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Informed Consent Form

A Prospective Single-arm Feasibility Clinical Study of Huangqi Yangyuan Formula for Capecitabine-Induced Adverse Reactions in Patients with Advanced Colorectal Cancer

Study Site: Hebei Provincial Hospital of Traditional Chinese Medicine

Expected total number of subjects: 35

This study has been reviewed and approved by the Medical Ethics Committee of Hebei Provincial Hospital of Traditional Chinese Medicine.

Dear Subject,

You are being invited to participate in a clinical research study conducted at Hebei Provincial Hospital of Traditional Chinese Medicine. This document will help you understand what this study involves. Please read it carefully. You may ask the research doctor any questions you have before you decide whether to take part.

Why are we doing this study?

Patients with advanced colorectal cancer carry high risks of recurrence and metastasis. Domestic and international clinical guidelines recommend single-agent oral capecitabine chemotherapy to control tumor progression, reduce recurrence-metastasis risk and prolong survival time. However, capecitabine is associated with notable toxic adverse reactions. Some patients may require dose reduction, treatment-cycle delay, or even permanent drug discontinuation, which impairs chemotherapy completion, therapeutic effect and patients' quality of life.

From the perspective of traditional Chinese medicine (TCM), the core pathogenesis of advanced colorectal cancer is spleen-kidney deficiency combined with damp-heat, stasis and toxin. Chemotherapy is regarded as "medicinal toxin" in TCM theory, which further consumes qi and blood of the human body. Huangqi Yangyuan Formula is an empirical TCM decoction for supporting healthy-qi and anti-cancer.

This is a single-arm feasibility exploratory study with no concurrent blank control group. The study is not designed to confirm definite efficacy of this TCM formula in reducing toxicity or anti-tumor effect. Its primary purpose is to evaluate the clinical implementation feasibility of the combined regimen of capecitabine plus Huangqi Yangyuan Formula. We will only preliminarily observe potential signals of relieved chemotherapy-related adverse reactions and improved quality of life, so as to provide evidence for future larger-sample clinical trials.

Who is suitable for participation (Inclusion Criteria)

1. Aged 18-80 years old.
2. Stage IIIB-IV colorectal adenocarcinoma that is unresectable, or with recurrence or metastasis after radical resection.
3. Eligible for initiation or ongoing single-agent oral capecitabine chemotherapy according to colorectal-cancer clinical guidelines.
4. Expected overall survival $\geq$ 6 months.
5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
6. Baseline hepatic, renal and bone-marrow function meets tolerance criteria for capecitabine chemotherapy.
7. Able to take Huangqi Yangyuan Formula decoction regularly, complete scale assessments, periodic laboratory re-examinations and imaging evaluations.
8. Fully understands the study content and voluntarily signs this informed consent form.

Who should NOT take part (Exclusion Criteria)

You cannot join this study if any of the following applies to you:

1. You are pregnant or breastfeeding.
2. You have a history of other malignant tumors within the past 5 years, or a history of gastrointestinal carcinoma in-situ.
3. You suffer from severe organic diseases of the heart, liver, kidney, respiratory or hematopoietic system.

4. You have persistent severe diarrhea, hand-foot ulcers or severe malnutrition at baseline that prevents chemotherapy tolerance.

5. You have disturbance of consciousness or psychiatric disorders and cannot independently complete scale assessments and follow-up visits.

6. You have confirmed allergy to any herbal ingredient in Huangqi Yangyuan Formula or to capecitabine.

7. You have regularly taken anti-tumor Chinese patent medicine, anti-tumor TCM decoction, anti-tumor acupuncture/moxibustion or anti-tumor health-care products within 2 weeks before enrollment and cannot complete the 2-week wash-out period.

8. You have received radiotherapy, other chemotherapeutic agents, targeted therapy or immunotherapy within 1 month prior to enrollment.

9. You are currently receiving dual-agent chemotherapy or immunotherapy.

10. You refuse to discontinue other anti-tumor TCM interventions or cannot truthfully report all your concomitant medications.

What will you need to do if you agree to participate?

This is a single-center study performed at Hebei Provincial Hospital of Traditional Chinese Medicine with a planned enrollment of 35 voluntary subjects. If you consent to participate, you will receive standard capecitabine chemotherapy combined with Huangqi Yangyuan Formula decoction. There is no concurrent control group.

1. Baseline period (within 1 week before treatment initiation)

You will complete blood routine test, hepatic-renal function test, electrolyte test, tumor-marker test, contrast-enhanced chest-abdomen-pelvis CT scan, EORTC-QLQ-C30 quality-of-life questionnaire and TCM Body-Constitution Questionnaire (BCQ). Peripheral-blood sample will be collected for detection of T-lymphocyte subsets.

