INPLASY PROTOCOL

To cite: Yin et al. Efficacy and safety of chemotherapy combined with different doses of IL-2 maintenance therapies for acute myeloid leukemia: A protocol for a Bayesian network meta-analysis. Inplasy protocol 202140106. doi: 10.37766/inplasy2021.4.0106

Received: 20 April 2021

Published: 21 April 2021

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Support: **No: 81974547; ZR2020KH023.**

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

Conflicts of interest:
None declared.

Efficacy and safety of chemotherapy combined with different doses of IL-2 maintenance therapies for acute myeloid leukemia: A protocol for a Bayesian network meta-analysis

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Review question / Objective: **Acute myeloid leukemia (AML) is the most common malignant tumor of the hematopoietic system, which seriously threatens the lives of patients. Most AML patients have acute onset, severe condition and poor prognosis. The present study aimed to comprehensively evaluate the effectiveness and safety of chemotherapy combined with different doses of IL-2 maintenance treatments in acute myeloid leukemia by Bayesian network meta-analysis (NMA).**
Condition being studied: **The study will contain all relevant randomized controlled trials (RCT) and systematic review/ meta-analysis of different doses of IL-2 maintenance therapies for acute myeloid leukemia (AML). Case reports, conference paper, 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.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 April 2021 and was last updated on 21 April 2021 (registration number INPLASY202140106).

INTRODUCTION

Review question / Objective: **Acute myeloid leukemia (AML) is the most common malignant tumor of the hematopoietic system, which seriously threatens the lives of patients. Most AML patients have acute onset, severe condition and poor prognosis. The present study aimed to comprehensively evaluate the effectiveness and safety of chemotherapy combined with different doses of IL-2 maintenance**

treatments in acute myeloid leukemia by Bayesian network meta-analysis (NMA).

Rationale: From its inception until October 2021, we will search PubMed, Cochrane Library, CNKI, Embase and other databases to comprehensively collect randomized controlled trials (RCTs) of chemotherapy combined with different doses of IL-2 maintenance therapies for acute myeloid leukemia. Two independent researchers will complete the literature screening and data extraction according to the inclusion and exclusion criteria, and then independently conduct a bias risk assessment of all the evidence. Bayesian network meta-analysis was used to evaluate all the evidence comprehensively. Use STATA16.0 and WinBUGS1.4.3 software to process and analyze all data, and classify the quality of evidence in NMA according to Grades of Recommendation, Assessment, Development, and Evaluation (GRADE).

Condition being studied: The study will contain all relevant randomized controlled trials (RCT) and systematic review/meta-analysis of different doses of IL-2 maintenance therapies for acute myeloid leukemia (AML). Case reports, conference paper, 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.

METHODS

Search strategy: We will carefully discuss the retrieval skills and precautions of literature retrieval, and formulate the final retrieval strategy after multiple pre-searches. And we will search all relevant RCTs in the following databases according to the efficacy and safety of chemotherapy combined with IL-2 maintenance therapy for AML. The search databases are as follows: Cochrane Library, PubMed, Cochrane Controlled Trial Center Registration, Chinese Biomedical Literature Database (SinoMed), EMBASE, CNKI, Chinese Journal Full-text Database, Wanfang Database, Chinese Science and Technology Journal Full-text Database, ScienceNet, VIP Database. At the same time, we will track the references included in the systematic review/meta-analysis. The search strategy consists of grid and keywords. We use a combination of medical subject headings (MeSH) and free words. The specific retrieval scheme of PubMed database is shown in Table 1.

Participant or population: (1) According to the clinical symptoms and signs of patients, morphological classification of bone marrow cells, peripheral blood routine, bone marrow immunological markers, cytogenetics and molecular biology, bone marrow aspiration biopsy conform to the relevant diagnostic criteria of AML in the "Diagnosis and Curative Effect Criteria for Blood Diseases" , and confirmed the type of leukemia after flow cytometry. (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) The blood routine is normal, tolerate chemotherapy, and the estimated life cycle was more than 3 months. (7) The functions of important organs are basically normal. (8) Patients with other complex and serious diseases are not included. No previous history of coagulopathy and other tumor diseases.

