INPLASY PROTOCOL

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None declared.

Efficacy and Safety of Ginseng-Containing Traditional Chinese Medicine Combined with Fluoropyrimidine-based Chemotherapy for Advanced Gastric Cancer: A Systemic review and Meta-Analysis

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Review question / Objective: **Ginseng-containing Traditional Chinese medicine (TCM) combined with fluoropyrimidine-based chemotherapy (FBC) is widely used in patients with advanced stomach cancer (AGC) in China, but the evidence on its efficacy is still limited. The purpose of this study is to evaluate the efficacy and safety of ginseng - containing TCM combined with FBC in the treatment of AGC.**
Condition being studied: **Advanced stomach cancer.**
Information sources: **RCTs were searched form inception to June 2021 in English or Chinese in the following electronic databases: PubMed, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP database), Wangfang Data Knowledge Service Platform and Chinese Biomedical Literature Database (CBM). We searched for additional trials by browing the reference lists of studies related to ginseng - containing TCM combined with FBC for AGC.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 August 2021 and was last updated on 25 August 2021 (registration number INPLASY202180096).

INTRODUCTION

Review question / Objective: **Ginseng-containing Traditional Chinese medicine (TCM) combined with fluoropyrimidine-based chemotherapy (FBC) is widely used in patients with advanced stomach cancer (AGC) in China, but the evidence on its efficacy is still limited. The purpose of this study is to evaluate the efficacy and safety**

of ginseng - containing TCM combined with FBC in the treatment of AGC.

Condition being studied: Advanced stomach cancer.

METHODS

Participant or population: Patients with stage III-IV gastric cancer.

Intervention: The experimental group patients received ginseng -containing TCM combined with FBC. Any forms of ginseng-containing preparation, including decoction, granules or injection, etc., and drug delivery were not restricted. Ginseng was defined as the dry root and rhizome of PanaxginsengC.A.Mey. and its processed products, while Codonopsis Radix, Panacis quinquefolii Radix, Pseudostellariae Radix, Salviae Miltiorrhizae Radix et Rhizoma, Glehniae Radix, Scrophulariae Radix and Adenophorae Radix are not included.

Comparator: The control group patients received FBC alone.

Study designs to be included: All Randomized controlled trials (RCTs) published in English or Chinese were included. Quasi-randomized trials and trails not stating to be randomized were excluded. Full journal publication with sufficient data for analysis was required.

Eligibility criteria: Patients with stage III-IV gastric cancer which was diagnosed by histopathological and cytological diagnostic criteria and the TNM staging system were included. The baseline data of patients in two groups were comparable. There was no restriction on age andgender.

Information sources: RCTs were searched form inception to June 2021 in English or Chinese in the following electronic databases: PubMed, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP database), Wangfang Data Knowledge Service Platform and Chinese Biomedical Literature Database (CBM). We searched for additional trials by browing the reference lists of studies related to ginseng - containing TCM combined with FBC for AGC.

Main outcome(s): The primary outcome was defined as tumor response 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) were used as indicators while CR plus PR was equal to ORR, CR plus PR and SD was equal to DCR.

Additional outcome(s): The secondary outcomes were defined as Quality of life (QOL), Adverse Drug Reactions (ADRs), the levels of peripheral blood lymphocytes and the cancer biomarkers. The interventions were considered to be effective for QOL when Karnofsky Performance Status (KPS) score was no more than ten points lower after being treated. Comparing the mean ± standardized difference of KPS scores before and after treatment was also allowed. ADRs were evaluated at I-IV levels by measuring gastrointestinal toxicity (diarrhea, nausea and vomiting), hematotoxicity (hemoglobin reduction, platelet reduction, WBC reduction), liver function disfunction and renal function disfunction, according to WHO Recommendations for Grading of Acute and Subacute Toxicity. The interventions were considered to result in ADRs when patients had the II-IV level ADRs above. The levels of peripheral blood lymphocytes were assessed by measuring the T-lymphocyte subsets such as the proportion of CD3+ and CD4+ T cells, while the ratio of CD4+/CD8+ T cells and the proportion of natural killer (NK) cells were also considered. The levels of cancer biomarkers were assessed by measuring the CA199, CA724 and CEA.

Quality assessment / Risk of bias analysis: Three reviewers independently evaluated the included studies by the Cochrane risk-of-bias tool for randomized trials according

to the guidance of the Cochrane Handbook for Systematic Review of Interventions (Version 5.1.0), which includes the following seven bias domains: selection bias due to random sequence generation, selection bias due to allocation concealment, performance bias due to blinding of participants and personal, detection bias due to blinding of outcome assessment, attrition bias due to incomplete outcome data, reporting bias due to selective reporting and other bias. An overall judgment about risk of bias for each domain which have three response options (low/high/unclear). Any disagreement arising from this process were resolved by consensus or a third reviewer.

Strategy of data synthesis: Two reviewers conducted a meta-analysis of the included studies using Review Manager 5.3. The risk ratio (RR) was used to present the dichotomous data while the standardized mean difference (SMD) was used to present the continuous data. The 95% confidence intervals (95%CIs) were given and p 50%. If the heterogeneity ($p < 0.10$, $I^2 > 50\%$) was eliminated, fixed-effect model (FEM) was performed to synthesize the RR, SMD and their 95%CI. Otherwise, random-effect model (REM) is performed. Sensitivity analysis was performed by sequentially excluding each trial to examine the robustness of the results. Publication bias is evaluated according to the noparametric trim-and-fill analysis of publication bias and Egger's test when there are more than 10 included studies.

Subgroup analysis: According to the KPS score, treatment process, the drug delivery of ginseng -containing TCM, chemotherapy regimen and follow-up time, subgroup analysis was performed to reveal the clinical heterogeneity and its influence on tumor response and the peripheral blood lymphocyte levels.

Sensitivity analysis: We analyzed the sensitivity of the main outcome indicators, including ORR and DCR, by excluding each trial in turn to check the robustness of the results.

Country(ies) involved: China.

Keywords: advanced gastric cancer, ginseng, traditional Chinese medicine, Meta-Analysis.

Contributions of each author:
Author 1 - Jiaqi Hu.
Author 2 - Mengqi Cheng.