Informed Consent

Comparative Study on the Efficacy of Mitomycin and Lobaplatin in the Treatment of Advanced Colorectal Cancer combined with Radical Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy

Version：	V1.0
Date：	2021.03.26
Acronym：	WUHIPEC02
NCT Number：	XXX
Organization：	Wuhan Union Hospital, Tongji Medical College of HUST

Dear patient:

You will be invited to participate in a research named "Comparative efficacy of mitomycin and lobaplatin in radical resection of colorectal cancer combined with Hyperthermic intraperitoneal chemotherapy in the treatment of patients with advanced colorectal cancer". This study was initiated by Professor Tao of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, and 201 patients are expected to participate voluntarily.

The following items describe the background, purpose, methods, benefits of the research and possible risks or inconveniences that this clinical research may bring to you during the research process, as well as your rights, etc. Please read carefully before participating in the clinical research. The information provided in this informed consent can help you decide whether to participate in this clinical study. If you have any questions, please ask the investigator in charge of the study to ensure that you fully understand the relevant content. Whether you participate in this study is voluntary. If you agree to participate in the clinical study, please sign in the statement of informed consent. This study has been reviewed by the ethics committee of this research institution.

Research Background

Colorectal cancer (Colorectal cancer, CRC) is the most common malignant tumor of the digestive system in the world. Its incidence rate ranks third, and its mortality rate ranks second. The recurrence and metastasis of tumor is the leading cause of death in patients with colorectal cancer. Peritoneal carcinomatosis (PC) is the most important causes of death in colorectal cancer patients after liver metastasis. Studies have shown that the 3-year peritoneal metastasis rate of pT4 colorectal cancer is as high as 20-36.7%. Prevention of peritoneal metastasis is a research hotspot in the treatment of colorectal cancer.

Sugarbaker et al. used cytoreductive surgery (CRS) combined with hyperthermic introperitoneal chemotherapy (HIPEC) for colorectal cancer peritoneal metastasis in the 1990s. After more than 20 years of clinical practice since the 1990s, it has been proved to extend the median survival time and improve the quality of life of patients.

Intraperitoneal chemotherapy drugs need to meet the following characteristics: First: be effective for systemic chemotherapy of colorectal cancer; second, consistent with the characteristics of intraperitoneal chemotherapy, which means the drug must be able to kill tumor cells through itself or other metabolites effectively, higher intraperitoneal concentration, Lower peritoneal permeability, less peritoneal irritation, and stronger tumor tissue penetration ability [6]. So far, there are many types of drugs, dosage, time, and drug combination for intraperitoneal medication, and there is no unified conclusion. The application of standardized clinical intraperitoneal medication has become an urgent key issue. Therefore, studying the safety and effectiveness of different chemotherapeutic drugs for HIPEC treatment of colorectal cancer is of great significance for improving the survival rate and quality of life of patients with advanced colorectal cancer.

According to the latest domestic expert consensus, the commonly used drugs for HIPEC treatment of colorectal cancer are mitomycin, oxaliplatin and 5-fluorouracil. Mitomycin (mitomycin C, MMC) and oxaliplatin are the most common drugs in international HIPEC. Meta-analysis shows that about 21% of patients receiving MMC treatment have serious complications, while the rate in the oxaliplatin group is 30%. MMC is safer than oxaliplatin during the HIPEC treatment.

Platinum drugs and mitomycin are cell cycle non-specific antitumor drugs that act on the chemical structure of DNA. Oxaliplatin is unstable in sodium chloride solution, so the perfusion fluid generally used is glucose or a mixture of glucose and distilled water. Studies have shown that the use of glucose in intraperitoneal hyperthermic infusion chemotherapy increases the risk of intraoperative hyperglycemia and postoperative infection. Lobaplatin is a third-generation platinum drug. It has no obvious nephrotoxicity, ototoxicity, neurotoxicity, mild gastrointestinal toxicity, and no cross-resistance with other platinum drugs. The perfusion fluid can be normal saline. Single-center preventive studies have shown that lobaplatin does not increase the occurrence of postoperative complications during intraperitoneal lavage and it has no significant effect on bone marrow suppression, liver and kidney function, which means it has good safety. There has been a clinical study registered on

Clinical Trials to explore the safety of lobaplatin for the treatment of colorectal cancer HIPEC (NCT03221608).

At present, there are few domestic and international clinical studies of HIPEC treatment for colorectal cancer. But there is only one prospective randomized controlled trial registered on Clinical Trials to evaluate colorectal cancer intraperitoneal hyperthermic perfusion chemotherapy (NCT02965248). In this study, randomized controlled experiments were conducted to explore the choice of clinical drugs for colorectal cancer and their safety and effectiveness to provide references for clinical treatment.

