INPLASY PROTOCOL

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Corresponding author:
Qiujun Guo

drguoqiujun@126.com

Author Affiliation:
Guang'anmen Hospital

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Conflicts of interest:
We declare that we have no financial and personal relationships with other people or organizations.

Clinical effect and safety of Chinese medicine injections on advanced stage non-small cell lung cancer (NSCLC) combined with chemotherapy: umbrella review of meta-analyses

Guo, Q[1].

Review question / Objective: **The aim of the review is to evaluate the clinical effect, safety Chinese medicine injections on advanced stage non-small cell lung cancer combined with chemotherapy, to systematically review the published evidence of clinical efficacy as well as the side effects. P: Advanced stage non-small cell lung cancer patients. I: Chinese medicine injections combined with chemotherapy. C: Chemotherapy combined with placebo. Chemotherapy regimens follow the NCCN NSCLC guidelines. Chemotherapeutic drugs are platinum compounds, taxanes, pemetrexed, gemcitabine, vinorelbine, etc. O: The investigated outcomes will include anti-tumor treatment effects (response rate (RR), disease control rate (DCR), 1 OR 3 year survival rate, progression free survival (PFS), overall survival (OS)), KPS score, myelosuppression outcomes (cell counting of white cells, red cells and platelets), gastrointestinal reaction outcomes (classification of nausea, vomiting, diarrhea and constipation), abnormal renal and liver function outcomes (anomaly degree of ALT, AST, GGT, Cr and BUN).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 June 2020 and was last updated on 06 June 2020 (registration number INPLASY202060022).

INTRODUCTION

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Condition being studied: Lung cancer is the second leading cancer in mortality and morbidity , non small cell lung cancer (NSCLC) is the most common type, accounting for about 85 percent. Though recently target-therapy, immunotherapy, etc. prolong the overall survival and enhance the clinical efficacy of NSCLC, chemotherapy is still the cornerstone of the advanced stage NSCLC treatment, especially for those who have no gene mutations or no target kinase mutations. Increasing researches have provided clinical efficacy evidences that Chinese Medicine combined with chemotherapy for the treatment of NSCLC . It was reported that Chinese medicine could reduce the toxicity and enhance the efficacy combining with chemotherapy in tumor treatment. Also, Chinese medicine was proved to regulate tumor immune environment, inhibit tumorigenesis, prevent tumor invasion and angiogenesis, etc. in basic researches.

METHODS

Participant or population: Our target populations are advanced stage NSCLC patients, who were treated by Chemotherapy combined with Chinese medicine injections or placebo.

Intervention: Chinese medicine injections combined with chemotherapy regimens.

Comparator: We will compare Chinese medicine injections combined with chemotherapy regimens to Chemotherapy combined with placebo.

Study designs to be included: To overview the clinical effect and safety of Chinese medicine injections on advanced stage non-small cell lung cancer combined with chemotherapy.

Eligibility criteria: Inclusion articles will meet the following requirements: studies that are meta analysis, systematic review or pooled analysis; meta-analyses that integrated the randomized controlled studies which evaluated efficacy or safety of Chinese medicine injections combine with chemotherapy on advanced stage NSCLC; meta-analyses that had substantial data and were up to date.

Information sources: We will search PubMed, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database up to May 2020. We will also hand-search all reference lists of the included studies to identify additional reviews of relevance. We will use the search strategy with those specified keywords: Chinese medicine injection AND (lung OR pulmonary) AND (cancer OR carcinoma OR tumor OR neoplasma) AND (systematic review OR meta analysis OR pooled analysis). We will modify the search strategy to suit all five databases. There is not language restriction in article selections.

Main outcome(s): The investigated main outcomes will include anti-tumor treatment effects * Measures of effect response rate (RR), disease control rate (DCR), 1 OR 3 year survival rate, progression free survival (PFS), overall survival (OS).

Additional outcome(s): Additional outcomes will include safety, side-effects and quality of life outcomes. * Measures of effect myelosuppression outcomes: cell counting of white cells, red cells and platelets gastrointestinal reaction outcomes: classification of nausea, vomiting, diarrhea and constipation

abnormal renal and liver function outcomes: anomaly degree of ALT, AST, GGT, Cr and BUN quality of life outcome: KPS score.

Data management: The study specific risk estimates will also be included, covering risk ratio, odds ratio, weighted mean difference, standard mean difference together with their 95% CI and number of incident events and total events in each study. If more than one meta-analysis evaluate the same Chinese injection combining with same chemotherapy drugs and evaluate the same outcome, we would look into their included original trials respectively, to save the common trials and add in the absent ones. We would synthesize all the available data to get a more comprehensive and objective result.

Quality assessment / Risk of bias analysis: If an outcome involved at least 3 articles, we will use Egger's test (conducted using Stata V.14.0) to evaluate if the reporting bias existed. Values of $p<0.1$ will be interpreted as statistically significant. AMSTAR2 tool will be used to assess risk of bias of the methodological quality of the eligible studies. AMSTAR 2 is a major revision of the original AMSTAR instrument, which was designed to appraise systematic reviews that included randomised controlled trials. AMTAR 2, like its predecessor, has an important role as a convenient teaching aid and a brief checklist for those conducting systematic reviews. However, as a creative point, it adds an ability to identify critical weaknesses that should reduce confidence in the findings of a review.

Strategy of data synthesis: Statistical analyses will be conducted with RevMan V.5.3 software provided by Cochrane Collaboration and Stata V.14.0 software. For each outcome, if the random model was already used, we will record the results, if not, we will extract original data and reanalyze them with the random effects methods, to get a new 95% confidence interval (CI), to increase credibility. We will also calculate 95% predication intervals (PI) for each random effect estimate, to represent the range in which the effect estimates of future studies will lie. The Q and I^2 test statistics will be calculated to determine the amount of heterogeneity. For the Q statistic, p50% indicates substantial heterogeneity, $I^2>75\%$ indicates considerable heterogeneity.

Subgroup analysis: In our analysis, when possible, we will stratify the comparisons into several groups according to the efficacy of injections (such as tonifying group or heat-clearing and detoxifying group), chemotherapy regimens (such as GP group, TP group or NP group, etc.), the doses of Chinese medicine injections and chemotherapy drugs are comparable.

Sensibility analysis: Sensitivity analysis will be performed by reanalysing the data using different statistical approaches.

Language: English.

Country(ies) involved: China.

Keywords: Chinese medicine injection, Lung cancer, Chemotherapy.

Contributions of each author:
Author 1 - Qiujun Guo.