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Research Article

A Combined Regimen of Quxie Capsule in Third-line Treatment of Metastatic Colorectal Cancer and Characteristics of the Dominant Population: A Clinical Study Protocol

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Abstract

Background: As the incidence is increasing year by year in China, Colorectal Cancer (CRC) now ranks the 3rd in malignant tumors and the 5th in mortality. The current survival time of metastatic colorectal cancer (mCRC) patients who are treated with western medicine standard third-line treatment is only 7.8-9.3 months, which is difficult to break through. In a subgroup analysis of a randomized clinical controlled trial by the department in the early stage, the survival time of those who were treated in combination with Quxie Capsule in third line treatment reached 17.6 months, with remarkable efficacy. However, there is no evidence-based medical evidence to support whether the combination of Quxie Capsule with standard treatment can synergistically increase the effectiveness. As a result, this study is designed to evaluate the efficacy and safety of Quxie Capsule combined with the western medicine standard three-line treatment, and to investigate the characteristics of the dominant population.

Methods: In this study, 110 patients who are diagnosed with mCRC by histopathology and have progression after second-line treatment will be enrolled and then grouped in a ratio of 1:1. The treatment group will be treated with the Quxie Capsule in combination with the standard western medicine third-line treatment regimen and the control group will be treated with western medicine standard third-line treatment regimen (including furoquintinib, regorafenib, and Trifluridine and Tipiracil Hydrochloride Tablets). All the patients are treated until disease progression or development of intolerable toxicity, followed up until death, and overall survival(OS), progression free survival(PFS), overall response rate(ORR), and disease control rate(DCR) of both groups are calculated. The treatment after disease progression will determined by the clinician and there are no restrictions in the protocol. The toxicity is evaluated according to NCI CTCAE 5.0.

Discussion: The study is a multicenter, prospective, open-label, non-randomized controlled trial to evaluate for the first time the efficacy and safety of Quxie Capsule in combination with western medicine standard third-line treatment and explore the characteristics of the dominant population.

Trial registration: Chinese Clinical Trial Registry: ChiCTR2200062652. Registered on 14 August 2022.

Keywords: Characteristics of the Dominant Population; Integrated Traditional Chinese and Western Medicine; Metastatic colorectal cancer; Third-line treatment; Quxie Capsule

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Background

Currently, the first and second-line standard treatment of mCRC is mainly chemotherapy combined with targeted therapy [1]. In recent years, more and more new oral targeted and oral chemotherapeutic agents have been added to the third-line treatment of mCRC. According to Guidelines of Chinese Society of Clinical Oncology (CSCO) Colorectal Cancer (2021) [2], regorafenib, fruquintinib, and trifluridine and tipiracil hydrochloride tablets (TAS102) are all recommended as Class I drugs for third-line treatment of microsatellite stable mCRC. The OS of mCRC patients treated with three third-line drugs is 9.3 months [3], 8.4 months [4] and 7.8 months [5], respectively and there is a treatment bottleneck with short survival time.

In a previous study on the pathogenesis of CRC and the law of syndrome differentiation in traditional Chinese medicine (TCM), it was noted that "Yang does not transform Yin, and it is blocked in the intestines" was the core pathogenesis of mCRC [6], and the treatment principle of "warming Yang and dredging intestines" was proposed. The "warming yang" is to make yang sufficient and restore the body's ability to resist external evil and regulate endogenous pathogenic factors while warming the yin to make it no longer condensed. "Dredging intestines " is to dredge the abdominal turbidity to allow Yin a way out, so as to realize that "the six Fu organs keep their dredging function". On the basis of Li Zhongzhi's classical formula "Yin-Yang Gongji Wan", Quxie Capsule has been developed according to this treatment principle, which has been applied clinically for more than 20 years with definite effect. A Randomized Controlled Clinical Trial (RCT) conducted in 2014 revealed that mOS of the patients in the Quxie Capsule group was prolonged by 9.6 months compared with that of placebo group, and a third-line treatment subgroup analysis demonstrated that the mOS of those treated in combination of Quxie Capsule was prolonged by 6.4 months (17.6 vs 11.2, p=0.034) compared with that of the placebo group. Besides, female, the old and

those with right-sided colon, RAS/BRAF mutant these western medicine non-dominant population all benefit from Quxie Capsule treatment [7,8]. It is believed that TCM and western medicine can complement each other and TCM may overcome the bottleneck that currently exists in western medicine treatment. Accordingly, this study is designed to evaluate the efficacy and safety of Quxie Capsule combined with western medicine standard three-line therapy for the first time, and to explore the characteristics of the dominant population.

