Study Protocol

Efficacy and influencing factors of Insect Compound Particle combined with chemotherapy for mismatch repair-related locally advanced stage III CRC who had undergone surgery and achieved R0 resection: a multicenter, double-blind, randomized, placebo-controlled clinical trial protocol

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Background: Colorectal cancer (CRC) is an insidious malignancy and the occurrence of chemotherapy resistance and toxicity seriously limits its clinical efficacy. Insect Compound Particle [Chong Yao Fu Fang (CYFF)] is a traditional Chinese medicine (TCM) compound based on the concepts of "invigorating spleen for strengthening vital qi" and "collateral disease theory". In long-term clinical application, it can reduce the toxicity of CRC chemotherapy and improve the anti-tumor effect. However, there is currently a lack of high-quality clinical evidence to prove the clinical efficacy and safety of CYFF in the treatment of CRC.

Methods: We plan to include 262 patients with locally advanced stage III CRC who had undergone surgery and achieved R0 resection. These patients will be randomized into a CYFF group (treated with CYFF combined with chemotherapy) and a control group (treated with placebo plus chemotherapy) at a 1:1 ratio. The patients were routinely followed-up every 2 weeks within 2 months and every 4 weeks after 2 months after the treatment, every 3 months within 1 year, and every 6 months after 1 year. The primary endpoint is disease-free survival (DFS), defined as the time from random assignment to recurrence of primary CRC or death from any cause. The secondary endpoints include overall survival (OS) (defined as the time from randomization to death from any cause), safety [any adverse events (AEs)], and the Colorectal Cancer-Specific Quality of Life Questionnaire (QLQ-CR38) score.

Conclusions: Compared with previous studies, our current study applies CYFF plus basic adjuvant chemotherapy, which is expected to achieve better efficacy and longer survival than standard chemotherapy, and reduce the toxic and side effects of chemotherapy, improve the safety of clinical treatment. In addition, our present study is the first clinical study to evaluate the safety and efficacy of CYFF in combination with

chemotherapy in the treatment of stage III CRC after R0 resection.

Trial Registration: This clinical trial has been registered in the Chinese Clinical Trial Registry (ChiCTR) (registration No. ChiCTR2000037568; August 28, 2020).

Keywords: Colorectal cancer (CRC); adjuvant chemotherapy; traditional Chinese medicine (TCM); randomized controlled trial; DNA mismatch repair (DNA MMR)

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Introduction

According to the Global Cancer Statistics 2020 released by International Agency for Research on Cancer (IARC) (1), there were 19.3 million new colorectal cancer (CRC) cases and 0.94 million deaths worldwide in 2020, accounting for 10% of global cancer incidence and 9.4% of cancer deaths (2). In general, CRC is the third most common malignancy and the second most deadly cancer, and there has been an apparent increase in the incidence of CRC in young adults (3). The incidence and mortality of CRC have risen rapidly in China; in the past 5 years, CRC ranks third in terms of incidence and fifth in terms of mortality among malignant tumors in China. With the socioeconomic development in China, the incidence of CRC has shown a sharp upward trend in recent years (4).

Despite the rising incidence of CRC worldwide in the past 20 years, the mortality rate of CRC has declined in many developed countries (e.g., the United States), which is related to improved prevention and intervention, early screening and diagnosis, and the establishment of precision treatment systems for CRC in these countries (5). The diagnosis and treatment of CRC have entered the era of molecular diagnosis and treatment with the application of new techniques (e.g., biotechnology and genetic information technology) in oncology and with the advances in research on signaling pathways and molecular markers. Precision treatment in CRC allows for more refined planning of a series of clinical links in surgical treatment, chemotherapy, targeted therapy, and immunotherapy.

The clinical prognosis of CRC patients is closely related to tumor stage and lymph node metastasis. However, due to the high genetic and molecular heterogeneities of CRC (6), the prognosis of patients with CRC at the same stage may vary due to different gene mutations (7). DNA mismatch repair (*MMR*) is a major genetic modification system for CRC, and its defects will result in a microsatellite instability (MSI) phenotype in 15% of CRC patients (8), which will affect patient prognosis and response to specific drug therapies (9).

Radical surgery remains the mainstream treatment for CRC. However, the risk of recurrence and metastasis after surgery is high, and about 30% of patients develop recurrence or distant metastasis after radical resection (10). Subsequently, palliative chemotherapy or chemotherapy combined with targeted therapy or immunotherapy is required under the guidance of genetic testing and immune targets. However, patients with stage IV CRC (i.e., with distant metastasis) at the first diagnosis often cannot benefit from preoperative neoadjuvant chemoradiotherapy, targeted therapy, or immunotherapy. Also, these therapies are extremely expensive and toxic, which seriously affects the quality of life of patients (11). In the context of precision medicine, traditional Chinese medicine (TCM), as an adjuvant therapy, has become a featured treatment in the multidisciplinary therapy of malignant tumors. Numerous clinical studies have demonstrated that TCM compound prescriptions can significantly improve the quality of life of patients who have undergone surgery for CRC or those with advanced CRC and prolong their overall survival (OS) and progression-free survival (PFS). The TCM compound prescription + chemotherapy often can achieve a better overall response (complete response + partial response) than chemotherapy alone (12).