Research Purpose:

Main purpose: To compare the perioperative adverse reaction rate, overall survival rate, and survival rate without peritoneal metastasis of different chemotherapy drugs (mitomycin, lobaplatin) used for colorectal and abdominal hyperthermic perfusion chemotherapy, etc. Assess its safety and effectiveness. Observation period is 3 years

Secondary purpose: Compare the blood routine, biochemical, immunological and ascites related tests before and after HIPEC, and analyze the evaluation value of related laboratory test results for patients with colorectal cancers.

Inclusion criteria:

1.18-75 years old；

2.Male and Non-pregnant or breastfeeding women；

3.Pathologically diagnosed as malignant tumor；

4. HIPEC is determined to be required during the operation；

5. The main organ function is normal, which meets the following standards：

Routine blood examination standards must meet：

a. HB≥90 g/L；

b. ANC≥1.5×109/L；

c. PLT≥125×109/L；

Biochemical inspections must meet the following standards：

a. TBIL<1.5ULN；

b. ALT 和 AST<2.5ULN；

c. serum Cr ≤1.25ULN or endogenous creatinine clearance>50ml/min （Cockcroft-Gault formula）；

d. ALB≥30g / L

6.ECOG scored 0-1；

7.sign informed consent willingly.

Exclusion criteria:

1.The patient has a history of other malignancies within 5 years；

2.Allergy to mitomycin, lobaplatin, mitomycin or other related chemotherapy drugs；

3.Suffer from epilepsy or other mental illness, unable to control his own behavior；

4.Inability to tolerate the surgery due to severe heart, lung or blood vessel diseases；

5.Pregnant or breastfeeding women.

Research methods and content:

1. Patient screening and evaluation

Strictly select patients according to the above-mentioned inclusion and exclusion criteria of this research program.

Complete the following projects within 1 week after admission:

(1) Improve medical history and physical examination

(2) Blood routine, biochemical, immunological indicators, CRP/PCT and tumor markers

(3) B-ultrasound, electrocardiogram, chest radiograph and stomach CT/MRI

(4) Gastroscopy

2. Intraoperative

(1). Colorectal cancer surgery standard: open/laparoscopic radical resection of colorectal cancer, follow the principle of mesangectomy and the principle of no-tumor operation, refer to the "Colorectal Cancer Diagnosis and Treatment Standards (2018 Edition)" from National Health and Family Planning Commission, surgery specimens were photographed and archived and submitted for inspection.

(2). Intraoperative randomization: Whole abdomen and pelvic exploration was performed to exclude distant metastases intraoperativly, combined with preoperative examination and intraoperative exploration to estimate staging. Patients meeting the enrollment criteria was randomized, and 4 drainage tubes were placed in the control and experimental groups during the operation.

Pathological section of intraoperative exfoliated cytology:

(3). Before and after the resection of the primary cancer and after HIPEC, rinse the attachment area of the primary cancer with more than 1000ml of normal saline, collect more than 500ml of rinsing solution, send it to the pathology department for 1000g centrifugation for 10min, collect nucleated cell smears, do HE stained microscopy.

3 Intraperitoneal hyperthermia

(1) Perfusion drainage tube:

During the operation, 4 drainage tubes (2 inflow and 2 outflow) were placed in the left and right subdiaphragmatic liver and kidney recesses, liver and spleen recesses, and pelvic floor, which are generally located in the anterior axillary plane;

(2) Drugs and dosage

Test group 1: Lobaplatin 50mg/m2/time

Test group 2: Mitomycin 30mg/m2/time

The dosage of HIPEC refers to the dosage of intravenous chemotherapy, the solvent is 0.9% NS (2000ml/m2+500ml),

The first time was performed after the operation, and the second time was 48 hours after the operation. The interval of HIPEC was no less than 24 hours. 43 degrees, 60 minutes.

(3) Testing during treatment:

ECG monitor side blood pressure, pulse, respiration, blood oxygen saturation, and record the control parameters of perfusion chemotherapy during the HIPEC.

(4) Postoperative pathological examination

Including histological classification, degree of differentiation, TNM staging

(5) Postoperative complications

1) The time of first ventilating, defecation and wound healing after operation;

2) Whether there are complications such as bleeding, infection, peritonitis, anastomotic leakage, intestinal obstruction, intestinal perforation, intestinal necrosis, death, etc. in the abdominal cavity (refer to CTCAE v5.0) and unplanned secondary operations;

3) Blood routine, biochemical, tumor markers, immunological examination 1 day before and after HIPEC

4) Number of days in hospital

Perfusion fluid inspection during HIPEC

1.Intraoperative exfoliative cytology and pathological examination: Wash the appendage area of the primary cancer with more than 1000ml of normal saline before and after the resection of the primary cancer and before and after two HIPECs, collect more than 500ml washing solute, and send it to the pathology department to centrifuge at 1000g for 10 minutes to collect nucleated cells Smear, do HE stain microscopic examination.

