INPLASY PROTOCOL

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Conflicts of interest:
No Conflicts of interest.

Efficacy and Safety of Astragalus-Containing Traditional Chinese Medicine Combined with Platinum-Based Chemotherapy for Advanced Gastric Cancer: A protocol of Systematic review and Meta-Analysis

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Review question / Objective: **This review aims to evaluate the comparative efficacy and safety for the addition of Astragalus-based Chinese medicines combined with Platinum-based chemotherapy (PBC) and PBC alone for advanced gastric cancer (AGC) treatment.**

Condition being studied: **Gastric cancer is the fifth-most commonly diagnosed cancer and the third leading cause of cancer-related death in the world. 70% or 80% of the patients with gastric cancer are diagnosed at advanced stage and lost the opportunity for surgical treatment. PBC is widely used in the treatment of AGC. However, the side effects and the development of resistance to chemotherapy in clinical practice reveal its limitations and have prompted more attention to be paid to the study of complementary treatments. Traditional Chinese Medicine (TCM) is the most common complementary therapy for cancer treatment and it has been shown to enhance the efficacy and reduce the side effects of anticancer strategies. Particularly, the Astragalus-based Chinese medicine are frequently combined with chemotherapy for AGC in clinic.**

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INTRODUCTION

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METHODS

Participant or population: Patients who had stage III-IV AGC and diagnosed by using the histopathological and cytological diagnostic criteria and the TNM staging system were included. And the patients who had received radiotherapy, chemotherapy or other anti-tumor therapy within one month before treatment, with concurrent infection, or other malignant tumors or severe illnesses were excluded. The baseline data of patients in two groups were comparable.

Intervention: The experimental group patients received Astragalus-based herbal therapy combined with PBC. Any form of Astragalus (Huang qi) preparation, including water decoction, extracts, granules or injection, etc., regardless of administration route.

Comparator: The control group patients received PBC alone.

Study designs to be included: Randomized controlled trials (RCTs).

Eligibility criteria: The Population, Intervention, Comparison and Outcomes (PICO) principles will be applied to the research design. Inclusion criteria are as follows: (1) All studies were randomized controlled trials (RCTs); (2) Patients who had TNM stage III-IV AGC and diagnosed by using the histopathological and cytological diagnostic criteria were included; (3) The experimental group patients received Astragalus-based herbal therapy combined with PBC. Any form of Astragalus (Huang qi) preparation, including water decoction, extracts, granules or injection, etc., regardless of administration route. The control group patients received PBC alone; (4) Outcomes was identified as tumor response, survival rate, QOL, ADRs and the levels of peripheral blood lymphocytes, at least one of the outcomes was reported; (5) For repeated publication studies, select the data with the most comprehensive report and the longest follow-up. The Exclusion Criteria are as follows: (1) Patients who had received radiotherapy, chemotherapy or other anti-tumor therapy within one month before treatment; (2) Patients with severe infection, other malignant tumors and severe medical diseases; (3) The prescription of Astragalus-based herbal therapy was not fixed; (4) Researches that cannot extract data; (5) The baseline data of patients in two groups were not comparable. Two authors will independently extract data. Any disagreements will be discussed with and resolved by the third author.

Information sources: 1.Electronic searches: Seven databases were used in our research: English databases searched included PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese databases searched included CBM, CNKI, CQVIP and Wanfang. Date from inception to 19 July 2020. The language was restricted to Chinese and English. The following search terms were used: ((gastr* OR stomach* OR digest* OR epigastr*) AND (carcin* OR cancer* OR neoplas* OR tumour* OR tumor* OR growth* OR adenocarcin* OR malig*)) AND (Astragalus OR radix astragali OR huang qi OR huangqi). 2. Searching other resources: Manual searches were included reviewing reference lists of identified studies, relevant reviews, meta-analysis. The

Clinical Trials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) were also searched for new relevant to the topic.

Main outcome(s): Tumor response and survival rate *; Tumor response will be assessed by using the objective response rate (ORR) and disease control rate (DCR) according to the WHO or RECIST criteria. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) will be used as indicators. CR plus PR is equal to ORR, CR plus PR and SD is equal to DCR.

Additional outcome(s): Quality of life (QOL), Adverse Drug Reactions (ADRs) and the levels of peripheral blood lymphocytes. QOL is considered to be improved when Karnofsky Performance Status (KPS) score is ten points higher after being treated. ADRs are accessed by measuring hematotoxicity (neutropenia, anemia, thrombocytopenia), gastrointestinal toxicity (nausea and vomiting, diarrhea), hepatic or renal dysfunction, neurotoxicity, alopecia and stomatitis, according to WHO Recommendations for Grading of Acute and Subacute Toxicity or NCI Common Terminology Criteria for Adverse Events (CTCAE). The levels of peripheral blood lymphocytes will be assessed by measuring the T-lymphocyte subsets such as the proportion of CD3+, CD3+CD4+, and CD3+CD8+ T cells; the ratio of CD4+/CD8+ T cells; and the proportion of natural killer cells (NK cells).

Quality assessment / Risk of bias analysis: Two reviewers will independently assess the quality of the selected studies according to the Cochrane Collaboration's tool for randomized controlled trials. Items will be evaluated in three categories: Low risk of bias, unclear bias and high risk of bias. The following characteristics will be evaluated: Random sequence generation (selection Bias), Allocation concealment (selection bias), Blinding of participants and personnel (performance bias), Incomplete outcome data (attrition bias), Selective reporting (reporting bias), Other biases. Results from these questions will be graphed and assessed using Review Manager 5.3.

Strategy of data synthesis: The meta-analyses will be performed by the Review Manager 5.3 and Stata V16.0 software. The dichotomous variables will be assessed by risk ratios (RR) with a 95% confidence interval (95% CI) and continuous variables will be analyzed with mean difference (MD) with a 95% CI. Chi-squared test and I2 statistic will be used to measure statistical heterogeneity. The random effects model will be applied to estimate the summary RR, MD and 95% CI. Outcomes will be calculated using P values and $P<0.05$ is considered statistically significant. If the meta-analysis is not feasible, we will provide a narrative description of the results.

Subgroup analysis: If the necessary data are available, subgroup analysis will be done according to different drug delivery of Astragalus-Containing Traditional Chinese Medicine, different platinum-based chemotherapy regimens, different treatment duration, and other relevant parameters.

Sensibility analysis: Sensitivity analysis will be performed by sequentially omitting each study to examine the robustness of the primary outcome, including ORR, DCR and survival rate.

Country(ies) involved: China.

Keywords: Astragalus, platinum, advanced gastric cancer, Traditional Chinese Medicine, meta-analysis.

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