Materials and Methods

Objective

The primary objective of this study is to evaluate the efficacy and safety of Quxie Capsule combined with standard treatment in the treatment of mCRC. The secondary objective is to investigate the characteristics of the dominant population of Quxie Capsule in the treatment of mCRC.

Study design

The study is designed as a prospective, non-randomized, controlled study and began on July 1, 2021, and is still ongoing. Patients who are diagnosed with mCRC by histopathology and have progression after second-line treatment are enrolled from the outpatient clinics and wards of Xiyuan Hospital of the Chinese Academy Medical Sciences, Department of Oncology of Guang'anmen Hospital of the Chinese Academy Medical Sciences, Xinjiang Uygur Autonomous Region Hospital of Traditional Chinese Medicine, and Beijing Cancer Hospital and grouped in a 1:1 ratio. The treatment group is treated with Quxie Capsule combined with western medicine standard three-line treatment regimen and the control group is treated with western medicine standard three-line treatment regimen (including furoquintinib, regorafenib, and trifluridine and tipiracil hydrochloride tablets). All the patients are treated until disease progression or development of intolerable toxicity, followed up until death. The subject flow chart is illustrated in figure 1. The protocol is made with referenced to the Standard Protocol items: Recommendations for Interventional Trials 2013 (SPlRIT 2013 statement) [9], and the screening, intervention, and evaluation schedule is shown in table 1.

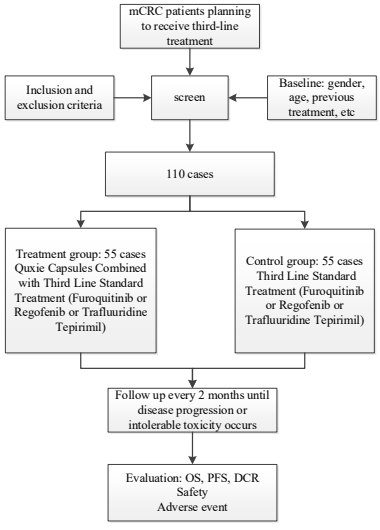

Figure 1: Subject flow chart.

Item	Before treatment (within 2 weeks)	Each treatment cycle	End of treatment or withdrawal
Collection of basic information			
Admission screening form	x		
Signing the informed consent form *	x		
Baseline information	x		
Effectiveness index			
CT/MRI a	x	Every 2 months or at a time point deemed appropriate by the investigator	x
Tumor marker b	x	x	x
Safety indicator			
Blood pressure	x	x	
Blood routine	x	x	
Blood coagulation function	x	x	
Thyroid gland function	x	Every 2 months or at a time point deemed appropriate by the investigator	
24-hour urinary protein quantification	x	Every 2 months or at a time point deemed appropriate by the investigator	
Liver and kidney function	x	x	
Electrocardiogram(ECG)	x	x	
Echocardiogram	x	x	
Urinalysis	x	x	
Stool routine+ Occult blood	x	x	
Recording adverse events		x	x

Table 1: Screening, intervention, evaluation schedule

Note: All study activities must be conducted after informed consent form is signed. a: CT or MRI of the head, chest, abdomen and pelvis and additional examination can be performed based on actual condition of the patients; b: required items for serum tumor indicator test are CEA, CA199 and the optional items are CA125, CA153, CA724 and CA242.

Inclusion criteria

The inclusion criteria are as follows (1) patients aged 18 to 85, (2) those who are to receive western medicine standard third-line treatment or had started third-line treatment (no more than 14 days), (3) those with measurable lesions that meet RECIST 1.1 criteria, (4) those with Eastern Cooperative Oncology Group (ECOG) score of 0-2, (5) those with expected survival ≥3 months, (6)those with no abnormality in heart, lung, liver and kidney function and (7) those with normal coagulation function and no active bleeding or bleeding risk (Bleeding risk included a. active peptic ulcer, b. history of black stool and vomiting of blood within 3 months, c. hemoptysis within 1 month prior to study entry and no thrombotic disease).

Exclusion criteria

The exclusion criteria are as follows (1) patients with symptomatic brain metastases, (2) those with other untreated malignancies, (3) those with dMMR for immunohistochemistry or MSI-H for genetic testing, (4) those with uncontrollable hypertension, (5) those with uncontrollable clinical cardiac symptoms or disease, such as a. NYHA II and above heart failure, b. unstable angina, c. myocardial infarction within 1 year and d. clinically significant supraventricular or ventricular arrhythmias requiring clinical intervention, (6) those with multiple factors that affect the absorption of oral medications, such as inability to swallow and intestinal obstruction and (7) those who have major surgery, open biopsy or significant trauma within 28 days prior to enrollment.