Intervention: The intervention group was treated with conventional chemotherapy as the control group, and at the same time, various adjuvant therapies such as different doses of IL-2 were used on the basis of conventional treatment. The chemotherapy regimen: combined chemotherapy with daunorubicin (DA), cytarabine, and homoharringtonine (HA). In actual treatment, in order to ensure that the vital signs of patients are normal, the control group and intervention group need to take drugs that protect organs and provide nutrition in accordance with conventional treatment, and perform regular blood tests at the same time. The number of blood

tests are ≥2 times per week and observation Patients are prescribed medications for clinical symptoms.

Comparator: In the control group, the patients were induced by general chemotherapy. The chemotherapy regimen: combined chemotherapy with daunorubicin (DA), cytarabine, and homoharringtonine (HA).

Study designs to be included: The study will contain all relevant randomized controlled trials (RCT) and systematic review/meta-analysis of different doses of IL-2 maintenance therapy for acute myeloid leukemia (AML). Case reports, conference paper, 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: (1) According to the clinical symptoms and signs of patients, morphological classification of bone marrow cells, peripheral blood routine, bone marrow immunological markers, cytogenetics and molecular biology, bone marrow aspiration biopsy conform to the relevant diagnostic criteria of AML in the "Diagnosis and Curative Effect Criteria for Blood Diseases" , and confirmed the type of leukemia after flow cytometry. (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) The blood routine is normal, tolerate chemotherapy, and the estimated life cycle was more than 3 months. (7) The functions of important organs are basically normal. (8) Patients with other complex and serious diseases are not included. No previous history of coagulopathy and other tumor diseases.

Information sources: According to the above-mentioned search strategy, all relevant documents searched in the database were imported into EndNoteX9, and two researchers (Yin Xuewei and Guo Chenchen) independently read the titles and abstracts of the documents obtained in the preliminary examination to perform document screening at the same time. According to the inclusion and exclusion criteria, the literatures were sorted out and the data were extracted, and the extracted data were cross checked. The controversial literatures are discussed to decide whether they should be included or not. Or, if necessary, a third-party researcher (Ding Yi) can help to discuss and solve the problem and explain the reasons. The lack of information is supplemented by contacting the corresponding author. Use Microsoft Excel 2019 software to record all data.

Main outcome(s): Overall survival (OS) and relapse-free survival time (RFs).

Additional outcome(s): Including physical signs, peripheral blood, bone marrow, ECG and other contents, as well as factors related to myocardial enzyme spectrum, liver and kidney function, as well as the incidence of toxicity and side effects. The clinical remission effect was divided into complete remission (CR), partial remission (PR) and no remission (NR).

Quality assessment / Risk of bias analysis: Two researchers will independently evaluate the methodological quality of the included RCT based on the bias risk assessment tool of Cochrane Collaboration 19, which mainly includes seven aspects. It includes random sequence generation method, allocation concealment, blind method, result data integrity, selective result reporting bias and other bias. Each aspect is divided into "yes", "no" and "not clear". If two researchers have different opinions, it is determined by discussing with the third researcher or contacting the original author.

Strategy of data synthesis: Due to the diversity of research designs, similar studies in different countries or regions will inevitably have differences in meta-analysis. 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. The heterogeneity caused by factors such as trial design and treatment time requires subgroup analysis and sensitivity analysis.

Subgroup analysis: When there is significant heterogeneity between the research results, we will conduct a subgroup analysis of the reasons for the heterogeneity according to the source of the heterogeneity. In addition, we will use several aspects such as treatment type, disease course, age, gender, country, publication year, onset time, and duration for group analysis in different design schemes.

Sensitivity analysis: We will also use the exclusion method to analyze the sensitivity of all outcome indicators to disease. Sensitivity analysis evaluates the excluded literature one by one to determine whether the literature has an impact on heterogeneity. After changing some important factors that may affect the results, if the heterogeneity changes, then this article is the cause of the heterogeneity. It can be further analyzed in terms of sample size difference, experimental design and outcome indicators. On the contrary, the quality has not changed, indicating that the sensitivity is low, and the result is stable and credible.

Country(ies) involved: China.

Keywords: chemotherapy, IL-2, AML, Bayesian, network meta-analysis, protocol.

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