Insect Compound Particle [Chong Yao Fu Fang (CYFF)] is a TCM compound based on the concepts of "invigorating spleen for strengthening vital qi" and "collateral disease theory", which commonly used in the Oncology Department of Shanghai Municipal Hospital of Traditional Chinese Medicine for the treatment of advanced CRC and has applied for an invention patent (application number: 202010190627.3). Tianlong (gecko)

and centipede are the main drugs of CYFF which have a long history of medicinal use in China. At present, they are widely used in the treatment of various tumor diseases, especially in the treatment of digestive system tumors with the obvious effect and low toxicity. In recent years, a large number of studies have been carried out on the material basis and pharmacological effects of CYFF-related drugs on anti-tumor. Tang *et al*. (13) separated the macromolecular components from the fresh gecko aqueous extract through the Sephadex G-25 column. The research results show that the active component has significant tumor inhibition effect. Ding *et al*. (14) isolated isoquinoline alkaloid 1–2 from the alcohol extract of centipede, proving that it can block the cell cycle of human glioma U87 cells at G0/G1 phase. A retrospective clinical study by our research group also showed that the 3-year survival rate after CYFF + chemotherapy was 94.6%, which was higher than that of chemotherapy alone (61.1%; P<0.05) and it also improved the chemotherapy-related adverse reactions such as hand-foot syndrome. In addition, there were no obvious adverse reactions during the treatment of patients with good safety. However, we cannot ignore that some studies show that long-term use of large doses of TCM compound may have certain hepatorenal toxicity (15). Therefore, in this study, the standardized TCM selected by Jiangsu Tianjiang Pharmaceutical Co., Ltd. of China is processed to prepare CYFF compound granules, and the clinical dosage of CYFF granules is within the safe dose range according to the dose requirements of the Chinese Pharmacopoeia.

To evaluate the clinical efficacy and safety of CYFF + chemotherapy in treating advanced CRC and improving the clinical outcomes of patients, we will perform a prospective, randomized, multi-center, placebo-controlled clinical trial to explore the correlation between CRC prognosis and the efficacy of CYFF, hoping that the integration of TCM and Western medicine will further improve the treatment efficacy and promote the research and development (R&D) of new anti-tumor TCM drugs.

Methods

Primary objective and study hypothesis

This multicenter, large-sample, stratified, randomized double-blind controlled study aims to evaluate the efficacy and safety of CYFF in the treatment of *MMR*-related stage III CRC and to explore the pharmacodynamic material basis of CYFF. We assume that CYFF + chemotherapy can effectively the improve clinical symptoms of CRC patients, reduce chemotherapy toxicities, and provide long-term survival benefits.

Trial design

This 24-week randomized, double-blind, placebo-controlled, clinical trial will be conducted in four clinical research centers in the Shanghai Municipal Hospital of Traditional Chinese Medicine, the Fudan University Cancer Hospital, the Zhongshan Hospital Affiliated to Fudan University, and the Changhai Hospital Affiliated to Navy Military Medical University. Participants will be randomized at a 1:1 ratio to receive CYFF + chemotherapy (CYFF group) or placebo + chemotherapy (control group) within 6 weeks after radical resection of CRC. The interventions will be initiated within 2 weeks after randomization. Therefore, medical treatment will begin within 8 weeks after surgery. The CYFF group will be treated with adjuvant chemotherapy combined with CYFF for 6 months, whereas the control group will receive adjuvant chemotherapy combined with a placebo for 6 months. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013) (16) and Good Clinical Practice (GCP) (17). Adverse events (AEs) were graded according to the US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 2.0) (18). The interventions will be terminated if there is unacceptable toxicity or evidence of disease progression. The research design is shown in *Figure 1*.

Sample size

This study is a superiority trial, according to the literature (19), the estimated median OS (mOS) is 16 months in the control group and 25 months in the CYFF group. The participants will be randomly assigned at a 1:1 ratio, The sample size was calculated by using PASS.11 software (NCSS, 329 North 1000 East Kaysville, Utah 84037, USA). Input Proportion in Control Group value 0.5, with α=0.05 (two-sided) and power =0.80. Based on clinical experience and the literature, N1 (control group) =16, N2 (test group) =25 months, enrollment mode is uniform entry. The expected drop-out rate is 15%, and the minimum sample size is 262.

Screening and recruitment of participants

A total of 262 patients with pathologically confirmed stage

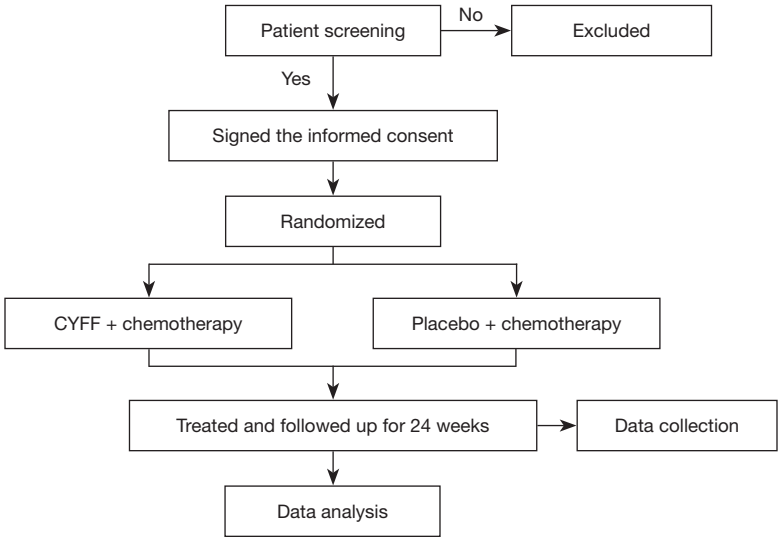

Figure 1 Research flow chart. CYFF, Chong Yao Fu Fang.

III CRC after radical resection will be included, with 66 patients each from the oncology departments in the four hospitals listed above: the Shanghai Municipal Hospital of Traditional Chinese Medicine, the Fudan University Cancer Hospital, the Zhongshan Hospital Affiliated to Fudan University, and the First Affiliated Hospital of Naval Military Medical University.

The following recruitment strategies will be used:

(I) The number of outpatients and inpatients in the oncology departments (sub-centers) of these four hospitals in past 3 years was analyzed in advance. It was found that each hospital had more than 80,000 outpatient visits in the oncology department per year. Therefore, each subcenter will have enough patients with stage III CRC to support the implementation of the study;

(II) Recruitment advertisements have been made and released in these sub-centers to recruit more eligible participants;

(III) To avoid patient dropout during the observation and follow-up processes, the subjects will be regularly contacted to remind and help them complete examinations and follow-up visits on time.

