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Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Efficacy and Safety of Compound Kushen Injection Combined With Oxaliplatin-Based Chemotherapy in the Treatment of Advanced Colorectal Cancer: a Systematic Review and Meta-Analysis

Zhou, T[1]; Wang, S[2]; Zhang, LX[3]; Gui, YR[4]; Dong, J[5]; Wang, DD[6]; Fan, BJ[7].

Review question / Objective: **The purpose of this study is to systematically evaluate the efficacy and safety of Compound Kushen Injection combined with oxaliplatin chemotherapy in the treatment of advanced colorectal cancer.**
Information sources: **Eight database including PubMed, Embase, Cochrane Library Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Database for Chinese Technical Periodicals (VIP) and SinoMed will be searched from their inception to October 2021 with language limitation of English and Chinese.**
Main outcome(s): **Clinical efficacy: According to the World Health Organization (WHO) criteria for efficacy evaluation of solid tumors, the clinical efficacy of treatment will be judged by Objective Response Rate(ORR) and Disease Control Rate(DCR).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 September 2021 and was last updated on 19 September 2021 (registration number INPLASY202190059).

INTRODUCTION

Review question / Objective: **The purpose of this study is to systematically evaluate the efficacy and safety of Compound Kushen Injection combined with oxaliplatin chemotherapy in the treatment of advanced colorectal cancer.**

Condition being studied: **Colorectal cancer, a malignant gastrointestinal cancer, is considered to be the second leading cause**

of death among cancers. From 1999 to 2017,The global incidence of colorectal cancer increased by 9.5 percent, that the incidence rate of East Asia increases about 85 percent, where was considered as the highest growth rate region. The chemotherapy regimens with Oxaliplatin, such as FOLFOX (oxaliplatin, 5-FU, and leucovorin) and XELOX (oxaliplatin, Capecitabine), remains the backbone of colon cancer patients. However, Oxaliplatin-Based Chemotherapy often induce immune impairment, Peripheral neurotoxicity, diminished quality of life, and others adverse drug reactions. Compound Kushen injection (CKI) is one of the anti-tumor Chinese patent medicines approved by the State Food and Drug Administration of China for the management of various cancers. CKI has been widely used in the adjuvant treatment of severe diseases, which has significant anti-tumor activities. Recently, the randomized controlled trials has increased rapidly which study using CKI combined with Oxaliplatin-Based Chemotherapy to treat colorectal cancer patient. CKI combined with oxaliplatin-based chemotherapy has shown obvious advantages in prolonging survival and improving quality of life.

METHODS

Search strategy: Eight database including PubMed, Embase, Cochrane Library Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Database for Chinese Technical Periodicals (VIP) and SinoMed will be searched from their inception to October 2021 with language limitation of English and Chinese. The authors will search the database by combining Medical subject heading(MESH) and free-text term. The MESH or key terms and their abbreviation or derivatives will be utilized, taking PubMed searching strategy for example: "Colorectal Neoplasms" or "Colonic Neoplasms" or "Rectal Neoplasms" or "colorectal cancer" or "rectal cancer" or "carcinoma of the rectum" or "intestinal cancer" and "Compound Kushen" or "Fufangkushen" or "Compound matrine" or "Yanshu".

Participant or population: Patients who were cytologically or pathologically confirmed cases of CRC and belong to Stage III or IV according to American Joint Committee on Cancer Staging System (8th edition) or mentioned "advanced".

Intervention: Intervention included Compound Kushen Injection combined with oxaliplatin-based chemotherapy, such as FOLFOX(oxaliplatin, 5-FU, and leucovorin) and XELOX (oxaliplatin, Capecitabine).

Comparator: Patients who accept oxaliplatin-based chemotherapy alone and no use of Chinese herbal injection.

Study designs to be included: All of randomized controlled trials using CKI combined with oxaliplatin-based chemotherapy to treat advanced colorectal cancer patients.

Eligibility criteria: Inclusion criteria: The researches which research type is randomized controlled trial aim to treat advanced colorectal cancer patients using CKI combined with oxaliplatin-based chemotherapy. Exclusion criteria:(1) receiving radiotherapy, targeted drugs and other non-chemotherapy methods. (2) Complete study data were not available.(3) duplicated publications or overlapping study data.

Information sources: Eight database including PubMed, Embase, Cochrane Library Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Database for Chinese Technical Periodicals (VIP) and SinoMed will be searched from their inception to October 2021 with language limitation of English and Chinese.

Main outcome(s): Clinical efficacy: According to the World Health Organization (WHO) criteria for efficacy evaluation of solid tumors, the clinical efficacy of treatment will be judged by Objective Response Rate(ORR) and Disease Control Rate(DCR).

Additional outcome(s): Secondary outcome indication consists of three points: (1)Quality of life: evaluated by the increase or decrease of Karnofsky performance scale;(2)Anti-tumor Adverse drug reaction: Assessed the severity of adverse drug reaction on a scale of I-IV,which including leukopenia, diarrhea, damage of liver function, peripheral neurotoxicity; (3)Immunity indication: the proportion of immune cells subgroup after treatment was valued as the indicator of immunologic function.

Quality assessment / Risk of bias analysis: Two investigators will evaluate the risk of bias of RCTs according to the Cochrane Systematic Review Manual 5.1.0 Bias Risk Assessment Tool. The RCTs will be assessed from 7 aspects: (1) Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. The evidence quality is determined by evaluation criteria of bias, which was classified as low risk, high risk, or unclear risk.

Strategy of data synthesis: Statistical analyses will be performed by using Review Manager 5.4.Relative Risk(RR) was used for the dichotomous data, such as clinical efficacy, quality of life, safety indication. Mean Deviation(MD) was used for continuous data, such as immunity outcomes. If $P > 0.1$ and $I2 \leq 50\%$, there was no significant statistical heterogeneity, and fixed effect model was used for analysis. If $P \leq 0.1$, $I2 > 50\%$, indicating significant inter-study heterogeneity, random effect model was used for analysis.

Subgroup analysis: If there is high clinical heterogeneity, we will conduct subgroup analysis in terms of tumor staging, therapeutic regimen, courses, treatment cycle, treatment frequency.

Sensitivity analysis: We will perform sensitivity analysis to explore possible source for high heterogeneity by deleting each RCT one by one. Compared with previous analysis outcomes, the robustness of results after deleting could have intuitive reflect.

Language: English, Chinese-Simplified.

Country(ies) involved: China.

Keywords: advanced colorectal cancer, Compound Kushen Injections, effectiveness, randomized controlled trial, systematic review.

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