

INPLASY PROTOCOL

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Conflicts of interest:
The authors declare that they have no competing interests.

Erythropoietin combined with TCM for Chemotherapy-Induced Anemias: a protocol of systematic review and meta-analysis

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Review question / Objective: This study aimed to assessment the efficacy and safety of erythropoietin combined with Traditional Chinese Medicine in the treatment of chemotherapy induced anaemia in patients with solid tumours.

Information sources: An experienced librarian will draw up a set of search terms. The source of literature will be a structured search of the following seven electronic databases: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM) and Wanfang database. Medical subject Heading (MeSH) and text words will be searched as our keyword. Other database can use this search strategy after being adapted and tailored that using Boolean operators (OR/AND), truncations, proximity operators, and MeSH, as appropriate for each database. Search of all database will be independently performed by two reviewers from inception to 1 August 2020. In search, there will be no language and publication status restrictions. In order to avoid missing potential study, we will manually search grey literature (e.g. trial registries), and search for reference lists of relevant trials and reviews.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 August 2020 and was last updated on 10 August 2020 (registration number INPLASY202080041).

Condition being studied: Erythropoietin combined with TCM for Chemotherapy-Induced Anemias.

METHODS

Search strategy: An experienced librarian will draw up a set of search terms. The source of literature will be a structured search of the following seven electronic

databases: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM) and Wanfang database. Medical subject Heading (MeSH) and text words will be searched as our keyword. Other database can use this search strategy after being adapted and tailored that using Boolean operators (OR/AND), truncations, proximity operators, and MeSH, as appropriate for each database. Search of all database will be independently performed by two reviewers from inception to 1 August 2020. In search, there will be no language and publication status restrictions. In order to avoid missing potential study, we will manually search grey literature (e.g. trial registries), and search for reference lists of relevant trials and reviews.

Participant or population: (1) Patients with solid tumors confirmed by histology or cytology, do not limit the type and stage of the tumor. (2) Patients must be at least 18 years old, and no restriction of gender, country and race. (3) Patients received chemotherapy, and no restriction of the type and course of drugs use. (4) $Hb \leq 10.0g/dl$, and confirmed caused by chemotherapy drugs.

Intervention: Patients in the experimental group received TCM treatment on the basis of the treatment in the control group. If necessary, patients in both the control group and the experimental group were to receive red blood cell transfusions or other basic therapy (e.g. iron). In addition, patients in both groups must have received identical care.

Comparator: Cancer patients in the control group must have received short or long acting ESAs to reduce CIAs. ESAs must be administered subcutaneously or intravenously. There are no treatment duration and dosage restrictions of ESA.

Study designs to be included: Randomized controlled trials (RCTs) and controlled clinical trials (CCTs) will be included in this systematic and meta-analysis. Other type of studies.

Eligibility criteria: The eligibility criteria for our systematic review and meta-analysis are as follows: **Participants:** (1) Patients with solid tumors confirmed by histology or cytology, do not limit the type and stage of the tumor. (2) Patients must be at least 18 years old, and no restriction of gender, country and race. (3) Patients received chemotherapy, and no restriction of the type and course of drugs use. (4) $Hb \leq 10.0g/dl$, and confirmed caused by chemotherapy drugs. **Interventions/comparators:** Cancer patients in the control group must have received short or long acting ESAs to reduce CIAs. ESAs must be administered subcutaneously or intravenously. There are no treatment duration and dosage restrictions of ESA. Patients in the experimental group received TCM treatment on the basis of the treatment in the control group. If necessary, patients in both the control group and the experimental group were to receive red blood cell transfusions or other basic therapy (e.g. iron). In addition, patients in both groups must have received identical care. **Outcomes:** The primary outcome is the efficacy, we expect to be evaluated from six aspects: (1) the proportions of patients with an Hb increase of $\geq 1 g/dl$; (2) the proportions of patients with an Hb increase of $\geq 2 g/dl$; (3).

Information sources: An experienced librarian will draw up a set of search terms. The source of literature will be a structured search of the following seven electronic databases: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM) and Wanfang database. Medical subject Heading (MeSH) and text words will be searched as our keyword. Other database can use this search strategy after being adapted and tailored that using Boolean operators (OR/AND), truncations, proximity operators, and MeSH, as appropriate for each database. Search of all database will be independently performed by two reviewers from inception to 1 August 2020. In search, there will be no language and publication status restrictions. In order to avoid missing potential study, we will

manually search grey literature (e.g. trial registries), and search for reference lists of relevant trials and reviews.

Main outcome(s): The primary outcome is the efficacy, we expect to be evaluated from six aspects: (1) the proportions of patients with an Hb increase of ≥ 1 g/dl; (2) the proportions of patients with an Hb increase of ≥ 2 g/dl; (3) time to first Hb increase of ≥ 1 g/dl; (4) time to first Hb increase of ≥ 2 g/dl; (5) the proportions of patients receiving blood transfusions, either RBCs or whole blood; and (6) time to first transfusion.

Additional outcome(s): The secondary outcome is the safety that will be assessed by occurrence of adverse events (AEs).

Quality assessment / Risk of bias analysis:

The quality of included studies was evaluated by two different tools. Cochrane Risk of Bias (RoB) tool was used to assess the quality of randomized controlled trials.³ The tool for evaluating the risk of bias consists of 7 specific domains: sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other bias. Each included study will be assigned a level of risk of bias (high risk, unclear risk, low risk) for each domain. Newcastle-Ottawa Scale (NOS) was used to assess the quality of case control studies. It is included items within 3 domains to evaluate bias in patient selection, comparability, and outcome assessments. Each included study will be awarded a maximum of 1 star for each numbered item among the items that evaluate patient selection and outcome assessments. A maximum of 2 stars will be given for comparability, and the total scores ranged from 0 to 9 points. Two reviewers will independently assess the quality for each included study, and a third reviewer will consult the disagreement.

Strategy of data synthesis: Review Manager 5.3 software (Cochrane Collaboration, Copenhagen Denmark) will

be used to perform meta-analysis. For dichotomous variables, odds ratio (OR) with 95% confidence intervals (CIs) will be obtained by Mantel-Haenszel method. For continuous data, mean difference (MD) with 95% CIs will be used. The statistical heterogeneity of studies included in the meta-analysis will be assessed using I² statistic (with values of 25%, 50%, and 75% is representative of the low, medium, and high heterogeneity, respectively). If the heterogeneity is high, the random effects model will be used for the analysis. And the fixed effects model will be used for studies with low or moderate heterogeneity. A sensitivity analysis will be performed by excluding one study at a time to test the robustness of the pooled results. If relevant data are available, subgroup analysis will be performed (e.g. kinds of TCM, course of treatment, patient's gender, types of cancers). Publication bias will be evaluated using the Egger test and Begg test when at least 10 studies are included. $P < 0.05$ will be considered to be statistically significant. In addition, meta-regression will be used to determine factors that may influence the outcome. For meta-regression analyses, STATA16 (Stata Corp LP, TX, USA) will be used.

Subgroup analysis: If relevant data are available, subgroup analysis will be performed (e.g. kinds of TCM, course of treatment, patient's gender, types of cancers).

Sensibility analysis: A sensitivity analysis will be performed by excluding one study at a time to test the robustness of the pooled results.

Language: English and Chinese.

Country(ies) involved: China.

Keywords: Erythropoietin; Tradition Chinese Medicine; Chemotherapy-induced anemias; Systematic review; Meta-analysis.

Contributions of each author:

Author 1 - Chuanhui Dou.