

## Original Article

## Effect of Jianpi Bushen Sequential Formula on Adjuvant Chemotherapy of Colon Cancer: Study Protocol for a Randomized Controlled Trial

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TANG Mo<sup>1</sup>, YAN Yun-zi<sup>1</sup>, MAO Jun<sup>3</sup>, and YANG Yu-fei<sup>1</sup>

**ABSTRACT** **Background:** The side effects of chemotherapy-induced nausea and vomiting (CINV) and myelosuppression reduce the cancer patients' adherence to chemotherapy. Many Chinese patients choose Chinese medicine (CM) during chemotherapy to reduce side effects; however, the evidence is lacking. The efficacy of a CM herbal treatment protocol, Jianpi Bushen Sequential Formula (健脾补肾续贯方, JBSF) will be evaluated on chemotherapy completion rate among patients with colon cancer. **Methods:** A multi-center double-blind randomized controlled trial (RCT) will be conducted on 400 patients with colon cancer who will receive 8 cycles of adjuvant chemotherapy with oxaliplatin and capecitabine (CAPEOX). Patients will be randomized 1:1 to receive the JBSF or placebo formula. The primary outcome is the overall chemotherapy completion rate. The secondary outcomes include individual chemotherapy completion rate, 4-cycle completion rate of chemotherapy, time to treatment failure, relative dose intensity and treatment toxicity. Follow-up visits will be scheduled before every and after last chemotherapy. **Discussion:** This study will provide evidence on whether JBSF can improve the chemotherapy completion rate and reduce side effects among patients with colon cancer. (Trial registration: [ClinicalTrials.gov](http://ClinicalTrials.gov), No. NCT03716518)

**KEYWORDS** Chinese medicine, Jianpi Bushen Sequential Formula, Liujun Anwei Formula, Qitu Erzhi Formula, colon cancer, chemotherapy induced nausea and vomiting, myelosuppression

Colorectal cancer is one of the most common malignant tumors of the human digestive system,<sup>(1)</sup> with the third incidence rate and second mortality rate in China.<sup>(2)</sup> After radical resection of colonic cancer, patients of stage III and high-risk stage II should receive adjuvant chemotherapy according to the "National Comprehensive Cancer Network (NCCN) clinical practice guidelines in colon cancer (version 2. 2018)" and the "Colon cancer diagnosis and treatment guidelines (2018.v1)" of the Chinese Society of Clinical Oncology (CSCO). Standard adjuvant chemotherapy regimens include CAPEOX and FOLFOX, which are composed of oxaliplatin and 5-fluorouracil, respectively.<sup>(3,4)</sup> Of these two regimes, CAPEOX is more favored by patients and clinicians because of its simpler medication and longer hospitalization interval.

Chemotherapy-induced nausea and vomiting (CINV) and myelosuppression are common side effects. There is a moderate risk of CINV in regimen including oxaliplatin of 30% to 90%.<sup>(5,6)</sup> Even though there are recognized routine preventive measures

such as glucocorticoids and 5-hydroxytryptamine inhibitors, some patients refuse chemotherapy due to an intolerance of CINV. Myelosuppression is another common side effect, and recovery time of bone marrow determines when the next chemotherapy cycle can be carried.<sup>(7)</sup>

In China, more than 80% of cancer patients used Chinese medicine (CM), which is often used for symptom control. It has been found that CM could control and alleviate CINV and myelosuppression. In previous research based on the theory of CM, side

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DOI: <https://doi.org/10.1007/s11655-021-3448-9>

effects of chemotherapy were addressed using the 'two steps of CM treatment' and the newly created Jianpi Bushen Sequential Formula (健脾补肾续贯方, JBSF), which achieved good therapeutic effects in controlling the effects of CINV and myelosuppression.<sup>(8)</sup> The first step is to treat Pi (Spleen) and Wei (Stomach), using Liujun Anwei Formula (六君安胃方, LAF) to alleviate any CINV after chemotherapy by strengthening Pi and Wei. The second step is to treat Pi and Shen (Kidney), using Qitu Erzhi Formula (芪菟二至方, QEF) to protect the hematopoietic function of bone marrow and reduce the myelosuppression after chemotherapy by warming Pi and Shen. Based on the National Key Research and Development Plan (2017YFC1700604), this study will provide evidence whether JBSF can reduce the side reactions of adjuvant chemotherapy for colonic cancer.

