INPLASY PROTOCOL

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The authors declare that they have no competing interests.

Brucea javanica oil emulsion injection (BJOEI) as an adjunctive therapy for patients with advanced colorectal carcinoma: A protocol for a systematic review and meta-analysis

Xu, CH[1]; Guo, XX[2], Zhou, CH[3], Zhang, HL[4].

Review question / Objective: **Is Brucea javanica oil emulsion injection (BJOEI) effective and safety for patients with advanced colorectal carcinoma (CRC)?**
Condition being studied: **Brucea javanica oil emulsion injection and colorectal cancer.**
Information sources: **Google Scholar, Medline, Web of Science (WOS), Excerpt Medica Database (Embase), Chinese BioMedical Database (CBM), China Scientific Journal Database (VIP), China National Knowledge Infrastructure (CNKI) and Wanfang Database, will be systematically searched for eligible studies from January 2000 to May 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 14 June 2020 and was last updated on 14 June 2020 (registration number INPLASY202060014).

INTRODUCTION

Review question / Objective: **Is Brucea javanica oil emulsion injection (BJOEI) effective and safety for patients with advanced colorectal carcinoma (CRC)?**

Rationale: **Brucea javanica oil emulsion injection (BJOEI) has been widely applied as a promising adjunctive drug for colorectal carcinoma (CRC). However, the exact effects and safety of BJOEI remains controversial. In this study, we aimed to summarize the efficacy and safety of BJOEI for the treatment of advanced CRC through the meta-analysis, in order to provide scientific reference for the design of future clinical trials.**

Condition being studied: Brucea javanica oil emulsion injection and colorectal cancer.

METHODS

Search strategy: To perform a comprehensive and focused search, experienced systematic review researchers will be invited to develop a search strategy. The plan searched terms are as follows: "colon cancer" or "colon neoplasm" or "colon carcinoma" or "colon tumor" or "rectal cancer" or "rectal neoplasm" or "rectal carcinoma" or "rectal tumor" or "colorectal cancer" or "colorectal neoplasm" or "colorectal carcinoma" or "colorectal tumor" or "CRC" or "CC" or "RC" and "Javanica oil emulsion injection" or "Brucea javanica oil emulsion" or "Brucea javanica oil emulsion injection" or "BJOEI" or "BJOE injection" or "Yadanzi" or "Yadanzi injection" or "Ya-dan-zi injection" et al. An example of search strategy for PubMed database shown in Table 1 will be modified and used for the other databases.

Participant or population: Patients must be cytologically or pathologically confirmed as having CRC at a clinically advanced stage. There will be no restrictions regarding gender, age, region, racial, economic and education status. Patients with other malignancies or non-primary CRC are not included.

Intervention: In the experimental group, advanced CRC patients must be treated with conventional treatment (including chemotherapy, radiotherapy, and targeted therapy) combined with BJOEI mediated therapy.

Comparator: In the control group, CRC patient treated with the same conventional treatment as intervention group in the same original study.

Study designs to be included: All available RCTs and high-quality control studies that investigated the efficacy and safety of BJOEI-mediated therapy for CRC will be included.

Eligibility criteria: This study will include randomized controlled trials (RCTs) or quasi-RCTs, and high-quality prospective cohort studies that compared the efficacy and safety of BJOEI with other treatments for patients with advanced CRC. Articles without sufficient available data, non-comparative studies, non-peer reviewed articles, literature reviews, meta-analysis, case reports and series, meeting abstracts, animal studies, letter to the editor, editorials, commentaries, and other unrelated studies will be all excluded from analysis.

Information sources: Electronic databases including PubMed, Cochrane Library, Google Scholar, Medline, Web of Science (WOS), Excerpt Medica Database (Embase), Chinese BioMedical Database (CBM), China Scientific Journal Database (VIP), China National Knowledge Infrastructure (CNKI) and Wanfang Database, will be systematically searched for eligible studies from January 2000 to May 2020. Language is limited with English and Chinese.

Main outcome(s): The primary outcomes in present analysis included short-term and long-term clinical efficacy, and adverse effects (AEs) according to Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumors 1.1 (RECIST Criteria 1.1). (I) Short-term clinical efficacy: the short-term tumor response included complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), overall response rate (ORR) and disease control rate (DCR). ORR was defined as the sum of CR and PR, and DCR was the sum of CR, PR and SD. (II) Long-term clinical efficacy: 1-5 year Overall survival (OS, which is defined as the time from the date of randomization to death from any cause); 1-5 year progression free survival (DFS, which is the time from date of random assignment to date of recurrence or death). (III) Adverse events: toxicity was graded from 0 to IV in severity on the basis of the WHO recommendations.

