INPLASY PROTOCOL

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

Conflicts of interest: No.

Comparison of the clinical superiority of first-line immunosuppressive treatment for large granular lymphocytic leukemia (LGLL) patients: a systematic review and network meta-analysis

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Review question / Objective: To evaluate the effectiveness of three immunosuppressive drugs (CTX, MTX and CsA) in LGLL. Condition being studied: To evaluate the effectiveness of the clinical superiority of MTX, CTX and CsA, using direct and indirect comparisons, we conducted this systematic review and network meta-analysis.

Information sources: Searches were performed in the electronic PubMed, Cochrane Library, Embase and Web of Science databases. We searched the Cochrane Central Register of Controlled Trials, MEDLINE via Ovid (from 1946), Embase via Ovid (from 1974), the Latin American and Caribbean Health Science Information database (from 1982), and the Global Resource of Eczema Trials database. We also performed searches of the following trial registers: the ISRCTN (International Standard Randomized Controlled Trial Number) registry, ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry, the World Health Organization International Clinical Trials Registry Platform, and the EU Clinical Trials Register. We searched all databases from inception until June 9, 2020.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 June 2020 and was last updated on 10 June 2020 (registration number INPLASY202060035).

INTRODUCTION

Review question / Objective: To evaluate the effectiveness of three immunosuppressive drugs (CTX, MTX and CsA) in LGLL.

Rationale: Immunosuppressive treatments were adopted in clinical practice, but massive enrollment of randomized controlled trials (RCTs) is still lacking, thus making the standardization harder.

Condition being studied: To evaluate the effectiveness of the clinical superiority of MTX, CTX and CsA, using direct and indirect comparisons, we conducted this systematic review and network meta-analysis.

METHODS

Search strategy: Searches were performed in the electronic PubMed, Cochrane Library, Embase and Web of Science databases. We searched the Cochrane Central Register of Controlled Trials, MEDLINE via Ovid (from 1946), Embase via Ovid (from 1974), the Latin American and Caribbean Health Science Information database (from 1982), and the Global Resource of Eczema Trialsdatabase.

Participant or population: 205 LGLL patients were enrolled for network meta-analysis.

Intervention: Methotrexate (MTX), cyclophosphamide (CTX), and cyclosporine A (CsA).

Comparator: Methotrexate (MTX), cyclophosphamide (CTX), and cyclosporine A (CsA).

Study designs to be included: Crosssectional studies, controlled trials that do not use random sequence to allocate interventions, prospective and retrospective cohort studies.

Eligibility criteria: This systematic review and NMA will involve full-text articles which meet the eligibility criteria outlined below: (1) We included studies of children and adults with large granular lymphocytic leukemia. No age or sex restrictions were set; (2) We included studies of systemic immunosuppressive therapies for patients with LGLL and any comparator, including placebo. (3) Treatment outcome named hematological clinical hematological response (CHR) was defined as achievement of normal complete blood count: (ANC) > 1.5 × 109/L; absolute lymphocyte count (ALC) < 4.0 × 109 / L; hemoglobin level (HGB) > 110 g/L; platelet

count (PLT) > 100 × 109/L). (4) Treatment outcome named partial response (PR) was defined as improvement in blood counts (ANC > 0.5 × 109/L; HGB increased by >1 g/dL; PLT > 50 × 109/L), and the absence of required transfusions. This network meta-analysis will include all therapeutic intervention outcomes published from inception to June 2020 in English.

Information sources: Searches were performed in the electronic PubMed, Cochrane Library, Embase and Web of Science databases. We searched the Cochrane Central Register of Controlled Trials, MEDLINE via Ovid (from 1946), Embase via Ovid (from 1974), the Latin American and Caribbean Health Science Information database (from 1982), and the Global Resource of Eczema Trials database. We also performed searches of the following trial registers: the ISRCTN (International Standard Randomized Controlled Trial Number) registry, ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry, the World Health Organization International Clinical Trials Registry Platform, and the EU Clinical Trials Register. We searched all databases from inception until June 9, 2020.

Main outcome(s): Treatment outcome named hematological clinical hematological response (CHR) was defined as achievement of normal complete blood count: (ANC) > 1.5 × 109/L; absolute lymphocyte count (ALC) < 4.0 × 109 / L; hemoglobin level (HGB) > 110 g/L; platelet count (PLT) > 100 × 109/L). Treatment outcome named partial response (PR) was defined as improvement in blood counts (ANC > 0.5 × 109/L; HGB increased by >1 g/dL; PLT > 50 × 109/L), and the absence of required transfusions.

Additional outcome(s): None.

Data management: Endnote.

Quality assessment / Risk of bias analysis: Two reviewers (JD and HSY) independently extracted the data from each studyincluding first author, publication year, study region, patient number, median age,

period of enrollment, treatment type, and study outcome. Disagreements between the two reviewers were resolved via discussion. Two researchers (JD and YY) accessed the quality of the included studies using the Newcastle-Ottawa Scale (NOS) . The NOS consists of nine items classified into three dimensions including selection (four items), comparability (two items), exposure, and outcome (three items). Based on the NOS, the quality of the studies was classified into high-quality (scores 7–9), intermediate-quality (scores 4–6), and low-quality (scores 1–3) studies.

Strategy of data synthesis: Endnote.

Subgroup analysis: We will explore whether treatment effects for our primary outcomes are robust in subgroup analyses using the following characteristics: CHR, PR.

Sensibility analysis: We will conduct a sensitivity analysis to determine the relative weight of constituent studies on the overall point estimate of our review outcome.

Language: English.

Country(ies) involved: China.

Other relevant information: None.

Keywords: Large granular lymphocytic leukemia (LGLL); first-line treatment; immunosuppressive agent; network meta-analysis.

Contributions of each author:
Author 1 - Jun Du - Author 1 drafted the manuscript.
Author 2 - Huisheng Yang - The author provided statistical expertise.
Author 3 - Yangmin Zhu - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Ying Yu - The author read, provided feedback and approved the final manuscript.
Author 5 - Dehui Zou - The author read, provided feedback and approved the final manuscript.

Author 6 - Gang An - The author read, provided feedback and approved the final manuscript.
Author 7 - Shuhua Yi - The author read, provided feedback and approved the final manuscript.
Author 8 - Lugui Qiu - The author read, provided feedback and approved the final manuscript.