## METHODS

### Inclusion and Exclusion Criteria

The inclusion criteria include the following: (1) patients who have completed radical surgery for colon cancer and will be given adjuvant chemotherapy with CAPEOX; (2) all patients will be over 18 and up to 75 years old; (3) no chemotherapy within 6 weeks after radical operation; (4) Eastern Cooperative Oncology Group Performance Score (ECOG-PS) of 0 to 2; (5) definite pathological diagnosis and negative pathological margin; (6) stage III and high risk in stage II according to TNM (American Joint Committee on Cancer, 8th edition). According to "NCCN clinical practice guidelines in colon cancer (version 2. 2018)", high risk factors for recurrence include poorly differentiated histology (exclusive of those cancers that are MSI-H), lymphatic or vascular invasion, bowel obstruction, less than 12 lymph nodes examined, perineural invasion, localized perforation and close, indeterminate, or positive margins.

Exclusion criteria include the following: (1) patients judged by the physician that do not need CAPEOX chemotherapy; (2) with severe cardiovascular system complications, cerebrovascular system complications, active hepatitis, or severe liver or kidney dysfunctions; (3) patients who are known or suspected to be allergic to the known ingredients in the study drug; (4) with intestinal obstruction that can not be treated by oral medicine and need intravenous high energy nutrition; (5) with severe malabsorption or other diseases affecting gastrointestinal absorption and colostomy.

### Participants

This double-blind multi-center randomized controlled study will be performed by the Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing Cancer Hospital, Tianjin Renmin Hospital, Affiliated Hospital of Nanjing University of Chinese Medicine, Guangdong Hospital of Chinese Medicine and the Beijing University of Chinese Medicine. The subjects will be recruited from Beijing, Tianjin, Shanghai, Nanjing, Guangzhou and other sub-centers. All sub-centers are Grade-A general hospitals or tumor specialized hospitals. They are able to follow NCCN clinical guidelines for colon cancer treatment in a high level of tumor diagnosis and treatment and have a high degree of consistency in treatment.

The study protocol has been registered on clinicalTrials.gov (No. NCT03716518). Ethics approval has been obtained from the Medical Ethical Committee of Xiyuan Hospital (approval No. 2018XLA048-2). This study will be conducted according to the principles of the Declaration of Helsinki (64th version, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO, 1-3-2006).

### Randomization and Blinding

In this study, a stratified block design will be used. Each site will be used as a stratification factor. Statisticians generate a random sequence by SAS (proc plan) statistical software. The selected 400 subjects will be divided into the treatment group and the control group at a 1:1 ratio. The random seed and sequences will be sealed in opaque envelopes as confidential data and the emergency envelopes will be securely stored by the Institute of Clinical Pharmacology of Xiyuan Hospital to ensure adequate masking of patients, researchers and outcome evaluators.

### Intervention

According to "NCCN clinical practice guidelines in colon cancer (Version 2. 2018)", the adjuvant chemotherapy regimen is CAPEOX, consisting of oxaliplatin 130 mg/m<sup>2</sup> on day 1 and capecitabine 1000 mg/m<sup>2</sup>, given twice daily on day 1–14 and repeated every 21 d.

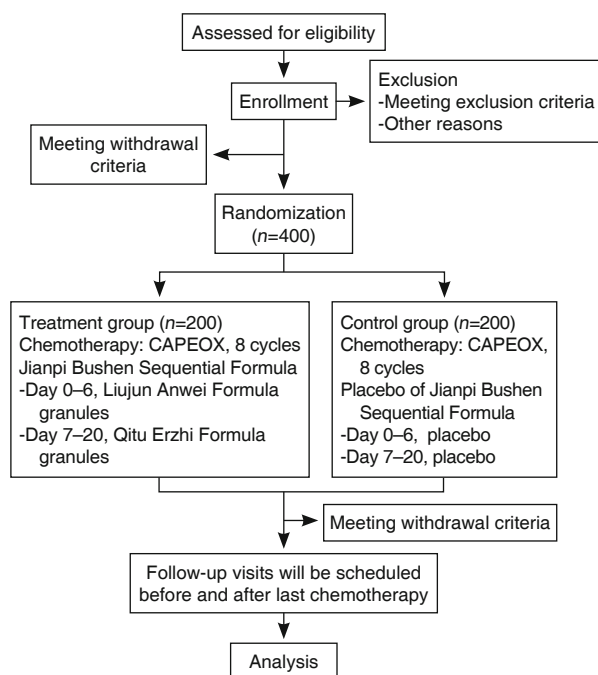
Patients assigned to the treatment group will receive JBSF, which included two prescriptions: LAF granules, composed of *Radix pseudostellariae*,

stir fried *Atractylodes macrocephala*, *Poria cocos*, and *Rhizoma Pinelliae*, will be given twice daily on day 0 to 6 in each cycle; QEF granules, composed of raw astragalus, dodder, *Ligustrum lucidum*, and *Angelica*, will be given twice daily on day 7–20 in each chemotherapy cycle.

