# INPLASY PROTOCOL

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**Conflicts of interest:**
**None declared.**

# Comparative Efficacy of Chinese Herbal Injections Combined Western medicine for Non-small cell lung cancer: A Bayesian Network Meta-Analysis of randomized controlled trials

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**Review question / Objective:** **Advanced lung cancer has become the top malignant tumor in terms of morbidity and mortality, and Chinese herbal injections combined with western drugs have been widely used to treat advanced non-small cell lung cancer. For this purpose, we conducted a Bayesian network analysis to systematically evaluate the efficacy of different herbal injections combined with western drugs in the treatment of NSCLC. Subjects: Patients diagnosed with NSCLC by pathological or cytological examination, locally advanced or those who refused surgical treatment were included, regardless of gender, age, stage, race, nationality and sample size; Interventions: Chinese herbal injections combined with three types of commonly used western drugs (platinum, targeted and immune agents) were used in the experimental group, while the control group was treated with western drugs alone; Study type: to report the efficacy of Chinese herbal injections combined with western drugs in the treatment of non-small cell lung cancer efficacy in a randomized controlled trial (rct) Eligible. No restrictions were imposed on language, year of publication, or publication status. Ending indicators: Main ending indicators: (1) disease control rate (DCR), DCR = (complete remission + partial remission + stable)/total number of cases. Efficacy rate = (number of improvement cases + number of stable cases)/total number of cases. (2) Secondary outcome indicators: quality of life, determined according to the KPS behavioral status scale, improvement was defined as an increase of ≥10 points in KPS score after treatment; stability was defined as an increase or decrease of <10 points in KPS score; decline was defined as a decrease of ≥10 points in KPS score. (3) The incidence of adverse reactions, including gastrointestinal reactions, white blood cell (WBC) reduction, hemoglobin (HGB) reduction, platelet (PLT) reduction, etc.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 November 2021 and was last updated on 17 November 2021 (registration number INPLASY2021110068).

## INTRODUCTION

**Review question / Objective:** **Advanced lung cancer has become the top malignant tumor in terms of morbidity and mortality, and Chinese herbal injections combined with western drugs have been widely used to treat advanced non-small cell lung cancer. For this purpose, we conducted a**

Bayesian network analysis to systematically evaluate the efficacy of different herbal injections combined with western drugs in the treatment of NSCLC. Subjects: Patients diagnosed with NSCLC by pathological or cytological examination, locally advanced or those who refused surgical treatment were included, regardless of gender, age, stage, race, nationality and sample size; Interventions: Chinese herbal injections combined with three types of commonly used western drugs (platinum, targeted and immune agents) were used in the experimental group, while the control group was treated with western drugs alone; Study type: to report the efficacy of Chinese herbal injections combined with western drugs in the treatment of non-small cell lung cancer efficacy in a randomized controlled trial (rct) Eligible. No restrictions were imposed on language, year of publication, or publication status. Ending indicators: Main ending indicators: (1) disease control rate (DCR), DCR = (complete remission + partial remission + stable)/total number of cases. Efficacy rate = (number of improvement cases + number of stable cases)/total number of cases. (2) Secondary outcome indicators: quality of life, determined according to the KPS behavioral status scale, improvement was defined as an increase of ≥10 points in KPS score after treatment; stability was defined as an increase or decrease of <10 points in KPS score; decline was defined as a decrease of ≥10 points in KPS score. (3) The incidence of adverse reactions, including gastrointestinal reactions, white blood cell (WBC) reduction, hemoglobin (HGB) reduction, platelet (PLT) reduction, etc.

**Condition being studied:** Advanced lung cancer has become the malignant tumor with the highest morbidity and mortality rate, and the treatment of advanced non-small cell lung cancer with traditional Chinese medicine injections combined with western medicine has been widely used. The combination of Chinese and Western medicines in the treatment of advanced lung cancer effectively prolongs the survival time and improves the quality of life, which is an important reference value for the treatment of advanced lung cancer patients and the selection of clinical treatment plan. The remission rate of conventional radiotherapy for lung cancer is only 15%-20%. Targeted therapy has achieved good efficacy in lung cancer treatment, but for advanced lung cancer without driver mutations, chemotherapy is still the main treatment, which is usually difficult to be tolerated by patients or has a short overall survival (OS), which greatly limits the clinical application. Immunotherapy has increased the 5-year survival rate of patients with advanced non-small cell lung cancer (NSCLC) from 5% to about 23%, but it has limitations in clinical practice due to low antigenicity, side effects, and drug resistance. Chinese medicine can reduce the toxic side effects of western drugs, enhance their sensitivity, and reverse drug resistance. Combination of Chinese medicine is not simply a superimposed effect, but can play a better synergistic role, which can better inhibit tumor development, improve patients' quality of life, prolong their survival, and regulate the immune microenvironment. For this purpose, we conducted a Bayesian network analysis to systematically evaluate the efficacy of different herbal injections combined with western drugs in the treatment of NSCLC.

## METHODS

**Participant or population:** Patients with pathologically or cytologically confirmed diagnosis of NSCLC, locally advanced or refusing surgical treatment, regardless of gender, age, stage, race, nationality and sample size were included.