2.Washing fluid laboratory inspection: collect the washing fluid before HIPEC and send 1 test tube of 5ml to ascites immunological examination; after HIPEC, collect 2 test tube washing fluid samples of 5ml each, and send it to ascites drug concentration inspection and ascites immunological examination respectively.

4 Postoperative intravenous chemotherapy

start 3-4 weeks after surgery, mFOLFOX6/XELOX is used as the chemotherapy

mFOLFOX6 chemotherapy regimen, before surgery:

On the 1st day, oxaliplatin 85mg/m2 + 500ml glucose solution, intravenous drip for 2h;

On the 1st day, leucovorin calcium 400mg/m2 + 250ml normal saline, intravenous drip for 2h;

On the 1st day, fluorouracil 400mg/m2 intravenously injected; then fluorouracil 1200mg/m2/day X 2 days (total 2400mg/m2), continuous intravenous infusion 46-48h.

Repeat every 2 weeks, 12 cycles

XELOX: Oxaliplatin 130mg/m2 IV d1+ capecitabine 1000mg/m2 po bid d1-14, q3w, 4-8 cycles

8-cycle chemotherapy monitoring: do a laboratory test before and after chemotherapy, including routine blood tests (hemoglobin Hb, red blood cell count RBC, white blood cell count WBC, platelet count Plt, neutrophil count NEUT), liver and kidney functions, etc. Biochemical indicators (glutamate aminotransferase ALT, aspartate aminotransferase AST, γ-glutamyltransferase γ-GT, lactate dehydrogenase LDH, alkaline phosphatase ALP, total protein TP, albumin ALB, white Protein/globulin ratio A/G, blood urea nitrogen BUN, blood creatinine Cr), tumor marker inspection (CEA, CA199, CA724).

The first time was performed after the operation, and the second time was 48 hours after the operation. The HIPEC interval was no less than 24 hours, 43 degrees, and 60 minutes. The expected number of participants in this study is 201. You need to complete the above process and strictly follow the clinical research follow-up. If you agree to participate in this study, we will number each subject and establish a medical record file. Researchers should keep all research data, including confirmation of all participating subjects (which can effectively check different records, such as CRF and original hospital records), all original signed patient informed consent forms, and all CRF records Detailed records, etc., and ensure the traceability of all laboratory inspections, keep all those until 3 years after the end of the clinical study.

Research process and duration: September 1, 2021 to September 1, 2025

Possible benefits:

Participating in this study, you will receive the most commonly used treatment options for advanced colorectal cancer in the control group, including surgical treatment and postoperative adjuvant chemotherapy. If you are in the experimental group, you will receive radical mastectomy + HIPEC treatment + intravenous chemotherapy treatment. HIPEC

regimen includes mitomycin regimen and lobaplatin regimen, and the overall therapeutic effect is expected to be better than the conventional regimen. The experimental group may not achieve the expected effect after your treatment, but your participation in obtaining safety and efficacy for HIPEC treatment will provide useful information for the research and provide guidance for the treatment of colorectal cancer patients with similar conditions to yours.

Possible risks and discomforts:

Although the clinical trials are rigorous and safe, it cannot be ruled out that there may be some serious and even life-threatening side effects. Of course, this probability is very low.

This study may have risks associated with radical surgery, including the risk of anastomotic leakage, delayed exhaust, intestinal adhesions, intestinal obstruction, tumor recurrence or metastasis. The risk is minimized by strictly following the protocol, performing the operation in the correct and standardized hospital environment, limiting the surgical operator, and closely monitoring the condition of the subject during and after the operation.

This study also has the risks associated with intraperitoneal hyperthermic perfusion chemotherapy. HIPEC must use special thermal perfusion tubing components, and there are adverse reactions such as heat injury, local infection, unexpected termination of the treatment process, environmental pollution, abdominal pain and bloating. The risk is minimized by strictly following the protocol, operating in the correct and standardized hospital environment, restricting the operator, and closely monitoring the conditions of the subjects after the operation, etc., and actively adjusting the treatment plan according to the patient's condition, and assisting with sedation and analgesics. Stop the treatment when necessary.

