agents has led to an improved survival of patients with MM, even in those with RI. Some studies have also indicated that reversibility of RI is associated with improved survival.

Daratumumab (Dara) is the first-in-class human monoclonal antibody targeting CD38 approved for the treatment of MM, an antigen that is highly and uniformly expressed on the surface of MM cells. Dara induces myeloma cell death via a variety of mechanisms including complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis and direct cellular apoptosis. Since its initial approval in 2015, Dara has had a tremendous impact on the treatment of MM. Currently, there is a significant unmet medical need for treatment of MM concomitant RI patients. So our study will review current evidence on RI patients treatment regimens by evidence mapping and evaluate the effect of Dara add on therapy for MM concomitant RI patients by meta-analysis.

Condition being studied: Eligible patients are who diagnosed with multiple myeloma (MM) concomitant renal insufficiency (RI) and treating with any anti-MM pharmacological therapy of currently available agents, regardless of newly diagnosed (NDMM) or relapse or refractory (RRMM). Patients with confirmed Multiple myeloma was defined by the International Myeloma Working Group (IMWG) criteria. RI was defined by National Kidney Foundation (KDIGO) criteria. There will be no limitation on gender, prior lines of therapy, co-morbidity and anti-MM treatment regimens.

METHODS

Search strategy: A systematic search in the databases of PubMed, EMBASE and Cochrane Library will be conducted from inception without limitations on language, time and document type, using indexing and free-text terms on “multiple myeloma”, “medication”.

Participant or population: Patients with RI in MM population. MM were defined by the International Myeloma Working Group (IMWG) criteria, RI was defined by National Kidney Foundation (KDIGO) criteria or original studies. There will be no limitation on gender, prior lines of therapy or co-morbidity.

Intervention: Mapping: current anti-MM pharmacotherapy agents. Meta analysis: addition of daratumumab to the backbone regimens. There will be no limitation on the agents, administration, dosage, frequency, treatment duration, and treatment lines.

Comparator: Mapping: none or current anti-MM pharmacotherapy agents. Meta analysis: the comparison will be intervention regimen without Daratumumab, with no limitation on agents, administration, dosage, frequency, treatment duration, or line of treatment.There will be no limitation on agents, administration, dosage, frequency, treatment duration, or line of treatment.

Study designs to be included: Mapping: Randomized controlled trials (RCTs), clinical controlled trials (CCTs), single arm trials, cohort studies, case series studies, and case control studies were considered eligible study designs. Meta analysis: RCTs.

Eligibility criteria: Mapping: available studies reporting any anti-MM pharmacological treatment in eligible patients who are diagnosed with multiple myeloma (MM) concomitant renal insufficiency (RI), regardless of newly diagnosed (NDMM) or relapse or refractory (RRMM). Meta analysis: Randomized controlled trials (RCTs) about addition of daratumumab to the backbone regimens

that investigating the efficacy and safety of Daratumumab and other treatment regimen for patients with RI in MM.

Information sources: A systematic search in the databases of PubMed, EMBASE and Cochrane Library will be conducted from inception without limitations on language, time and document type, using indexing and free-text terms on "multiple myeloma", "medication". Reference lists of included studies will be checked for relevant studies to identify any additional published or unpublished material (grey literature) not retrieved by the electronic search. Search strategies for all databases will be described in detail.

Main outcome(s): Mapping: no limitation. Meta analysis: 1) Progression-free survival (PFS), defined as original studies. 2) Overall survival (OS), defined as original studies.

Additional outcome(s): 1) Percentage of patients with response of better than complete response (≥ CR). 2) minimal residual disease (MRD) negativity rate.

Data management: Data from each literature will be extracted by one reviewer and double checked by another reviewer by using a standardized data extraction form. Any disagreements will be resolved by discussion, with the assistance from a third party if necessary. Where more information relating to a potentially included study is lacking, we will contact literature authors and request further information. A PICOS structure will be used to formulate the data extraction, as follows (Appendix 3):General study characterizes: the first author's name, the published year, trial registration number, location, centers.
Participants: NDMM/RRMM.
Interventions: type of treatment, treatment frequency, dosage, and treatment duration.
Comparison: type of treatment, treatment frequency, dosage, and treatment duration.
Study design: randomized controlled trials (RCTs), clinical controlled trials (CCTs), single arm trials, cohort studies, and descriptive studies.

Quality assessment / Risk of bias analysis: Meta analysis: two reviewers will independently assess the risk of bias in the included studies. We will use the Cochrane risk of bias tool 1.0 to assess the risk of bias of RCTs. Disagreements will be resolved by discussion, with assistance from a third party if necessary.

Strategy of data synthesis: For dichotomous outcomes, we will use incidence, proportions, rates, or risks and its 95% credible intervals (CI) to describe and pool the data. For time-to-event outcomes (such as OS, PFS), we will use hazard rates and its 95% credible intervals (CI) to describe and pool the data. For data expressed as median and interquartile range (IQR)/range, we will narratively describe the data.

Subgroup analysis: We plan to perform subgroup analysis on primary outcomes according to patients disease status (newly diagnose; refractory or relapsed) and baseline creatinine clearance stage (renal insufficient; normal renal function).

Sensitivity analysis: We will conduct sensitivity analysis according to the particular factor to identify the source of heterogeneity. Particular factors include age, type of regimen, lines of therapy, baseline creatinine clearance stage, eGFR level, baseline ECOG performance, etc.

Country(ies) involved: China.

Keywords: Multiple myeloma, renal insufficiency, daratumumab, evidence mapping, meta-analysis.

Contributions of each author:
Author 1 - Hua Jiang.
Author 2 - Lu Li.
Author 3 - Meiyu Guo.
Author 4 - Meizhang Li.
Author 5 - Hao Wu.
Author 6 - Xiaomei Chen.
Author 7 - Mingzhao Gao.
Author 8 - Qianqian Xu.
Author 9 - Jia Mi.
Author 10 - Canchan Cui.
Author 11 - Weijun Fu.