INPLASY PROTOCOL

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None declared.

Compound Kushen injection combined with chemotherapy for patients with non-Hodgkin lymphoma: A protocol for systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: **The purpose of this study is to formulate a protocol for the systematic review and meta-analysis of the effectiveness and safety of Compound Kushen Injection combined with chemotherapy in the treatment of non-Hodgkin lymphoma.**
Condition being studied: **Chemotherapy is the first choice of treatment for various types of non-Hodgkin lymphoma, and its efficacy and adverse reactions are not satisfactory. In recent years, the traditional Chinese medicine compound Sophora flavescens injection has been widely used in clinical non-Hodgkin lymphoma, which has the effects of improving the efficacy of chemotherapy and reducing adverse reactions.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 February 2021 and was last updated on 19 February 2021 (registration number INPLASY202120063).

INTRODUCTION

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METHODS

Search strategy: According to the Eligibility criteria, we will search the literature database by combining both Medical Subject Heading (MeSH) and free-text terms which contain various synonyms. Medical Subject Heading or key words such as "Fufangkushen" or "compound Kushen injection" or "CKI" or "non-Hodgkin lymphoma" or "chemotherapy" will be used and the Chinese form of the above terms ('ku_shen', 'fu_fang_ku_shen_zhu_she_ye', 'fei_huo_qi_jin_lin_ba_liu', 'hua_liao') will be used for Chinese searches.

Participant or population: Patients who are pathologically or histologically diagnosed as NHL according to Standards for diagnosis and treatment of lymphoma (2018 edition)[18], the classification standard is according to 2019 WHO lymphoma classification[19], and the treatment methods include at least one chemotherapy will be included. There is no restriction on age, gender or race. Patients with severe primary diseases such as arrhythmia, heart failure, acute myocardial infarction, severe neurosis, menopausal syndrome and hematopoietic system illness will be excluded.

Intervention: It is clearly proposed that the main therapeutic intervention should be CKI treatment combined with chemotherapy which can anti-inflammatory, anti-viral, anti-allergic, anti-fibrosis, and anti-cancer activities.

Comparator: Patients who received chemotherapy drugs were considered as control group. The dosage of chemotherapy drugs used in the treatment groups should be the same as used in the control groups. There are no restrictions on the duration of medication.

Study designs to be included: RCTs using compound kushen injection combined with chemotherapy to treat non-Hodgkin lymphoma. In addition, this research will contain some clinical trials. All related and published RCTs will be included, for example, earlier I/II, Phase III trials. Only consider studies in English and Chinese and published as full-text articles.

Eligibility criteria: Randomized controlled trial (RCT) using compound kushen injection (CKI) combined with chemotherapy to treat non-Hodgkin lymphoma. In addition, this research will contain some clinical trials. All related and published RCTs will be included, for example, earlier I/II, Phase III trials. Only consider studies in English and Chinese and published as full-text articles. We will exclude non-therapeutic research, animal experiments, review literature, case reports, meta-analysis, duplicate publications, outcome effect not clear, and studies with insufficient results or wrong statistical method.

Information sources: From the beginning of the relevant studies until 1 January 2021, this research will be searched from the electronic literature databases as follow: PubMed, Embase, Cochrane library, China National Knowledge Infrastructure (CNKI), Wangfang Database, VIP database and Chinese Biomedical Literature Database.

Main outcome(s): The main outcomes. (1) Overall response rate (ORR) and disease control rate which contain complete response and partial response will be all evaluated using the Recist criteria; (2) Randomization to death from any reason; (3) Disease-free survival (DFS) which refers to time from the date of random assignment to the date of relapse or death. The secondary outcomes. (1) Karnofsky score, Quality of Life (QOL) scale score, improvement of symptoms;

(2)Immunological related indicators: the percentage of CD3 +, CD4 +, CD8 + and NK cells, the ratio of CD4 + / CD8 + cells, and the level of serum cytokines (such as IL-2, IL-4, IFN-γ and TNF- α); (3) Treatment-related adverse reactions: the severity of treatment-related toxic reactions range from 0 to IV according to the recommendations of the World Health Organization.

Quality assessment / Risk of bias analysis: Two reviewers (Qiyuan Mao and Lanchun Liu) will separately evaluate the quality of the RCTs included, they will use the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions Review Manual: The generation of random sequences, the concealment of allocation, the blinding of participants and personnel, the blinding of result assessment, incomplete data of result, selective reporting and other biases. The quality of evidence will be judged into "low risk", "high risk" or "unclear risk". Assessing non-RCT risks will use effective nursing practices and organizational guidelines. Any differences will be resolved through discussions with the third researcher (Xueqian Wang).

Strategy of data synthesis: Statistical analysis will be performed using STATA 15.0 and RevMan 5.3. The 95% CIs and HRs will be used to evaluate the OS and DFS. The included studies will be tested for statistical heterogeneity. The fixed effects model will be considered if there is no statistical heterogeneity in the included literature (P≥0.1, I2<50%). If there is statistical heterogeneity in included literature (P<0.1, I2≥50%), the source of heterogeneity between multi-studies will be evaluated.

Subgroup analysis: Subgroup analysis will be used to analyze clinical heterogeneity such as the age, sex ratio, tumor staging of NHL, region, therapeutic regimens and courses. If there is no obvious clinical and methodological heterogeneity, random effect model will be used to conduct and analyze the statistical heterogeneity. For studies with high clinical heterogeneity, we will only perform descriptive analysis instead of meta-analysis.

Sensitivity analysis: If necessary, a sensitivity analysis will also be carried out, the purpose of which is to eliminate the influence of trials that may have a high risk of bias on the reliability and robustness of the assessment results. The results of the sensitivity analysis will be reported in the summary table.

Language: English, Chinese-Simplified.

Country(ies) involved: China.

Keywords: Compound Kushen injection, chemotherapy, non-Hodgkin lymphoma, efficacy, safety, meta-analysis, study protocol.

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