Consent procedures

All participants have the right not to participate or to end their participation in the trial at any time. The enrolled patients will be randomly assigned after signing a written informed consent form. The informed consent forms will be kept by the principal investigators (PIs) at each subcenter and will be regularly reviewed and archived by the Data and Safety Monitoring Board (DSMB) and the hospitals' ethics review boards.

Study criteria

Diagnostic criteria

CRC is diagnosed according to the relevant criteria in the Chinese Protocol of Diagnosis and Treatment of Colorectal Cancer (2020 edition) (20) released by the National Health Commission of the People's Republic of China and the Chinese Society of Oncology, and all the diagnoses will be confirmed by pathology and clinical imaging.

The clinical staging is based on the tumor-node-metastasis (TNM) classification on cancer staging (8^{th} edition) (21), jointly developed by the American Joint Commission on Cancer (AJCC) and the Union for International Cancer Control (UICC).

Inclusion/exclusion criteria

The inclusion criteria were as follows:

(I) Meeting the above diagnostic criteria of stage III CRC;

(II) Agreeing to undergo radical surgery and having been clinically diagnosed with any $TN_{1-2}M_0$ after consultations, physical examinations, laboratory

tests, and imaging;
(III) Agreeing to undergo CRC tissue sampling, pathological testing, *MMR*, rat sarcoma viral oncogene homolog (*RAS*), metastasis associated lung adenocarcinoma transcript 1 (*MALTA1*), and neurofibromatosis 2 (*NF2*) gene detection, and Merlin protein (Moesin-Ezrin-Radixin-Like protein) expression determination;
(IV) Agreeing to have their peripheral circulating blood collected for TCM metabolomic analysis;
(V) Men or women aged ≥18 years;
(VI) With an expected survival of ≥6 months and Eastern Collaborative Oncology Group (ECOG) performance status score of ≤2;
(VII) Agreeing to be followed up;
(VIII) With complete follow-up and clinical data;
(IX) With voluntarily signed informed consent.

The exclusion criteria were as follows:
(I) Complicated with other primary malignant tumors;
(II) Complicated with severe heart, brain, liver, and/or kidney diseases, electrolyte Abnormality, and/or mental illness;
(III) Allergic to the drugs used in this study or their ingredients;
(V) Pregnancy, lactation, or planned pregnancy;
(VI) With serious or uncontrollable infections;
(VII) Received orally administered with other TCM herbs or participated in other clinical trials within the past 2 weeks.

Excluded criteria

(I) Do not take drugs in accordance with the trial protocol, have poor compliance, or take other related therapeutic drugs on their own decision;
(II) Conditions that are inconsistent with the inclusion criteria or meeting the exclusion criteria are found to be concealed or occur after enrollment;
(III) Natural dropout during the observation period;
(IV) A clinician believes that the patient should be withdrawn from the study due to other conditions.

Exit/dropout case criteria

Enrolled cases that do not complete the clinical trial for the following reasons should be considered dropouts:
(I) Initiation of the withdrawal mechanism due to the lack or loss of efficacy: For patients who have been evaluated for efficacy at least once within 12 weeks after drug treatment, the withdrawal mechanism may be initiated if there is disease progression or a serious adverse reaction; these patients will be categorized as evaluable cases and classified as non-responders. The lack or loss of efficacy will be assessed by investigators (non-participants);
(II) Spontaneous withdrawal of patients (due to poor response and adverse reactions);
(III) Lost to follow-up or death;
(IV) Abnormal liver function (NCI-CTCAE grade 4) bleeding (NCI-CTCAE grade 3 or higher), and any other fatal adverse reactions (grade 4);
(V) Pregnancy;
(VI) A request of withdrawal by the investigator (poor adherence and/or severe AEs).

The case report forms (CRFs) and the existing clinical data of the withdrawn subjects will be recorded and saved for subsequent reference. Any patient who withdraws from the study within 2 weeks of receiving treatment will be considered a withdrawal case and the relevant data will be treated as missing data.

Trial suspension criteria

The trial will be suspended if a serious AE (SAE) occurs during its implementation.

AEs: the research group has long been committed to clinical and basic research on the application of TCM for the prevention and treatment of CRC. CYFF has been investigated in a series of basic and clinical studies, showing good clinical efficacy. An invention patent has been applied (application number: 202010190627.3). The CYFF granules used in this trial are in line with the dosage requirements in the Chinese Pharmacopoeia. The dose is within the safe dosage range, as quality is controlled by China Jiangsu Tianjiang Pharmaceutical Co., Ltd. The probability of SAE is small in clinical practice. Any allergic reaction can be managed by symptomatic treatment.

Chemotherapy has the potential risk of causing liver, kidney, and cardiac toxicities, and is often accompanied by myelosuppression, peripheral neuropathy, and other toxic reactions, which limits its clinical application (22,23). If NCI-CTCAE grade 2 drug-induced myelosuppression, as well as drug-induced liver function impairment, rash, vomiting, diarrhea, or pain, occur during the trial, granulocyte colony-stimulating factor, erythropoietin, hepatoprotective and enzyme-lowering drugs, emollients, anti-itch drugs, anti-allergic drugs, stomach acid drugs, and/or antidiarrheal drugs can be used to treat the

symptoms. The frequency of medications is not limited, and hepatoprotective or hematopoietic drugs cannot be used as a routine prophylactic.

All AEs will be systematically collected during the every 2-week follow-up visits and recorded in detail on specific forms throughout the study, and will eventually be described in the published articles.

SAEs: events that may lead to any of the following outcomes are included in the SAEs, which will be observed, monitored, and judged by the investigators and managed promptly; in addition, SAEs should be reported to the relevant authorities.