Patients assigned to the control group will receive placebo granules of LAF and QEF granules, which are prepared with 2% of the test drugs and 5% of balsam pear extract. The appearance, dosage form, weight, color and smell of placebo granules are consistent with those of the test drugs. All the granules are produced by Beijing Kang Ren Tang Pharmaceutical Co., Ltd., China.

### Assessments

If patients were given a different chemotherapy regimen due to the researcher or were affected by the side effects of chemotherapy, or were unwilling to continue chemotherapy for other reasons, the outcomes will be assessed in the interview after the last chemotherapy. Figure 1 shows a study flowchart and Table 1 gives an overview of all outcome measures. Patient and treatment characteristics and demographic variables like age, gender and living situation will be obtained from the medical records and a baseline questionnaire. Medical data will be extracted from medical records.



**Figure 1. Study Flowchart of Jianpi Bushen Sequential Formula on Adjuvant Chemotherapy of Colon Cancer**

**Table 1. Outcome Measures of JBSF on Adjuvant Chemotherapy of Colon Cancer**

Measurement	Time point
Completion of chemotherapy	C
Adverse reactions of chemotherapy	C
Complete blood count	C0, C
Medical evaluation scales (ESAS, FACT-C, Symptom scale of CM, etc.)	C0, C
CT/MRI	C0, C4, Ce
Tumor marker	C0, C4, Ce
Analysis of intestinal flora	C0, C1-2
Function of immunity	C0, C4, Ce
Cytokine detection	C0, C4, Ce
Safety index	C

Notes: JBSF: Jianpi Bushen Sequential Formula; CT/MRI: computer tomography/magnetic resonance imaging C: every cycle; C0: prior to chemotherapy; C1-2: during the first 2 cycles; C4: after the 4th cycle; Ce: after the last cycle.

### Primary Outcome

The overall chemotherapy completion rate is defined as: patients who completed 8 cycles of chemotherapy/total number of patients  $\times 100\%$ , when completion is defined as the progression of chemotherapy for a patient to the end of 24 weeks, when the 8th cycle of chemotherapy is started. If the last chemotherapy is in progress, it will be regarded as completed. If the patient suspends chemotherapy due to side effects, such as myelosuppression and could continue to receive chemotherapy after treatment, the total number of chemotherapy cycles at the end of 24 weeks will be calculated. Patients who reach the clinical end point will continue to receive treatment according to the guidelines.

### Secondary Outcomes

Secondary outcomes include individual chemotherapy completion rate, 4-cycle completion rate of chemotherapy, time to failure, relative dose intensity and delayed time of chemotherapy and toxicity.

### Treatment Related and Exploratory Outcomes

This study will use some medical evaluation scales, such as Edmonton Symptom Assessment System (ESAS),<sup>(9)</sup> Functional Assessment of Cancer Therapy-Colorectal (FACT-C),<sup>(10)</sup> to evaluate the quality of life of patients during chemotherapy. This study will also use some self-made CM scales such as Pi (Spleen) deficiency scale of CM, Shen (Kidney) deficiency scale of CM, symptom scale of CM, to evaluate the degree of Pi and/or Shen deficiency

and the improvement of CM symptoms during chemotherapy. Analysis of intestinal flora, function of immunity and cytokine detection will be carried out according to the specified schedule as exploratory outcomes.

### Sample Size

Sample size was calculated according to the primary outcome-overall chemotherapy completion rate. The proportion in the treatment group is assumed to be 78%. The proportion in the control group is 64%.<sup>(11)</sup> SPSS (22.0, IBM Corp. Armonk, NY) software was used for the calculation. The significance level of the test was targeted at 0.05. Group sample sizes of 164 in each group will achieve 80% power to detect a difference between the group proportions of 0.14. Therefore, we plan to recruit a total of 200 patients per group to account for loss to follow-up (18%).