Dropout criteria and treatment: (1) All study subjects who sign an informed consent form and are eligible for observation shall be referred to as drop-out cases as long as they do not complete the observation period specified in the protocol, regardless of time and reason for withdrawal and (2) if a study subject is dropped out, the investigator should try to contact the subject to inquire reasons and record the time of the last dose, and complete as many assessment items as possible.

Setting and Participants

Participant recruitment and screening

Subjects are enrolled by means of WeChat public website of each hospital, recruitment advertisements placed in outpatient clinics, electronic bulletin board in each hospital, and recommendations of front-line clinicians. Subjects are screened by senior attending or associate chief physicians of oncology departments in each hospital. All patients are required to provide previous pathology reports to demonstrate the diagnosis and detailed clinical examination reports to determine the treatment stage. Also, the subjects also are subjected to blood tests, Computed Tomography (CT), color ultrasound, and so on to determine whether they meet the inclusion criteria.

Study protocol

Eligible subjects choose whether to combine with the Quxie Capsule according to their own wishes, and those agree to combine Quxie Capsule are included to the treatment group, otherwise included to the control group. Efficacy evaluation is performed every 2 months.

Interventions

- **Control group:** According to Guidelines of Chinese Society of Clinical Oncology (CSCO) Colorectal Cancer (2021) [2], regorafenib, fruquintinib, and trifluridine and tipiracil hydrochloride tablets (TAS102) are the recommended drugs for the third-line standard treatment until the disease progresses or an intolerable adverse reaction occur and the therapeutic agent and dosage are determined by the investigator.
- **Treatment group: Quxie Capsule (Ingredients: croton, Chinese honeylocust fruit, Radix Aconiti, Euodia rutaecarpa, Rhizoma Zingiberis, Cinnamon, etc.) is combined on the basis of the control group. Efficacy:** Activating Yang and warming the lower body, dispersing nodules and detoxicating. Usage: Take orally, 5 Capsule twice a day for 21 days with a 7-day discontinuation interval until disease progression or intolerable adverse reactions occur.

Regulations on western medical treatment dose and protocol adjustment

- **Dose adjustment:** A first dose adjustment is made to reduce the dose to 80% of the full dose if the subject do not recover from a Grade 3 adverse reaction after symptomatic management. The second dose is adjusted to 50% of the full dose.
- **Protocol adjustment:** The treatment regimen should be changed in case of third occurrence of a 3rd degree adverse reaction. The PFS of subjects who undergo treatment regimen change due to intolerance and not accept disease progression (PD) evaluation according to RECIST 1.1 is not temporarily calculated and the PFS is calculated based on PD evaluated according to RECIST 1.1. The treatment regimen is changed upon the decision of the investigator for those whose PD is evaluated.
- If the patient is still intolerable after the treatment regimen change (multiple times allowed), the conventional western medicine treatment is discontinued and the investigator may change the treatment regimen according to the patient's treatment needs and wishes.

Follow-up treatment

Treatment after disease progression is at the discretion of the clinician and there are no restrictions in the protocol.

Supervision and quality control

This study has been reviewed and revised by experts in oncology, methodology, and statistics. Prior to the trial, the investigator has to be trained in pre-specified standard operating procedures, including inclusion and exclusion criteria, interventions, details of completing case report forms, RECIST evaluation and data management. Specialist personnel are engaged to supervise the study process. Beijing Yijia Medical Technology Co., Ltd is responsible for data entry, management and supervision of the study process.

TCM quality control

The Quxie Capsule were manufactured by Xiyuan Hospital Pharmaceutical Factory of China Academy of Chinese Medical Sciences.

Ethical review

This study was approved by the ethics committee of Xiyuan Hospital, Chinese Academy of Chinese Medical Sciences (batch number: 2021xla092-2).

Sample size

The main objective is to evaluate the efficacy of Quxie Capsule combined with standard therapy in the third line treatment of mCRC, which would be used as basis of sample size calculation. Assuming that the test control is superior to the control group, i.e., longer survival time, the sample size formula for comparing the means of the two samples is selected, according to the ratio of 1:1 and the test level unilateral α=0.05, 1-β=0.9,according to the pre-experiment δ=5, σ2=72.25, and the sample size of 50 cases per group can be obtained by substituting the parameters and the expected loss rate is 10 %, n = 55, a total of 110 people in the two groups.