(I) Requiring prolonged hospital stay or long-term treatment;
(II) Leading to disability or death;
(III) Leading to fetal congenital malformations.

Randomization

Generation of random codes: The Central Randomization and Trial Supply Management (RTSM) (Bioknow, Beijing, China) is used for stratified randomization and drug distribution in each subcenter. The CYFF granules are manufactured by Jiangyin Tianjiang Pharmaceutical Co., Ltd. under the supervision of the Shanghai Municipal Hospital of Traditional Chinese Medicine and then delivered to the warehouse managers, who will first distribute and package the drugs according to the random codes and then deliver them to each subcenter, where the investigators will administer the drugs to the enrolled patients according to the random codes. After allocation, the subjects will receive appropriate treatment, during which the investigators at each subcenter will ensure the continuous supply of medicines and offer the treatment service for 24 weeks.

Blinding

A double-blind method will be applied. The blinding of subjects and drugs will be carried out using RTSM (Bioknow), and neither the subjects nor the investigators will know whether a specific subject belongs to the CYFF group or the control group.

The subjects will be randomized into a CYFF group and a control group at a 1:1 ratio. Unblinding will be performed twice by staff members who are responsible for keeping the unblinded results. After the blinding status is confirmed to be reliable and flawless, the data files will be locked for the first session of unblinding, which lists only the group to which each case belongs (e.g., group A or B). A second session of unblinding will be performed after the statistical analysis is completed to identify which one is the CYFF group or control group.

Emergency treatment plan

When SAEs occur or if an enrolled patient requires emergency rescue, the staff member should immediately report the situation to the PI and supervisor and then open the emergency envelope to break the blind, which will help to clarify whether the adverse reactions are caused by the experimental medications. Various adverse reactions should be promptly managed and recorded.

Intervention

Patients diagnosed with stage III CRC and treated with radical surgery will be randomized into CYFF or control groups after the patients signed the informed consent forms.

CYFF group

Subjects randomized into the CYFF group will receive CYFF combined with conventional chemotherapy for CRC.

Dosage and duration

CYFF granules: tianlong (gecko) 3 g, centipede 3 g, milkvetch root 30 g, fried largehead atractylodes rhizome 12 g, white poria 18 g, hedyotis 15 g, radix actinidiae 15 g, and liquorice root 6 g. Two packs (7.9 g/pack) of CYFF granules will be administered with boiled water twice daily in the morning and evening for 24 consecutive weeks.

According to the US National Comprehensive Cancer Network (NCCN) guidelines on CRC (24,25), CRC patients shall undergo chemotherapy using the mFOLFOX6 regimen: oxaliplatin 85 mg/m^2 intravenously guttae (ivgtt) d1; calcium folinate 400 mg/m^2 ivgtt d1; 5-fluorouracil 400 mg/m^2 intravenously (iv) d1, 1,200 mg/(m^2·d) iv d2–d3, continuous intravenous injection (civ) (2,400 mg/m^2, civ 46–48 h); repeated every 2 weeks. The interventions are shown in *Figure 2*.

Control group

Subjects randomized into the CYFF group will receive a

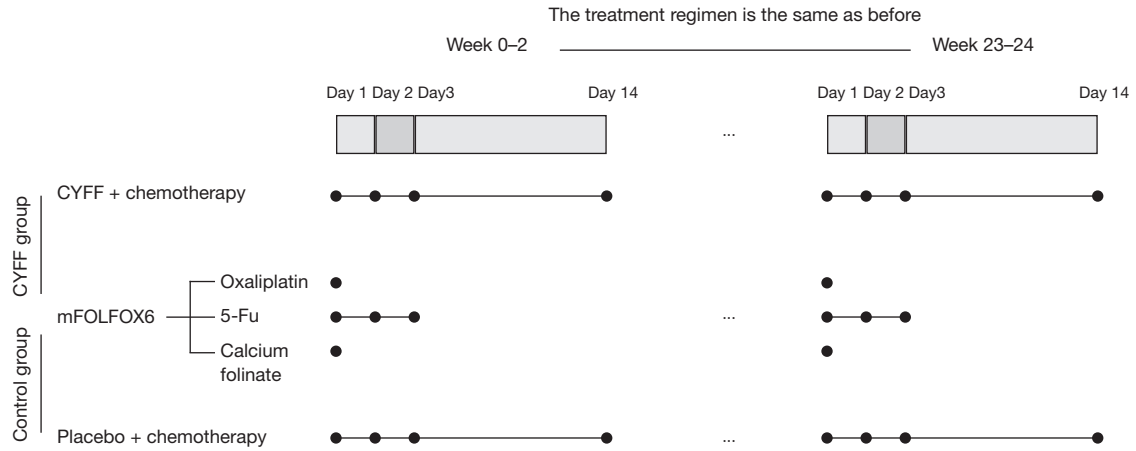

Figure 2 Interventions. CYFF, Chong Yao Fu Fang; 5-Fu, 5-fluorouracil.

CYFF placebo combined with conventional chemotherapy for CRC. The placebo granules were produced by the same manufacturer of CYFF, which require that the same amount, color, odor, taste and appearance as the CYFF granules but contains only 10% CYFF granules.

The above TCM dosage is the recommended dose, and the use of modified regimens is based on the requirements of the *Chinese Pharmacopoeia*. All of the drugs are manufactured by Jiangyin Tianjiang Pharmaceutical Co., Ltd. under the supervision of Shanghai Traditional Chinese Medicine Hospital.

Concomitant medications

The use of concomitant medications should be avoided as much as possible during the trial. During the trial, drugs that are orally administered for treating chronic underlying diseases (e.g., diabetes, hypertension, and coronary heart disease) can be used. Comorbidities or symptoms that have already existed before the start of the trial shall be recorded in detail. For drugs or other therapies that need to be continued or added, the generic name, dosage, reason for use, and frequency and timing of use must be recorded in the CRF.

