INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Clinical efficacy and safety of Chinese herb injections combination with platinum-based chemotherapy for advanced non-small cell lung cancer: A protocol for Bayesian network meta-Analysis

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Review question / Objective: **The aim of this study will to be assess the clinical efficacy and safety of different Chinese herb injections(CHIS) combined with platinum-based chemotherapy for advanced non-small cell lung cancer and to provide evidence for rational selection of CHIs by using network meta-analysis.**
Information sources: **Eight public domain electronic databases will be systematically searched with a time frame of build to December 2021. The databases are as follows: PubMed, Cochrane Library, Embase, Web of Science, Chinese National Knowledge Infrastructure, WanFang database, China Biology Medicine Database and Chongqing VIP Chinese Scientific Journals Full-text Database. Searches will be performed using the following keywords: herbal injections and (lung cancer or lung malignancy or NSCLC) and platinum-based chemotherapy. We will modify the search strategy to accommodate all databases. The language of articles is limited to Chinese and English.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 November 2021 and was last updated on 29 November 2021 (registration number INPLASY2021110105).

INTRODUCTION

Review question / Objective: **The aim of this study will to be assess the clinical efficacy and safety of different Chinese herb injections(CHIS) combined with platinum-based chemotherapy for advanced non-small cell lung cancer and to provide evidence for rational selection of CHIs by using network meta-analysis.**

Condition being studied: **As one of the major diseases threatening human health, lung cancer has received widespread**

attention all around the world, because of its high incidence, recurrence and mortality rates. Studies have shown that non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancer, and the 5-year survival rate is less than 15%. Because the pathological mechanism of NSCLC is complex and not yet well understood, there is no fundamental therapy for the disease. The current platinum-based two-drug combination chemotherapy regimen as first-line therapy has resulted in significantly higher objective response rate and significantly longer median Overall survival in patients with NSCLC, especially for those who cannot receive targeted therapy. However, the side effects of chemotherapy often increase patients' pain and affect their quality of life. Studies have confirmed that CHIS, as a product of the modernization process of traditional Chinese medicine, can improve clinical efficacy and have good safety in combination with conventional chemotherapy. However, there is still no direct or indirect comparison between multiple CHIS, thus limiting the clinical evidence-based application.

METHODS

Participant or population: Patients with stage III-IV NSCLC were diagnosed by pathological or cytological examination. Gender, race, age, economic and educational status were not restricted. Patients did not receive any concomitant radiotherapy, non-platinum-based chemotherapy, or herbal therapy in this study.

Intervention: In the experimental group, platinum-based chemotherapy combined with at least one herbal injection were involved. There were no restrictions on the type, dose, duration of chemotherapy drugs or herbal injections. Patients was treated with platinum-based chemotherapy only in the control group.

Comparator: We will compare the efficacy and safety of CHIS combined with platinum-based chemotherapy regimens to platinum-based chemotherapy regimens alone.

Study designs to be included: We will plan to include only randomized controlled trials (RCTs) comparing the efficacy and safety of CHIS in combination with platinum-based chemotherapy and platinum-based chemotherapy alone for the treatment of advanced NSCLC. Studies will be excluded if data are not available by contacting the authors.

Eligibility criteria: Only RCTs will be included in this study to compare the efficacy and safety of Chinese herbal injections in combination with platinum-based chemotherapy and platinum-based chemotherapy alone for the treatment of advanced NSCLC. The patients must be confirmed by cytology or pathology as non-small cell lung cancer. In the experimental group, platinum-based chemotherapy combined with at least one herbal injection were involved.

Information sources: Eight public domain electronic databases will be systematically searched with a time frame of build to December 2021. The databases are as follows: PubMed, Cochrane Library, Embase, Web of Science, Chinese National Knowledge Infrastructure, WanFang database, China Biology Medicine Database and Chongqing VIP Chinese Scientific Journals Full-text Database. Searches will be performed using the following keywords: herbal injections and (lung cancer or lung malignancy or NSCLC) and platinum-based chemotherapy. We will modify the search strategy to accommodate all databases. The language of articles is limited to Chinese and English.

Main outcome(s): The primary outcome include the effect of antitumor therapy. These include objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), overall survival (OS).

Additional outcome(s): Additional outcomes will include safety and quality of life outcomes. These include indicators of

bone marrow suppression, gastrointestinal symptoms, indicators of abnormal liver and kidney function, and Karnofsky scores.

Quality assessment / Risk of bias analysis: The risk of bias for each included study will be assessed by using the Cochrane Risk of Bias (RoB) tool for randomised controlled trials. Seven domains will be assessed in terms of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The methodological quality of the included RCTs will be assessed independently by 2 researchers, and if there will be disagreement between the two researchers, we will resolve the inconsistency through discussion or with the help of senior researchers.

Strategy of data synthesis: The direct Meta-analysis and Bayesian Network Meta-analysis will be performed using ADDIS 1.16. 8 software, in which the odds ratio (OR) and 95% confidence interval (CI) will be used for the direct Meta-analysis, and the $\chi 2$ test combined with I2 will be used to determine the size of heterogeneity. I2 ≤ 50% indicates less heterogeneity between studies and comparative studies can be performed, while I2 > 50% indicates greater heterogeneity between studies and further sensitivity analysis will be performed. The OR and 95% CI will be used to express the outcome effect size in Bayesian Network Meta-analysis. For studies that could generate node split nodes, the node split model will be used to compare the consistency between direct and indirect comparisons, and P>0.05 indicated good consistency, and the consistency model will be used for analysis, otherwise he inconsistency model will be used for the opposite. The study of ungenerated node split nodes will be analyzed using the consistency model. For all studies using the consistency model, the stability and reliability of the results should be tested by the inconsistency model. If inconsistency factors can be generated and the 95% CI includes 0, and in-consistency standard deviation 95% CI includes 1, the consistency model results can be considered stable and reliable, otherwise the inconsistency model will be used for analysis. The potential scale reduction factor (PSRF) will be applied to all models to determine the convergence of the results. If the PSRF is between 1. 00 and 1. 05, the convergence of the iterative effect is good and the model is stable and reliable. Otherwise, we will use Extend button to iterate more parameters until the PSRF is between 1. 00 and 1. 05. In addition, Stata 14. 0 software will be applied to plot the Bayesian Network relationship.

Subgroup analysis: If heterogeneity is high, we will perform a subgroup analysis.

Sensitivity analysis: Stata 15.0 software will be used to conduct sensitivity analyses on the stability of the study results and to generate funnel plots to evaluate whether there is a small sample effect or publication bias for the intervention. Differences will be statistically significant if P < 0.05.

Language: Chinese and English.

Country(ies) involved: China.

Keywords: Chinese herb injection, platinum-based Chemotherapy, non-small cell lung cancer, Protocol, Network meta-analysis.

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