INPLASY PROTOCOL

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Conflicts of interest: **None.**

Efficacy of Chinese herbal injections combined with fluoropyrimidine and oxaliplatin-based chemotherapy for advanced colorectal cancer: a protocol for systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: **The aim of this systematic review and meta-analysis of randomized controlled trials is to evaluate the efficacy of Chinese herbal injections combined with fluoropyrimidine and oxaliplatin-based chemotherapy for advanced colorectal cancer.**
Condition being studied: **Over 1.8 million new colorectal cancer cases and 881, 000 deaths are estimated to occur in 2018, accounting for about 1 in 10 cancer cases and deaths. Overall, colorectal cancer ranks third in terms of incidence but second in terms of mortality. The current treatment for patients with early CRC is surgical treatment, while 30%~40% of patients have reached the advanced stage at the time of diagnosis and cannot be treated with surgery, and more than 50% of patients have metastasis or recurrence within 5 years after radical resection. Now fluoropyrimidine combined with oxaliplatin-based chemotherapy have became the first-line treatment for advanced colorectal cancer. However, Toxicity like myelosuppression and gastrointestinal reactions may occur. Traditional Chinese medicine (TCM) is one of the important methods in the treatment of advanced stage colorectal cancers. Chinese herbal medicine injections (CHIs) are an important part of TCM. Many studies have indicated that CHIs can reduce toxicity of chemotherapy and relieve symptoms, In addition, CHIs combined with chemotherapy in treating advanced colorectal cancer has shown efficacy in prolonging survival and improving quality of life.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 October 2020 and was last updated on 14 October 2020 (registration number INPLASY2020100050).

INTRODUCTION

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oxaliplatin-based chemotherapy for advanced colorectal cancer.

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METHODS

Participant or population: Patients with advanced colorectal cancer.

Intervention: Chinese herbal injections combined with fluoropyrimidine (5-FU or capecitabine) and oxaliplatin-based chemotherapy, with or without bevacizumab or cetuximab.

Comparator: Fluoropyrimidine (5-FU or capecitabine) and oxaliplatin-based chemotherapy, with or without bevacizumab or cetuximab.

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

Eligibility criteria: Inclusion criteria: (i) The study design should be prospective randomized controlled trails (RCTs). (ii) Patients included in each trails were cytologically or pathologically confirmed cases of colorectal cancer. (iii) Patient belonging to Stage III or IV. (iv) Participants in treatment group received CHIs combined with fluoropyrimidine (5-FU or capecitabine) and oxaliplatin-based chemotherapy, with or without bevacizumab or cetuximab.(v) The control group was only given fluoropyrimidine (5-FU or capecitabine) and oxaliplatin-based chemotherapy, with or without bevacizumab or cetuximab. (vi) CHIs are given intravenously. (vii) Reported at least one of the outcomes of interest. Exclusion criteria: (i) Duplicated publications or overlapping study population. (ii) Multiple TCM intervention in the treatment group. (iii) Documents of data errors. (iv) Off-label use of CHIs.

Information sources: A comprehensive search will be conducted on 31 August 2020, in 7 electronic medical databases, including 3 English-language databases (PubMed, EMBASE, Cochrane) and 4 Chinese-language databases (China National Knowledge Infrastructure [CNKI], Wanfang Data, VIP, SinoMED). The language will be limited to English and Chinese.

Main outcome(s): (i) Objective response rate (ORR). According to WHO guidelines for solid tumor responses or Response Evaluation Criteria in Solid Tumors (RECIST), the tuomr responses were evaluated as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). ORR refers to the proportion of petients with CR plus PR. (ii) Disease control rate (DCR), calculated as the proportion of petients with CR plus PR plus SD.

Additional outcome(s): (i) Progression-free survival (PFS), the time from study entry to relapse or death. (ii) Survival rate, the proportion of persons alive at the beginning of a time interval who survive to the end of the interval. (iii) Quality of life

(QOL), evaluated manily by scales, such as Karnofsky performance scale (KPS), European Organization for the Research and Treatment of Cancer QLQ-C30 (EORTCQLQ-C30), Functional Assessment of Cancer Therapy-Colorectal (FACT-C), etc.(iv) Adverse effects, focused on incidence of grade 2 or greater myelosuppression (hemoglobin, leukocyte or thrombocyte decreasing) and gastrointestinal adverse reaction (nausea and vomiting, constipation and diarrhea) measured based on Standard Classification of WHO or National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Quality assessment / Risk of bias analysis: 2 evaluators will independently assess the methodological treatment of the included literature by "Risk of Bias Assessment Tool" of the Cochrane Handbook for Randomized Controlled Trials. The risk of bias will be evaluated in 7 items including random sequence generation, allocation concealment, blinding of participants, personnel and assessors, incomplete outcome data, selective reporting, and other sources of bias, and finally evaluated as "low risk," "unclear risk," or "high risk". Any differences will be resolved by the third evaluator.

Strategy of data synthesis: We will use Revman 5.3 software for statistical analysis. the heterogeneity will judged based on the P value and the I^2 value. If the studies have non-significant heterogeneity ($P>0.1$, $I^2<50\%$), We will use a fixed effects model; If there is great heterogeneity within the studies ($P\leq0.1$, $I^2\geq50\%$), we will use the random effects model. If the data quantitative synthesis is not possible, we will analysis the available data qualitatively.

Subgroup analysis: If the collected data are sufficient, we will perform a subgroup analysis according to the following variables: The type of the Chinese herbal injections, the treating principle of Chinese herbal injections based on TCM theories, the duration of Chinese herbal injections treatment, patient's characteristics, and the stage of colorectal cancer, etc.

Sensibility analysis: We will perform sensitivity analysis to determine the robustness of results.

Country(ies) involved: China.

Keywords: Chinese herbal injections, advanced colorectal cancer, fluoropyrimidine and oxalipatin-based chemotherapy, efficacy, systematic review, meta-analysis.

Contributions of each author:
Author 1 - Shuo Wang - SW wrote the protocol and revised the manuscript.
Author 2 - Xueqian Wang - XQW wrote the protocol and revised the manuscript. SW and XQW contributed equally to this work and are co-first authors.
Author 3 - Tong Zhou - TZ developed the criteria and conducted statistical methods.
Author 4 - Shuaihang Hu - SHH developed the criteria and conducted statistical methods.
Author 5 - Peiyu Tian - PYT developed the criteria and conducted statistical methods.
Author 6 - Zheng Li - ZL developed the search strategy.
Author 7 - Yuxiao Li - YXL developed the search strategy.
Author 8 - Yuerong Gui - YRG advised on protocol design.
Author 9 - Jun Dong - JD advised on protocol design.
Author 10 - Ying Zhang - YZ designed and conceptualized the study.
Author 11 - Wei Hou - HW designed and conceptualized the study.