Follow-up

All patients will be followed up face-to-face at every 2 weeks within 2 months after the initiation of treatment, every 4 weeks after 2 months of treatment, will collect the efficacy outcomes, repeat measurement of routine laboratory tests. Every 3 months within 1 year after treatment, and every 6 months after 1 year, the patients will be followed up by telephone interviews, mainly to follow up the survival of patients.

Items to be measured and the time points of data collection

Patient data and efficacy-related indicators will be collected and recorded before the start of treatment, and during follow-up. The timing of tests and data collection is shown in *Table 1*.

Blood and CRC tissue samples will be collected at each subcenter, stored in the department of pathology, and detected, analyzed, and finally destroyed at the Shanghai Municipal Hospital of Traditional Chinese Medicine. No additional sample set will be obtained for storage or future testing during this trial. All samples will be encoded with their unique identifiers and recorded in the Electronic Data Capture (EDC). The researchers who analyze these samples will not be unable to obtain information on any participants or interventions.

The following methods will be used to reduce possible errors during this clinical trial:

(I) Before the start of the trial, the investigator will explain the study protocol to the subjects in detail, so that the subjects can fully understand the whole research process and the possible risks;

(II) Researchers will contact the subjects regularly according to the timing of follow-up visits and treatment regimens and help the subjects receive treatment and examinations on time;

Table 1 Study flow chart: items to be examined and the timing of data collection

Visit	Screening period (month)	Drug intervention period (months)								After drug withdrawal	Further follow-up (months)		
	0	0.5	1	1.5	2	3	4	5	6		9	12	18
Baseline data													
Demographic data	X												
Vital signs	X	X	X	X	X	X	X	X	X	X			
Body weight/body mass index	X									X			
History of CRC and its treatment	X												
Inclusion/exclusion criteria	X												
Random code	X												
Signed the informed consent	X												
History of other diseases and their treatments	X												
Concomitant diseases	X												
Complications	X	X	X	X	X	X	X	X	X	X			
Efficacy measures													
Traditional Chinese Medicine Syndrome Scale score	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life score (QLQ-CR38)	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X	X							X				
Blood pressure	X	X							X				
Abdominal CT or MRI	X					X				X			
Colonoscopy	X					X				X			
Safety assessment													
Kidney function	X	X							X				
Liver function	X	X							X				
Electrocardiogram	X	X							X				
Routine blood test	X	X							X				
Routine urine test	X	X							X				
Routine stool test/FOBT	X	X							X				
Baseline treatments		X	X	X	X	X	X	X	X				
Study drugs given		X	X	X	X	X	X	X	X				
Drugs distributed, recovered, and recorded		X	X	X	X	X	X	X	X				
AEs		X	X	X	X	X	X	X	X				
Stage-specific evaluation of therapeutic efficacy						X							
Treatments that affect the prognosis										X	X	X	X
Survivals										X	X	X	X
Conclusions									X	X	X	X	X

"X" means this item will be recorded. CRC, colorectal cancer; QLQ-CR38, Colorectal Cancer-Specific Quality of Life Questionnaire; CT, computed tomography; MRI, magnetic resonance imaging; FOBT, fecal occult blood test; AEs, adverse events.

(III) The test results will be entered into the EDC system, and the original reports will be photographed and saved.

Outcomes

Primary efficacy outcome

The primary efficacy outcome is disease-free survival (DFS).

Secondary efficacy outcomes

The secondary efficacy outcomes include the following: OS; changes in tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen (CA)199, and CA125; active ingredients in CYFF: high-performance liquid chromatography (HPLC) is used in pharmacometabolomic studies to detect the endogenous markers and exogenous TCM components in the sera of subjects to discover and identify the pharmacoactive components of TCM drugs.

In addition, the TCM symptoms, quality of life, and subjective symptoms will be scored, and the number of episodes in each subject will be recorded. Meanwhile, the vital signs and AEs in all participants will be monitored throughout the trial.

Safety indicators

Routine blood, urine, and stool tests, liver/kidney function examinations, and electrocardiogram (ECG) will be performed before and after the treatment. The possible AEs will be documented. AEs during chemotherapy will be evaluated according to the NCI-CTCAE version 2.0. The common adverse reactions include myelocytopenia, gastrointestinal perforation, proteinuria, hypertension, hand-foot syndrome, acneiform rash, and diarrhea.

Therapeutic effect evaluation

TCM syndrome scores

According to the efficacy grading criteria in the *Guiding Principles for Clinical Research of New Chinese Medicines* (26), the overall score of TCM symptoms and the score of individual symptoms will be compared before and after treatment and between two groups to determine the efficacy. The main syndrome is spleen deficiency, with the primary symptoms including abdominal pain, diarrhea, constipation, fatigue, poor appetite, nausea/vomiting, and weight loss, and the secondary symptoms including insomnia, dizziness, tinnitus, dysphoria with feverish sensation in the chest, palms, and soles, spontaneous sweating, night sweating, fever, dry mouth, waist and knee soreness, and hematochezia. These symptoms will be scored according to their severity. The primary symptoms are scored as 0, 2, 4, and 6 points, corresponding to none, mild, moderate, and severe, respectively; and the secondary symptoms will be scored as 0, 1, 2, and 3 points, corresponding to none, mild, moderate, and severe, respectively.

The TCM syndrome scores of each patient before treatment and in the 24th week after treatment will be added to calculate the efficacy score index of individual patients using the following formula: efficacy index of a single case = [(total points before treatment – total points after treatment)/ total points before treatment] × 100%. Overall response rate = cure rate + complete response rate + partial response rate. Complete response: the symptoms are improved, with an efficacy index reduced by ≥70%. Partial response: the symptoms are alleviated, with an efficacy index reduced by 30–70%. No response: the symptoms have no change or even become worse, with an efficacy index reduction of <30%.

