INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Effect of traditional Chinese medicine (TCM) on survival, quality of life, and immune function in patients with ovarian carcinoma: a systematic review and meta-analysis protocol

Ge, SX[1]; Xing, QQ[2]; Zhang, AQ[3]; Wang, YC[4].

Review question / Objective: Is traditional Chinese medicine (TCM) effective on survival, quality of life (QoL), and in immune function patients with ovarian carcinoma (OC)?

Condition being studied: Traditional Chinese medicine and ovarian carcinoma.

Information sources: Relevant clinical trials of TCM for the treatment OC patients will be searched in Cochrane Library, Web of Science, Google Scholar, PubMed, Medline, Embase, China Scientific Journal Database, China National Knowledge Infrastructure, Chinese Biomedical Literature Database and Wanfang Database from their inception to November 2020. Language is limited with English and Chinese.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 November 2020 and was last updated on 24 November 2020 (registration number INPLASY2020110104).

INTRODUCTION

Review question / Objective: Is traditional Chinese medicine (TCM) effective on survival, quality of life (QoL), and in immune function patients with ovarian carcinoma (OC)?

Rationale: Traditional Chinese medicine (TCM) has been widely applied as promising adjunctive drugs for ovarian carcinoma (OC) in China and other Asian countries. However, its exact clinical efficacy and safety is still not well investigated. In this study, we aimed to

summarize the efficacy of TCM on survival, quality of life (QoL), and immune function in patients with OC through the meta-analysis.

Condition being studied: Traditional Chinese medicine and ovarian carcinoma.

METHODS

Search strategy: Experienced systematic review investigators will be invited to develop a search strategy, in order to perform a comprehensive search. The search terms include "ovarian cancer" or "ovarian oncology" or "ovarian tumor" or "ovarian carcinoma" or "epithelial ovarian carcinoma" or "oophoroma" or "luan cao ai" or "luan cao zhong liu" or "OC" or "EOC" and "traditional Chinese medicine" or "traditional Chinese drug" or "Chinese herbal preparation" or "traditional Chinese preparation" or "Chinese materia medica preparation" or Chinese patent medicine" or "zhongyao" or "TCM" et al. The preliminary retrieval strategy for PubMed is provided in Table 1, which will be adjusted in accordance with specific databases.

Participant or population: Patients with histologically proved OC were included in this study. No restrictions regarding age, gender, racial, region, education and economic status. Patients with other malignancies are not included.

Intervention: In the experimental group, OC patients must be treated with TCM alone or in combination with other conventional treatment methods including surgery, radiotherapy, chemotherapy, and et al. TCM involving extracts from herbs or insects or animals, single or mixture formulas regardless of their compositions or forms. There will be no restrictions with respect to dosage, duration, frequency, or follow-up time of treatment.

Comparator: There will be no restrictions with respect to the type of comparator. The comparators are likely to include surgery, radiotherapy, chemotherapy, supportive care, and other therapeutic methods.

Study designs to be included: All available comparative clinical trials that investigated the efficacy and safety of TCM for patients diagnosed with OC will be included in this systematic review. There will be no restrictions for blinding, population characteristics and duration of trials.

Eligibility criteria: This study will include randomized controlled trials (RCTs) or prospective controlled clinical trials that investigated the efficacy and safety of TCM for patients diagnosed with OC. Duplicated studies, papers without sufficient available data, non-comparative clinical trials, literature reviews, meta-analysis, meeting abstracts, case reports and series, and other unrelated studies will be excluded from analysis.

Information sources: Relevant clinical trials of TCM for the treatment OC patients will be searched in Cochrane Library, Web of Science, Google Scholar, PubMed, Medline, Embase, China Scientific Journal Database, China National Knowledge Infrastructure, Chinese Biomedical Literature Database and Wanfang Database from their inception to November 2020. Language is limited with English and Chinese.

Main outcome(s): The primary outcomes will include: i) Overall survival (OS), the time from the date of randomization to death from any cause; ii) Quality of life (QoL) obtained from the corresponding scale; iii) Immune function indicators: CD3+, CD4+, CD8+, NK cells percentage, CD4+/CD8+ cell ratios, and serum cytokines level (IL-2, IL-4, IFN-γ , TNF-α, and et al.).

