Clinical effect and safety of Chinese medicine injections combined with chemotherapy in treating advanced non-small cell lung cancer: Study protocol of an umbrella review of systematic reviews and meta-analyses

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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 09 July 2020 and was last updated on 09 July 2020 (registration number INPLASY202070026).
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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. AMSTAR 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, p<50%
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.

Other relevant information: Chinese
medicine injection, Lung cancer,
Chemotherapy.

Keywords: Chinese medicine injection,
Lung cancer, Chemotherapy.

Contributions of each author:
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