Colorectal Cancer-Specific Quality of Life Questionnaire (QLQ-CR38)

The European Organization for Research on Treatment of Cancer (EORTC) QLQ-CR38 quality of life questionnaire for CRC (27): in the functional scales and symptoms scales, 38 items are divided into 12 dimensions (i.e., four functional dimensions and eight symptom dimensions). Furthermore, the raw scores will be transformed into standardized scores (with values from 0 to 100) using the linear transformation method. A higher functional domain score indicates better functional status and quality of life, whereas a higher symptom domain score signifies more severe symptoms (*Table 2*).

Survivals

DFS and OS are two common endpoints for cancer trials. DFS refers to the time from random assignment to disease recurrence or death (due to any reason). OS is defined as the time from random assignment to death from any cause and is considered the gold standard of endpoints in cancer clinical trials. DFS can be used as both a surrogate endpoint for OS and a primary endpoint in cancer trials (28). We will record the time from randomization to the date of the last visit (and the time to disease recurrence or death from any cause), and perform comparisons at the end of the trial.

Serum tumor biomarkers

Serum tumor biomarkers can not only be used as an

Table 2 The EORTC QLQ-CR38 quality of life questionnaire for CRC

Domain (dimension)	Code	SS
Functional scales and items		
Body image	BI	100 – [(CR13 + CR14 + CR15)/3 – 1] × 100/3
Sexual functioning	SX	[(CR17 + CR18)/2 – 1] × 100/3
Sexual enjoyment	SE	(CR19 – 1) × 100/3
Future perspectives	FU	100 – (CR16 – 1) × 100/3
Symptoms scales and items		
Micturition problems	MI	[(CR1 + CR2 + CR3)/3 – 1] × 100/3
Chemotherapy side effects	CT	[(CR10 + CR11 + CR12)/3 – 1] × 100/3
Symptoms in the gastrointestinal tract area	GI	[(CR4 + CR5 + CR6 + CR7 + CR8)/5 – 1] × 100/3
Defecation problems	DF	[(CR25 + CR26 + CR27 + CR28 + CR29 + CR30 + CR31)/7 – 1] × 100/3
Stoma-related problems	STO	[(CR32 + CR33 + CR34 + CR35 + CR36 + CR37 + CR38)/7 – 1] × 100/3
Male sexual problems	MSX	[(CR20 + CR21)/2 – 1] × 100/3
Female sexual problems	FSX	[(CR22 + CR23)/2 – 1] × 100/3
Weight loss	WL	(CR9 – 1) × 100/3

EORTC, European Organization for Research on Treatment of Cancer; QLQ-CR38, Colorectal Cancer-Specific Quality of Life Questionnaire; CRC, colorectal cancer; SS, standardized score.

auxiliary diagnosis of CRC but also assess the survival rates and prognosis of CRC patients. The combined detection of neuron-specific enolase (NSE), CEA, CA199, CA125, and CA242 is an important tool for the diagnosis of CRC (29). We will detect the serum CEA, CA199, and CA125 levels in all participants before treatment and 24 weeks after treatment.

Safety evaluation

Routine blood, urine, and stool tests [including fecal occult blood test (FOBT)], liver/kidney function examinations, and EEC will be performed before and after the treatment. We will keep in touch with the subjects to learn of any AE or emergencies and record possible adverse reactions. The relationship between the trial medicine and the AEs will be assessed according to the US NCI-CTCAE. The number of AEs during chemotherapy will be recorded, and the frequencies will be compared between these two groups. Each complication will be classified as grades 1–4 according to its severity.

Post-trial care and compensation

We will take all the necessary measures to ensure the safety of subjects during the trial. Expenses incurred by each participant to participate in the study, such as transportation and nutrition for additional blood collections, will be reimbursed. If any injuries related to the study occur, the subject can apply for compensation/indemnification in accordance with the relevant laws of the People's Republic of China. However, accidents judged to be caused by negligence (including those caused by serious breaches of the research protocol) will not be covered by the study insurance policy.

Management of test drugs

The test drug used in this trial will be provided by Jiangyin Tianjiang Pharmaceutical Co., Ltd. It will be delivered to the warehouse manager, who will dispense and package the drugs according to random codes and then distribute them to qualified pharmacists in each subcenter for special management. The test drug will not be offered to any individuals who are not participants in this clinical trial and will only be used by patients registered in this trial. The dose and usage of the test drug will strictly follow the research protocol. The unused test drugs will be recovered or destroyed as required. The timing, quantity, and recipients of the distribution and recovery of the test drugs will be recorded, and the recording and modification

Table 3 Roles and responsibilities of committees during the research period

Committee	Members	Roles and responsibilities
DSMB	PIs, research physicians, administrators, senior statisticians, and molecular pathologists	Fully understand the research protocol
		Have relevant professional qualifications; be familiar with the research processes and have relevant professional knowledge
		Organize a review meeting on the study (participated by investigators)
		Review the interim data to assess the feasibility of continuing the study
		Advise the lead investigators
		Organize the collection, analysis, and final destruction of samples in subcenters
		Submit risk reports to regulators and ethics committees
SC	Supervisors, lead investigator, and coordinators	Review the final research proposal
		Organize professional training for researchers
		Monitor data collection and analysis in each subcenter
		Review the progress of the study and, if necessary, agree to modify the research protocol to facilitate the implementation of the study

DSMB, Data and Safety Monitoring Board; PIs, principal investigators; SC, Steering Committee.

specifications will be strictly followed.

Data management and statistical analysis

The roles and responsibilities of committees in this study

The DSMB and Steering Committee (SC) will be established to monitor the research conduct and data collection to ensure the integrity of the trial and maintain the safety and health of subjects. The investigators will be responsible for the recruitment of subjects, the signing of informed consent forms before the start of the trial, the randomization of participants, follow-up, data collection, and data entry to ensure that the trial is conducted in accordance with the GCP requirements, as detailed in *Table 3*.