Additional outcome(s): Secondary outcomes will include: (I) QoL: QoL was evaluated using Karnofsky score; (II)

Immune function indicators: the immune function of CRC patients was assessed in terms of CD3+, CD4+, CD8+ , NK cells percentage, and CD4+/CD8+ cell ratios.

Data management: Two investigators (Xu CH and Guo XX) will be responsible for the data extraction independently according to the Cochrane Handbook for Systematic Reviews of Intervention. The following data will be extracted from eligible literatures: Study characteristics: country of study, the first author, year of publication, sample size, periods of data collection, total duration of study and follow-up duration, et al. Participant characteristics: tumor stage (staging of the tumor according to the AJCC TNM classification for esophageal cancer), age, gender, ethnicity, pathology diagnosis, pathologic tumor size, inclusion and exclusion criteria, et al. Interventions: therapeutic means, manufacturer of the drugs, dosage of BJOEI, administration route and cycles and duration of treatment, et al. Outcome and other data: CR, PR, SD, PD, ORR, DCR, OS, DFS, QoL, immune indexes (CD3+, CD4+, CD8+ , NK cells percentage, and CD4+/CD8+ cell ratios) and adverse effects, et al. For survival outcomes, Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) will be extracted from trials or be estimated from Kaplan–Meier survival curves by established methods. Dealing with missing data: we will attempt to contact the authors to request the missing or incomplete data. If those relevant data are not acquired, they will be excluded from the analysis. Any disagreements will be resolved by discussion, and a third reviewer (Zhou CH) will make the final decision. Excluded studies and the reasons for exclusion will be listed in a table.

Quality assessment / Risk of bias analysis: The quality of the included clinical trials will be assessed independently by 2 investigators (Xu CH and Guo XX) in terms of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other bias, according to the guidance of the Cochrane Handbook for Systematic Review of Interventions. Evidence quality will be classified as low risk, high risk, or unclear risk of bias in accordance with the criteria of the risk of bias judgment. EPOC guidelines will be used to assess the risks of non-RCTs. Any disagreements will be resolved via discussion with a third researcher (Zhou CH). If necessary, consulting with the fourth author (Zhang HL).

Strategy of data synthesis: Data from studies judged to be clinically homogeneous will be pooled using Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 14.0 (Stata Corp., College Station, TX, USA) statistical software. Heterogeneity between studies will be assessed using the Cochran's Q and Higgins I2 statistic. $P < 0.1$ for the Chi2 statistic or an $I2 > 50\%$ will be considered as showing considerable heterogeneity. A fixed effect model will be used to calculate the outcomes when statistical heterogeneity is absent; otherwise, the random effects model was considered according to the DerSimonian and Laird method. The Mantel–Haenszel method will be applied for pooling of dichotomous data and results will be presented as relative risk (RR) with their 95% confidence intervals (CIs). Inverse variance method will be used for pooling of continuous data and results will be presented as standardized mean difference (SMD) with their 95% CIs. A two-tailed $P < 0.05$ was considered statistically significant.

Subgroup analysis: If the data are available and sufficient, subgroup and meta-regression analysis will be conducted to explore the source of heterogeneity with respect to age, gender, region, tumor stage, course of treatment and therapeutic regimens.

Sensibility analysis: Sensitivity analysis will be conducted to assess the reliability and robustness of the aggregation results via eliminating trials with high bias risk. 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: Publication bias analysis: We will detect publication biases and poor methodological quality of small studies using funnel plots if 10 or more studies are included in the meta-analysis. Begg's and Egger regression test will be utilized to detect the funnel plot asymmetry. If reporting bias is suspected, we will consult the study author to get more information. If publication bias existed, a trim-and-fill method should be applied to coordinate the estimates from unpublished studies, and the adjusted results were compared with the original pooled RR. Evidence evaluation: The evidence grade will be determined by using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). The quality of all evidence will be evaluated as 4 levels (high, moderate, low, and very low).

Keywords: Brucea javanica oil emulsion injection, colorectal cancer, efficacy, safety, meta–analysis.

Dissemination plans: We will disseminate the results of this systematic review by publishing the manuscript in a peer-reviewed journal or presenting the findings at a relevant conference.

Contributions of each author:
Author 1 - Chunhong Xu - Conceptualization, Investigation, Methodology, Supervision, Writing-original draft, Writing-review & editing.
Author 2 - Xinxin Guo - Investigation, Methodology, Writing-original draft.
Author 3 - Changhui Zhou - Investigation, Methodology, Funding acquisition.
Author 4 - Hualing Zhang - Conceptualization, Project administration, Supervision, Writing-review & editing.