Note: The collected peripheral-blood sample is only used for T-lymphocyte-subset testing in this study. Residual blood samples will be completely destroyed after testing. No long-term storage will be performed, and samples will not be used for other research projects outside this study.

2. Treatment phase

Capecitabine will be administered orally in 21-day cycles for a planned total of 8 cycles. You will take Huangqi Yangyuan Formula decoction concurrently. At the end of the 4th chemotherapy cycle, Huangqi Yangyuan Formula will be temporarily paused for one week, while capecitabine chemotherapy will continue according to the original schedule. Laboratory tests, scale assessments and immune-indicator detection will be repeated at the end of cycle 4 and cycle 8.

3. Follow-up phase

After completion of all chemotherapy cycles, you will be followed-up for 3 months to record your physical condition, adverse events, and status of tumor recurrence or metastasis.

Note: Huangqi Yangyuan Formula decoction, TCM-body-constitution assessment and peripheral-blood T-lymphocyte-subset testing are study-related interventions and examinations. Even if you do not join this study, capecitabine chemotherapy, blood-routine tests, hepatic-renal-function tests, tumor-marker tests and CT scans are routine clinical examinations for advanced colorectal cancer.

What possible risks may you encounter by participating?

All medications may cause side-effects.

1. Capecitabine is standard chemotherapy for advanced colorectal cancer. It may cause hand-foot skin reaction, diarrhea, nausea and vomiting, myelosuppression, fatigue, decreased appetite, oral mucositis, hepatic-renal function abnormality and other adverse events. These side-effects may occur even if you do not participate in this study but receive capecitabine chemotherapy.

2. Huangqi Yangyuan Formula is a TCM decoction; it may cause gastrointestinal discomforts such as abdominal distension, diarrhea or constipation. In very rare cases, risks of hepatic-renal function abnormality exist.

3. Blood collection may bring minor risks including puncture-site pain and local bruising.

4. Even with this combined treatment, there remains a possibility of treatment failure, tumor progression, recurrence or metastasis.

Please inform your study doctor promptly if you feel unwell during the study. Corresponding clinical management will be provided in a timely manner.

Statement regarding research-related harm

If physical injury is directly caused by study-related procedures, the hospital will provide corresponding medical treatment. No special compensation fund is available for this study. Injuries caused by your underlying disease, inherent adverse reactions of chemotherapeutic drugs or non-study-related factors are not covered by this medical-treatment benefit.

What benefits can you get from participation?

During this study, your condition will be systematically assessed following unified study procedures. Your disease changes, laboratory results and scale scores will be documented, which can serve as references for your future clinical management. You will also receive more regular disease follow-up and medical consultation. Your condition may or may not improve through participation. The information from this study may help determine safer and more effective treatments for other patients with similar disease.

Will you need to pay any costs for participation?

This study does not provide free treatment or examinations. All costs including capecitabine, Huangqi Yangyuan Formula decoction, laboratory tests, scale assessments, imaging examinations and other study-related items shall be borne by yourself. Expenses for treatment or examinations for other concurrent diseases, as well as costs for switching to alternative therapies due to treatment failure, are also at your own expense. Regular laboratory tests will be performed to monitor and manage potential drug-related adverse reactions.

Will your personal information be kept confidential?

Your medical records will be stored in the hospital. Investigators, study-administrative authorities and the ethics committee are permitted to access your medical records. No personal identifying information about you will be disclosed in

any public report of study results. Within the scope permitted by law, every effort will be made to protect the privacy of your personal medical data.

Is participation mandatory?

Your participation in this study is completely voluntary. You may refuse to join, or withdraw from the study at any time during the research process. This will not affect your routine medical care. Even if you withdraw, you are advised to complete necessary health examinations to protect your physical health. If you decline participation, other clinically feasible treatment options are still available for you. Please contact your study doctor in time if you decide to withdraw.

Subject Statement: I have read the above introduction to this study and fully understand the potential risks and benefits of participation. I voluntarily agree to take part in this research study.

I agree ☐ **or refuse** ☐ to allow my medical records and pathological specimens to be used for other research projects outside this study.

Subject's signature:_____ Date:_____

Subject's contact phone number:_____

Researcher Statement: I confirm that I have explained the detailed circumstances of this study to the participants, including the potential risks and benefits of participating in this study.

Researcher's signature:_____ Date:_____

Researcher's contact phone number:_____

Medical Ethics Committee Office of Hebei Provincial Hospital of Traditional Chinese Medicine Contact Number: 0311-69095606