Data entry and management

EDC will be used for data entry and management, and a dedicated data manager will be available at each subcenter. Participants with account permissions can only log in to their own accounts to view and enter data, and they are not allowed to perform unauthorized operations, nor do they know the assignment results. Data collected during the study will be kept strictly confidential until the completion of the trial. At the end of the trial, the system will automatically generate an electronic CRF (eCRF), avoiding possible data errors in the CRFs. According to the requirement of GCP, data will be stored for 5 years after the completion of the trial.

Statistical analysis

The data analysis of the trial will be performed according to two strategies: intention-to-treat (ITT) and per-protocol population (PP). ITT will be applied to the Full Analysis Set (FAS), which includes all of the randomized participants for survival analyses. Participants who have completed the 24-week treatment will be included in the PP population. Before unblinding, data and the reasons for all withdrawals and dropouts should be clearly documented. At the end of the trial, the results of the two groups will be compared and analyzed.

Baseline data, efficacy indicators, and safety profiles will be statistically analyzed by using the SPSS 25.0 software package (Copyright IBM Corporation, Armonk, NY, USA). Some statistical images will be drawn using the GraphPad Prism software (version 8.0.2) (GraphPad Software Inc., San Diego, CA, USA). In case there is a high proportion of missing data, sensitivity analysis will be performed using multiple imputations.

All statistical tests were conducted by using the two-sided test, and a P value of <0.05 is considered statistically significant. If the measurement data obey normal distribution, the mean and standard deviation are used; Two independent sample t tests were used for differences

between groups, and paired t tests were used for comparison before and after treatment within the group; If the data as a whole does not conform to the measurement data of normal distribution, the median (the 1st quartile and the 3rd quartile) is used to express the difference between groups, Wilcoxon rank sum test is used, and paired sample rank sum test is used for comparison before and after treatment within the group; The counting data were expressed by frequency and constituent ratio, and the inter-group differences were expressed by chi-square test (Fisher exact probability test was used if the chi-square test was not met); The grade data were expressed by frequency and constituent ratio, and the inter-group differences were tested by Wilcoxon rank sum of independent samples. DFS and OS are analyzed by the Kaplan-Meier method. In particular, Kaplan-Meier curves will be created to highlight the potential differences between the two groups. The estimation of treatment effect will be expressed by the hazard ratio (HR) estimated by the stratified Cox model and its 95% confidence interval (CI).

Quality control of data

Data quality will be strictly controlled from the following aspects:

(I) The members of the project team will include oncologists, senior statisticians, and molecular pathologists, ensuring a reasonably structured multidisciplinary team. The trial protocol is designed based on the professional background and clinical expertise of all stakeholders and researchers to ensure that the protocol is scientifically reliable and operable;

(II) This project is sponsored by the Shanghai University of Traditional Chinese Medicine & Cancer Institute, which has the required technology and conditions for carrying out molecular pathological detection and TCM pharmacological research;

(III) A DSMB will be established to ensure the integrity of the research and maintain the safety and health of the subjects;

(IV) The subjects will be recruited in strict accordance the with inclusion and exclusion criteria;

(V) The principles of a randomized, controlled, double-blind trial will be strictly followed throughout the study;

(VI) The protocols for medications, follow-up visits, and efficacy assessment will be strictly obeyed;

(VII) Outpatient cases will be collected using the TCM Health Consultation Questionnaire. Tongue and face color data will be collected using an integrated TCM tongue/face color acquisition instrument, and pulse data will be collected using a Z-BOX pulse analyzer. Each collection team consists of at least one attending physician (or a physician with a higher professional title or a doctorate). To ensure the standardization and consistency of the data collected, regular training on the structure and content of the consultation questionnaire and the meaning of each symptom or sign in the scale will be arranged for the collection personnel;

(VIII) Researchers, case observers, laboratory staff, statisticians, and data entry personnel will be trained regularly to ensure that all observations and test results are true, accurate, and complete, and will be promptly entered into the EDC. The DSMB and Ethics Committee will monitor the tests in all subcenters throughout the study;

(IX) The data in the EDC will be derived from the subjects' original laboratory reports and will be consistent with them, and any arbitrary change is prohibited. Any changes will be recorded in the EDC system, with the generated signature of the person who makes the change. The original records must be legible after any change is made;

(X) The safety of the subjects must be maintained, and any safety issue must be promptly recorded. If AEs occur during the trial, the subjects must be treated accordingly, and the AE must be reported to the PI immediately;

(XI) Statisticians will be involved in the study design and data analysis until the completion of the study.

Confidentiality

All personal identifiers (e.g., name, date of birth, and address) will be replaced by a code (a unique patient ID) so that no one can identify a specific subject. All data collected will be kept confidential and assured by the PIs at each subcenter for 5 years, and will then be destroyed. The biological specimens collected during the research will be stored at the biobank of the Shanghai Municipal Hospital of Traditional Chinese Medicine for 2 years before being destroyed. Except for this study, this information will not be used again in the future.

Only data administrators with account passwords can

Table 4 Names of ethics committees and approval numbers

Name	Approval number
Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine	2021SHL-KY-01-01
Medical Ethics Committee of Fudan University Cancer Hospital	2105235-21-2108
Medical Ethics Committee of Zhongshan Hospital Affiliated to Fudan University	B2021-197R2
Medicine Ethics Committee of Shanghai Changhai Hospital	B2021-042

log in to EDC to view data, and they can only operate under their own authority. All hard-copy documents (e.g., informed consent forms) will be stored in a vault with limited access. Our database is password-protected and any access to the database is strictly restricted. All study records, including reports and point-of-care test samples, will be identified by ID numbers to maintain participant confidentiality.

