INPLASY PROTOCOL

To cite: Wang et al. Efficacy and safety of haploidentical hematopoietic stem cell transplantation on severe aplastic anemia using busulfan-based myeloablative regimenA protocol for a Bayesian network meta-analysis. Inplasy protocol 202210116. doi: 10.37766/inplasy2022.1.0116

Received: 23 January 2022

Published: 23 January 2022

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Support: **82174181; 2018WS184.**

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

Conflicts of interest:
None declared.

Efficacy and safety of haploidentical hematopoietic stem cell transplantation on severe aplastic anemia using busulfan-based myeloablative regimen
A protocol for a Bayesian network meta-analysis

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Review question / Objective: **In order to select the best treatment, this study will conduct network meta-analysis(NMA) to compare these treatments. Bayesian NMA is better than traditional analysis in comparing multiple treatments while the latter usually compares 2 interventions. Therefore, this article compares the efficacy and safety of haplo-HSCT on SAA using busulfan-based myeloablative regimen through the idea of NMA to provide corresponding help for clinicians and SAA patients.**
Information sources: **We will carefully discuss the details and precautions about literature retrieval, and then ascertain the search strategy after pre-retrieving literature. The retrieval time is from the establishment of the database to December 2021. All patients qualified in the trial are diagnosed as SAA. Search databases are as follows: PubMed, Cochrane Library, Cochrane Controlled Trial Center Registration, EMBASE, Web of Science, VIP database, CNKI, Wanfang database. In addition, we will proceed to follow up the literature in systematic review/meta-analysis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 January 2022 and was last updated on 23 January 2022 (registration number INPLASY202210116).

INTRODUCTION

Review question / Objective: **In order to select the best treatment, this study will conduct network meta-analysis(NMA) to compare these treatments. Bayesian NMA is better than traditional analysis in comparing multiple treatments while the latter usually compares 2 interventions. Therefore, this article compares the efficacy and safety of haplo-HSCT on SAA using busulfan-based myeloablative**

regimen through the idea of NMA to provide corresponding help for clinicians and SAA patients.

Condition being studied: Severe aplastic anemia (SAA) is a bone marrow failure disease with high mortality and poor prognosis. Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the available curative approach. Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) should be considered as an alternative source in the absence of a matched related donor (MRD) or a matched unrelated donor (MUD). However, haplo-HSCT presents a higher incidence of graft failure and graft-versus-host disease (GVHD).The success of transplantation mainly depends on the conditioning regimen which no agreement has been reached internationally. As a myeloablative drug, busulfan has been used in the conditioning regimen for malignant hematological diseases. In recent years, it has also been used in Haplo-HSCT of SAA, but its efficacy and safety are the focus of attention. Therefore, we will evaluate the efficacy and safety of haplo-HSCT on SAA using busulfan-based myeloablative regimen by Bayesian network meta-analysis(NMA).

METHODS

Participant or population: Patients with SAA, whether diagnosed by a clinician, or by any recognized criteria diagnosis of SAA, 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: In the treatment group, patients are treated with haplo-HSCT using busulfan-based myeloablative regimen. Conditioning regimen include busulfan plus cyclophosphamide plus anti-thymocyte globulin, busulfan plus cyclophosphamide, etc. In the control group, patients are treated with haplo-HSCT without busulfan conditioning regimen.

Comparator: In the treatment group, patients are treated with haplo-HSCT using busulfan-based myeloablative regimen. Conditioning regimen include busulfan plus cyclophosphamide plus anti-thymocyte globulin, busulfan plus cyclophosphamide, etc. In the control group, patients are treated with haplo-HSCT without busulfan conditioningregimen.

Study designs to be included: This study will include RCTs and systematic review/meta-analysis of the efficacy and safety of haplo-HSCT on SAA using busulfan-based myeloablative regimen. Case reports, reviews, animal experiments, non-RCT, or semi-RCT trials, will not be included in this study. The language will be restricted in Chinese or English.

Eligibility criteria: According to the above-mentioned search strategy, all relevant documents searched in the database were imported into EndNoteX9, and two researchers (Yan Wang and Zhenzhen Wang) independently perform document screening at the same time. The controversial literatures are discussed to decide whether they should be included or not. Or, if necessary, a third-party researcher can help to solve the problem and explain the reasons.

Information sources: We will carefully discuss the details and precautions about literature retrieval, and then ascertain the search strategy after pre-retrieving literature. The retrieval time is from the establishment of the database to December 2021. All patients qualified in the trial are diagnosed as SAA. Search databases are as follows: PubMed, Cochrane Library, Cochrane Controlled Trial Center Registration, EMBASE, Web of Science, VIP database, CNKI, Wanfang database. In addition, we will proceed to follow up the literature in systematic review/meta-analysis.

Main outcome(s): The primary outcomes include engraftment.

Additional outcome(s): The secondary endpoints were OS, failure free survival

(FFS), GVHD, immune reconstitution and performance status at the last follow-up.

Quality assessment / Risk of bias analysis: The quality will be assessed using the Cochrane Collaboration's Risk of Bias Tool by 2 researchers independently [14]. The main contents comprise 7 items and each item will be divided into 3 levels: "high," "unclear," and "low." If two researchers have different opinions, it is determined by discussing with the third researcher or contacting the original author.

Strategy of data synthesis: We will apply the chi-square test to estimate the heterogeneity and use i2 statistics to assess the heterogeneity of each pair of comparisons. When i250%, the heterogeneity is obvious, we will use the random effects model.

Subgroup analysis: Considering the heterogeneity, we will perform subgroup analysis in the light of the characteristics of research related to the source of heterogeneity. In addition, with regard to different design schemes, we will adopt subgroup analysis in accordance with age, gender, treatment type and course of disease.

Sensitivity analysis: Sensitivity analysis will be assessed by excluding the literature one by one to ascertain whether the literature has an impact on heterogeneity. Once the heterogeneity of the study changes, this article may be the source of heterogeneity, and further analysis will be carried out, such as the difference in sample size and the reference standard of outcome indicators. If there is no obvious change before and after exclusion, it manifests that the results are stable and credible.

Country(ies) involved: China.

Keywords: severe aplastic anemia, busulfan, Haplo-HSCT, network meta-analysis, protocol.

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