Outcome

In each cycle (28 days), an investigator is arranged to follow up by telephone or outpatient service and every 2 cycles, repeated CT/MRI is performed to explore the size of tumor and blood is sampled for tumor marker detection.

Primary outcome

Overall survival (OS) of primary outcome indicator is from the time that a subject signs the informed consent to the death of the subject.

Secondary outcomes

PFS of secondary outcome indicator is the time a subject signs the informed consent to the time of first tumor progression or death of the subject. Objective Response Rate (ORR) refers to the percentage of cases with response [Partial Response (PR) + Complete Response (CR)) after treatment in the number of evaluable cases. i.e. ORR = CR+PR/sample size of the group × 100%. Tumor efficacy is evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The dominant population characteristics are screened by subgroup analysis, and the subgroups covers age, sex, left-sided and right-side colons, treatment regimen, genotype, liver metastasis, and peritoneal metastasis.

Safety indicators are assessed by Adverse Events (AEs) and Adverse Drug Reactions (ADRs). AEs refer to adverse medical events that occur after a patient or clinical trial subject receives the drug treatment, which are not necessarily causally related to the treatment. ADR refers to a harmful but unintended causal response that occurs during the normal administration of a drug at the prescribed dose. In order to clarify AE and ADR, blood routine, urinalysis, stool routine, blood biochemistry and coagulation function are regularly monitored and the treatment-related toxicity is defined according to NCI CTCAE version 5.0. All AEs shall be recorded in detail, properly handled and followed up until properly resolved or in stable condition. Moreover, the SAE and emergency events should be reported to the ethics committee, competent authorities and drug regulatory authorities timely according to the regulations. The principal investigator should regularly review all AEs and conduct cumulative reviews, and if necessary, convene a meeting of researchers to assess the risks and benefits of the study.

Statistical analysis

The data collection is performed with Excel function and SAS JMP Pro 14.0 is adopted for statistical analysis. Normally distributed data are expressed with $\bar{x} \pm s$ and non-normally distributed ones are expressed as median MQ. At baseline analysis, Chi-square test is used to test the balance among groups, including age, sex, left-sided and right-sided colons, treatment plan, and gene type. Fisher's exact probability method is employed if the sample size that does not satisfy the chi-square test. Survival time curves are plotted using Kaplan-Meier method for the main index OS, and compared using Log-rank test between groups.The test level α=0.05.

Discussion

With the development of precision treatment, despite that western medicine in treatment of CRC has made considerable progress, some characteristic population still are difficult to break through the treatment bottleneck, namely "non-dominant population". Different from the precise treatment of western medicine, the essence of individualized treatment of traditional Chinese medicine lies in the holistic concept and dialectical argument, which intends to adjust the relationship between "positive qi" and "negative qi" by means of making up the loss, so that the body gradually restores to a state of near-equilibrium health. Therefore, even "non-dominant population" such as female, the old and those with right-sided colon, RAS/BRAF mutant, CRC patients who have not accepted targeted treatment can also benefit from the treatment [10,11]. The combination of Chinese and Western treatment may be favorable for overcoming bottleneck of "non-dominant population" in western medicine.

Currently, the OS of patients treated with regorafenib, furoquintinib, and TAS102 in standard third-line therapy for mCRC is only 7.8-9.3 months. In the RCT we conducted in 2014, the OS of patients treated with Quxie Capsule combined with best supportive care (BSC) alone reached 17.6 months, which was 6.4 months longer that of BSC (p=0.034). However, there is lack of evidence-based medical evidence to support whether Quxie Capsule combined with standard third-line treatment has synergistic effect and provides a better survival benefit. There are some limitations in the present study. Thus the main outcome indicator OS is selected, and in this protocol, the treatment is limited to third-line treatment, and there are no restrictions on fourth-line and later treatments, making it difficult to avoid the effect of later-line treatments on OS, and propensity scores will be used to reduce the effect.

Our department has carried out study on Quxie Capsule for more than 10 years. In the series protocols of Quxie Capsule combined with western medicine to treat mCRC, the arrangements from preventing recurrence and metastasis after operation, increasing efficiency and reducing toxicity in the first to the third line to combining BSC at the end line are made. In summary, this series of studies can be used to screen out the characteristics of Quxie Capsule dominant population in addition to the "Yin pathogen as the main pathogenic mechanism". Besides, a preliminary Chinese and western medical treatment regimen containing the Quxie Capsule has developed for mCRC for clinical use.

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