**Intervention:** The test group used Chinese herbal injections in combination with three commonly used western drugs (platinum, targeted and immune agents).

**Comparator:** Treatment with Western medicine alone.

**Study designs to be included:** A randomized controlled trial (rct) reporting the efficacy of Chinese herbal injections in

combination with western drugs for the treatment of non-small cell lung cancer was eligible, with no restrictions imposed on language, year of publication, or publication status.

**Eligibility criteria:** Inclusion and exclusion criteria of the literature Inclusion criteria: (1) meet the requirements of the previous inclusion population requirements; (2) the type of study is a randomized controlled trial; (3) the outcome indicators are: a: disease control rate (DCR), DCR = (complete remission + partial remission + stable)/total number of cases. Effective rate = (number of improved cases + number of stable cases)/total number of cases. b: Secondary outcome indicators: quality of life, as determined by the KPS behavioral status scale, improvement as an increase of ≥10 points in KPS score after treatment; stability as an increase or decrease of <10 points in KPS score; decline as a decrease of ≥10 points in KPS score. c: incidence of adverse effects, including gastrointestinal reactions, white blood cell (WBC) decrease, and WBC decrease. The incidence of adverse reactions included two of them, such as gastrointestinal reactions, white blood cell (WBC) reduction, hemoglobin (HGB) reduction, platelet (PLT) reduction, etc. Exclusion criteria: (1) non-randomized controlled trials; (2) non-lung cancer patients; (3) animal testing.

**Information sources:** Computer search of China Knowledge Network, Wanfang database, China Biological The database of medical literature, Vipul.com, and foreign language databases Pubmed, EMBase, and Cochrane Library were searched. EMBase, Cochrane Library, etc. The RCTs of Chinese medicine injections in combination with western drugs were searched compared with western drugs alone for NSCLC, and the search period was from the date of creation to November 01, 2021. In addition, the literature can be supplemented by retrospective references and other resources such as conferences and books.

**Main outcome(s):** Endpoint indicators: Main outcome indicators: (1) Disease control rate (DCR), DCR = (complete remission + partial remission + stable) / total number of cases. Efficacy rate = (number of improvement cases + number of stable cases)/total number of cases. (2) Secondary outcome indicators: quality of life, determined according to the KPS behavioral status scale, improvement was defined as an increase of ≥10 points in KPS score after treatment; stability was defined as an increase or decrease of <10 points in KPS score; decline was defined as a decrease of ≥10 points in KPS score. (3) The incidence of adverse reactions, including gastrointestinal reactions, white blood cell (WBC) reduction, hemoglobin (HGB) reduction, platelet (PLT) reduction, etc.

**Quality assessment / Risk of bias analysis:** Information from the eligible RCTs was extracted by two researchers independently based on a custom-made form. The data consisted of the following items: (I) basic information of the eligibility: the first author, nationality, publication year, and study design; (II) basic characteristics of patients: sample size, sex composition, average age, course of disease, and cardiac function classification; (III) details of intervention; and (IV) the results of outcomes and information about quality assessment of RCTs. For dichotomous outcomes, the number of responders and the total number of participants for each study arm were extracted. For continuous outcomes, the mean and standard deviation for the mean in each group of the trial were extracted along with the total number. The quality assessment was independently performed by two reviewers with the Cochrane Collaboration's tools (version 5.1.0, http://handbook-5-1.cochrane.org/). The quality assessment items of Cochrane tools included the following: (I) selection bias: random sequence generation and allocation concealment; (II) performance bias: blinding of the participants and personnel; (III) detection bias: blinding of the outcome assessment; (IV) attrition bias: incomplete outcome data; (V) reporting bias: selective reporting; and (VI) other bias. Each aspect was categorized into

three levels: high risk, unclear risk, and low risk. Any disagreements were resolved by a third researcher.

**Strategy of data synthesis:** Bayesian network analysis was performed by applying R64.4.1.1 and Stata 17.0 software. If the difference of DIC between the two models is ≤5, the two models are considered to have the same fit and the model with smaller I2 is selected; if the difference is >5, the model with smaller DIC is selected. If there was a closed loop in the indirect comparison relationship, nodal analysis was performed to detect inconsistency, and the inconsistency was determined by Z-test, and if P>0.05, the inconsistency was considered not to exist and the consistent model was analyzed by using R software, and vice versa, the inconsistent model was analyzed by using Gemtc software. Each model was set with 4 Markov chains for initial values, and the number of iterations was set to 50,000, and the first 20,000 iterations were used for annealing to eliminate the influence of the initial values, and the model convergence was diagnosed by Potential Scale Reduction Factors (PSRF), and the PSRF value converged to 1 to indicate that the model converged Satisfactory, otherwise continue to increase the number of iterations.

**Subgroup analysis:** Subgroup analysis based on herbal injections and different types of western drugs.

**Sensitivity analysis:** Sensitivity analysis based on heterogeneity.

**Country(ies) involved:** China.

**Keywords:** Chinese medicine injection; Western medicine; lung cancer; Bayesian network analysis.

**Contributions of each author:**
Author 1 - Ciyan Peng.
Author 2 - Jing Chen.
Author 3 - Sini Li.
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