### Statistical Analysis

The statistical analysis will be completed by the Evidence-based Medicine Center of Beijing University of Chinese Medicine. Data will be analyzed using SPSS (22.0, IBM Corp. Armonk, NY, USA) for descriptive and statistical analyses. All analyses will be performed according to the intention-to-treat principle. For quantitative data, descriptive statistical analysis will be made by case number, mean  $\pm$  standard deviation or median, upper quartile and lower quartile, according to data distribution type. Descriptive statistical analysis of qualitative data will be shown by frequency table, percentage or composition ratio after treatment. The quantitative data will be tested by *t* test or rank sum test, while the qualitative data will be tested by Chi-square or rank sum test. Survival probabilities will be estimated using the Kaplan-Meier method.

## DISCUSSION

Chemotherapy causes a series of side effects, affects the compliance and quality of life of patients, affects the efficacy of chemotherapy and the survival time of patients. The efficacy and tolerance of chemotherapy in postoperative adjuvant chemotherapy for colorectal cancer patients has been reported.<sup>(12)</sup> Some researchers found that the tolerance of Chinese people to adjuvant chemotherapy with oxaliplatin containing regimens was worse than that of Western patients.<sup>(13)</sup> Of the 111 patients who received the 3 week regimen,

only 54% completed 6 cycles of chemotherapy. Intolerance of side reactions was the main reason for early termination of treatment. Nausea (88.8%), peripheral neurotoxicity (71.2%), thrombocytopenia (55.6%), vomit (45.6%), and neutropenia (38.0%) were the most common side reactions.<sup>(13)</sup> More attention should be paid to the control of side effects of chemotherapy and to improve the quality of life during chemotherapy. This study is designed to provide evidence-based medicine evidence for whether JBSF can reduce the side effects of adjuvant chemotherapy in patients with colon cancer.

During chemotherapy, nausea, vomiting, anorexia and other side effects of the digestive tract and myelosuppression symptoms are usually summarized as disharmony of Spleen and Stomach and insufficiency of Pi and Shen in CM. The disease is caused by the damage of Spleen and Wei (Stomach) qi caused by chemotherapy drugs, and the main treatment principle is to strengthen these organs. It has been shown that CM has an auxiliary when combined with chemotherapy, to improve immune function, protect hematopoiesis function, reverse multidrug resistance of tumors and better reduce the toxic side effects caused by the interaction of chemotherapy drugs.<sup>(14,15)</sup> According to the theory of syndrome differentiation and treatment of CM, Prof. YANG Yu-fei invented JBSF to target the effects of chemotherapy on the gastrointestinal system and bone marrow suppression. The first step is to treat Pi and Wei, using LAF granules to alleviate the digestive tract reaction after chemotherapy by strengthening Pi and Wei. The second step is to treat Pi and Shen, using QEF granules to protect the hematopoietic function of bone marrow and reduce the myelosuppression after chemotherapy by warming Pi and Shen.

There are still some limitations in this study, which was designed and funded in 2017. In 2018, the American Society of Clinical Oncology proposed as the main conclusion of IDEA research, that the period of postoperative adjuvant chemotherapy for colorectal cancer should be adjusted to 3 to 6 months according to the different stages and risk factors after radical resection. For patients with low risk factors, postoperative adjuvant chemotherapy for 3 months could be selected.<sup>(11)</sup> This meant that this study needed to screen more patients with high risk factors, put forward higher requirements for

the recruitment and enrollment of the subjects and this indirectly affected the enrollment speed. This study cannot test the intestinal flora distribution of all subjects during chemotherapy due to limited research funding, research progress and other factors, but it can still test the intestinal flora of subjects in the first two chemotherapy cycles, which provides a certain basis for further research. Limited by the research conditions, the whole process dynamic monitoring of T, B lymphocyte subsets and cytokines of all subjects could not be realized in this study, only in the sub centers with the examination conditions.

In January 2020, the outbreak of 2019 coronavirus disease has been having extensive influence on the society and people's daily life in China.<sup>(16,17)</sup> During this period, treatments for cancer patients will be impacted to a certain extent and this will affect the management of the study and the recruitment of the subjects, which is likely to lead to the postponement of the study.

### Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

### Acknowledgements

The authors appreciate MAO Jun, LIU Jian-ping, YANG Pei-ying, LI Qing, and YANG Ge-liang for their contributions to this study and this paper.

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(Accepted January 11, 2021; First Online August 25, 2021)  
Edited by YUAN Lin