Unblinding

This trial will be administered using the RTSM (Bioknow), and the unblinding will be performed twice. After the data collection is completed, the first session of unblinding will be performed, which lists only the group to which each case belongs (e.g., group A or B). The second session of unblinding will be performed after the statistical analysis is completed to identify which is the CYFF group or control group. When a SAE occurs and requires emergency unblinding, the site-PI (PI at a subcenter) should log in to the system for emergency unblinding and then record and report the reason and time of the emergency unblinding. When an unexpected AE occurs, the "safety" may log in to the system and perform the pharmacovigilance (PV) unblinding.

Ethics approval

The study was approved by institutional ethics board of Shanghai Municipal Hospital of Traditional Chinese Medicine (No. 2021SHL-KY-01-01), Fudan University Cancer Hospital (No. 2105235-21-2108), Zhongshan Hospital Affiliated to Fudan University (No. B2021-197R2), and Shanghai Changhai Hospital (No. B2021-042) (*Table 4*).

Any major modification of the protocol (e.g., changes in study design and/or sample size) that may affect the conduct of the study shall be reported and agreed upon by all stakeholders (e.g., funders, trial registries, and journals) and approved by the ethics committees before study implementation.

Dissemination

Future trial reports or publications will be disseminated to the PIs at each subcenter. Substantive contributions to the design, conduct, interpretation, and reporting of the clinical trial are recognized via the granting of authorship on the final trial report. No professional writer is required.

Discussion

At present, the clinical treatments of CRC include surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy. Surgical resection is the mainstay of treatment for stage III CRC; however, surgery alone is not effective and involves a high risk of postoperative recurrence in advanced CRC due to the presence of high-risk factors such as lymph node metastasis and deep invasion. Therefore, postoperative adjuvant therapy (such as chemotherapy) is often required in advanced CRC patients to prolong their survival (30). Although chemotherapy can effectively alleviate the clinical symptoms and increase survival, it is often accompanied by myelosuppression, peripheral neuropathy, and other toxic reactions, which limits its clinical application. Therefore, new treatments that can attenuate chemotherapy-related toxicities and promote its therapeutic effect are urgently required for advanced CRC.

CYFF is a TCM compound prescription composed of eight TCM medications, including tianlong (gecko), centipede, milkvetch root, white poria, radix actinidiae, hedyotis, fried largehead atractylodes rhizome, and liquorice root, and has been widely used in clinical practice. Our research group has long been engaged in clinical and basic research on CRC. In a previous study (30), we found that the Jian Pi Fu Fang (spleen-invigorating compound prescription), which is based on the principle of "invigorating spleen for strengthening vital qi", has good efficacy in treating CRC. Through network pharmacological analysis, we found that the Jian Pi Fu Fang contains a variety of active pharmacological components, which can regulate the occurrence and

development of CRC through multiple signaling pathways such as *p53*, *Wnt*, programmed death ligand 1 (*PD-L1*), and vascular endothelial growth factor (*VEGF*). We further constructed nude mouse models of lung metastasis and subcutaneous murine xenograft models and found that the Jian Pi Fu Fang could inhibit the expressions of MALAT1, polypyrimidine tract binding protein 2 (PTBP-2), β-catenin, matrix metallopeptidase 7 (MMP7), c-Myc, and cyclin D1 in these animal models, suggesting that Jian Pi Fu Fang may inhibit CRC cell invasion and metastasis via the Wnt/β-catenin pathway.

Modern experimental studies have confirmed that insect-derived TCM medicines can induce apoptosis, inhibit cell proliferation, prevent angiogenesis, and improve immunity (31,32). Tianlong (gecko) and centipede are commonly used insect-derived TCM drugs in clinical practice and have shown significant anti-tumor effects. It has been reported that the alcohol extract of centipede scolopendra (AECS) can exert anti-tumor effects by inducing the apoptosis of epidermal growth factor receptor (EGFR)-overexpressing cells and regulating EGFR signaling pathways (33). Therefore, we believe that CYFF could be a safer and more effective option for the treatment of CRC.

CRC has high rates of morbidity and mortality, while chemotherapy may cause gastrointestinal reactions, peripheral neurotoxicity, heart, liver, and kidney toxicities, and bone marrow suppression. Therefore, we designed this multicenter, double-blind, randomized, controlled clinical trial to explore the clinical efficacy and safety of CYFF combined with chemotherapy in alleviating clinical symptoms, inhibiting disease progression, and reducing chemotherapy toxicities in CRC patients. We expect that this combination therapy will prolong survival in patients with stage III CRC, inhibit tumor recurrence and metastasis, and reduce toxicities and AEs caused by chemotherapy alone.

CRC patients may experience a variety of moderate to severe systemic symptoms in the first year following treatment completion, including diarrhea, abdominal distension, abdominal pain, frequent urination, nausea/vomiting, and fatigue, some of which will persist and seriously affect their quality of life (34). We hope that this new clinical treatment can improve the clinical symptoms, such as diarrhea, abdominal distension, and nausea/vomiting, and reduce the toxicities caused by chemotherapy alone, thereby helping to reduce the postoperative symptom burden and improve the quality of life and prognosis of patients.

In summary, we hope that this trial will provide clinical evidence for the precise targeted treatment of CRC by TCM combined with chemotherapy and inform the clinical use of TCM, combination therapy, and toxicity alleviation.

Trial status

This clinical trial has been registered in the Chinese Clinical Trial Registry (ChiCTR) (registration number: ChiCTR2000037568; August 28, 2020). Subject recruitment began in December 2020 and is expected to be completed in December 2022.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-144/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Shanghai Municipal Hospital of Traditional Chinese Medicine (No. 2021SHL-KY-01-01), Fudan University Cancer Hospital (No. 2105235-21-2108), Zhongshan Hospital Affiliated to Fudan University (No. B2021-197R2), Shanghai Changhai Hospital (No. B2021-042) and informed consent will be taken from all the patients.

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