Additional outcome(s): Secondary outcomes will include: i) Overall response rate (ORR) and disease control rate (DCR); ii) Tumor markers: HE4, CA125, CEA and CA199; iii) Adverse effects: Gastrointestinal adverse reactions, leukopenia, hepatorenal toxicity, and et al.

Data management: After screening the text, the two investigators (Shuxia Ge and Qianqian Xing) will independently extract the information contained in the eligible

literature. The extracted data are as follows: i) Study characteristics and methodology: country of study, the first author's name, year of publication, randomization, sample size, periods of data collection, follow-up duration, outcome measures, inclusion and exclusion criteria, et al. ii) Participant characteristics: age, gender, tumor stage, tumor size, diagnostic criteria, et al. iii) Interventions: therapeutic means, types of TCM, dose, administration route, course of treatment, and duration of treatment, et al. iv) Outcome and other data: ORR, DCR, OS, QoL, immune indexes [(CD3+, CD4+, CD8+, NK cells percentage, and CD4+/CD8+ cell ratios), tumor markers (HE4, CA125, CEA and CA199) and serum cytokines level (IL-2, IL-4, IFN-γ and TNF-α)], and adverse effects, et al. When any data are missing or insufficient, we will contact original authors by using email. If those relevant data are not acquired, we will only analyze the available data, and discuss its impact as a limitation.

Quality assessment / Risk of bias analysis: Two researchers (Shuxia Ge and Qianqian Xing) will independently assess the quality of the included RCTs in accordance with the Cochrane Handbook of Systematic Reviewers. This assessment tool includes seven items: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting and (7) other bias. Each item will be evaluated at three levels: low risk, unclear, and high risk. Effective Practice and Organisation of Care (EPOC) guidelines will be used to assess the risks of non-RCTs. Any disagreements will be resolved via discussion with a third researcher (Anqi Zhang).

Strategy of data synthesis: Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 14.0 (Stata Corp., College Station, TX, USA) statistical software will be used to pool the data and carry out the data analysis. Continuous data will be presented as mean difference (MD) or standardized mean difference (SMD) with their 95% confidence intervals (CIs). Dichotomous data will be recorded as risk ratio (RR) with 95% CIs. A two-tailed $P < 0.05$ was considered statistically significant. Heterogeneity of treatment effects across trials was assessed by $\chi 2$ statistics and the I2 statistics. When the P value was >0.1, and I2 was <50%, it suggested that there was no statistical heterogeneity and the Mantel-Haenszel fixed-effects model was used for meta-analysis. Otherwise, a random-effects mode will be used to calculate the outcomes.

Subgroup analysis: We will explore sources of heterogeneity with respect to age, tumor stage, region and types of TCM by subgroup analysis and meta-regression when the P value was 50%.

Sensibility analysis: Sensitivity analysis will be conducted to assess the reliability and robustness of the aggregation results via eliminating trials with low-quality. A summary table will report the results of the sensitivity analyses.

Language: Language is limited with English and Chinese.

Country(ies) involved: China.

Other relevant information: i) Publication bias. Funnel plot will be performed to analyze the existence of publication bias if 10 or more literatures are included in this meta-analysis. If the funnel diagram has poor symmetry, it indicates publication bias. Begg's and Egger regression test are used to further verify the existence of publication bias. If publication bias existed, a trim-and-fill method should be applied to adjust the pooled OR. ii) Assess the quality of evidence. The guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) will be used to assess the quality of evidence and the strength of the main result recommendations. The quality of all evidence will be assessed at four levels: high, moderate, low, and very low.

Dissemination plans: The results of this study will be published in a peer-reviewed journal, and provide reliable evidence for clinicians to formulate the best postoperative adjuvant treatment strategy for OC patients.

Contributions of each author:
Author 1 - Shuxia Ge - Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing-original draft.
Author 2 - Qianqian Xing - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.
Author 3 - Anqi Zhang - Funding acquisition, Methodology, Validation, Writing-review & editing.
Author 4 - Yucui Wang - Conceptualization, Project administration, Resources, Software, Supervision, Validation, Writing-review & editing.