This study involves surgery and chemotherapy drugs lobaplatin, mitomycin, the main adverse reactions include: gastrointestinal tract, blood system and liver function. The most common adverse reactions in the gastrointestinal tract are mainly nausea, vomiting, diarrhea, and loss of appetite; the hematopoietic system is mainly white blood cells, neutrophils, thrombocytopenia and anemia; the liver function is mainly affected by the reversible increase of ALT and AST. Adverse reactions mainly include: 1. Neurotoxicity is mainly manifested as hypoesthesia, paresthesia, and aggravated by cold, occasionally reversible acute throat

paresthesia; 2. Gastrointestinal reactions are mainly mild and moderate nausea, vomiting and diarrhea, mucosal Inflammation; 3. Anemia of the blood system, leukopenia, and neutropenia. Diarrhea, nausea, vomiting and mucositis; the main hematological side effects of this type of chemotherapy drugs in the blood system are: anemia, leukopenia, neutropenia and thrombocytopenia. During the implementation of this study, the general conditions of the patients were fully monitored and evaluated in each treatment cycle. If there are corresponding adverse reactions during the process, the corresponding complications will be actively handled in accordance with clinical strategies.

In addition, the treatment of clinical trials may be ineffective and lead to disease progression, severe complications in the process require further treatment, increase treatment costs, and even lead to patient death. The Ethics Committee of Union Hospital of Huazhong University of Science and Technology will supervise the entire research process of this clinical project.

Other therapeutic intervention methods:

In addition to participating in this research, you have the following options

1. Routine surgical treatment;

2.Routine adjuvant chemotherapy regimens: XELOX, mFOLFOX6, etc.;

3.According to the results of the examination, assist with chemotherapy and targeted drug therapy.

Private issues:

If you decide to participate in this study, your participation in the study and your personal information in the study are confidential. For you, all information will be kept confidential. Information that can identify you will not be disclosed to members other than the research team unless we have your permission. All research members and research sponsors are required to keep your identity confidential. Your files will be stored uniformly and are only available to researchers. In order to protect your privacy, the personal name will be hidden in the data, saved in the form of initials and research code, and stored in the clinical

research special file cabinet, only for researchers to view; your specimen will be marked with the research number instead of the name. To ensure that the research is conducted in accordance with the regulations, when necessary, members of the government management department or the ethics review committee can consult your personal data in the research unit as required. When the results of this research are published, your information will be kept confidential.

Costs and compensation:

There is no additional treatment cost in this study. The cost of surgery and HIPEC treatment is based on the charging standards of Union Hospital, Tongji Medical College of Huazhong University of Science and Technology. HIPEC is a routine treatment item for advanced gastrointestinal tumors in the hospital. It is helpful for the treatment of your condition. The patient voluntarily participates after signing the informed consent, and the relevant treatment costs are borne by themselves. If an adverse reaction occurs during the experiment, the subjects should be given to reduce their suffering. If you are harmed because of participating in the research: the damage related to the research causes permanent damage to the patient or even death, we will provide the subjects with corresponding financial compensation in accordance with the Chinese law after being authenticated by a specialized agency.

Voluntary participation and withdrawal of research:

As a subject, you can learn about the information and research progress related to this research at any time, and voluntarily decide (continue) to participate or not (continue) to participate. After participating, you can choose to notify the investigator to withdraw from the study at any time, regardless of whether the injury has occurred or whether it is serious. Your data will not be included in the study results, and any of your medical treatment and rights will not be affected.

However, during the study period, please provide the true information about your medical history and current physical condition; tell the research doctor whether you have participated in other studies recently or are currently participating in other studies. If you did

not comply with the research plan, or if there was a research-related injury or for any other reason, the research physician can terminate your continued participation in this research.

You can choose not to participate in this research, or you can withdraw from the research after notifying the researcher at any time without being discriminated against or retaliated. Any of your medical treatment and rights will not be affected by this.

If you need other diagnosis/treatment, or you did not comply with the research plan, or for any other reasonable reason, the investigator can terminate your continued participation in this research.

You can keep abreast of the information and research progress related to this research, if you have any questions related to this research, or if you have any discomfort or injury during the research process, or have questions about the rights of participants in this research You can contact Dr. XXX (name of investigator or related personnel) at XXXXXXXX (phone number).

Subject statement

I have read this informed consent form carefully and have the opportunity to ask questions and all questions have been answered. I understand that participation in this research is voluntary. I can choose not to participate in this research, or I can withdraw after notifying the researcher at any time without being discriminated against or retaliated. Any of my medical treatment and rights will not be affected by this.

If I need other diagnosis/treatment, or I did not follow the research plan, or have other reasonable reasons, the researcher can terminate my continued participation in this clinical research.

I voluntarily agree to participate in the clinical study, and I will receive a signed copy of the "Informed Consent".

Subject's signature: Date:Year Month Day

If the subject is unable to sign the informed consent due to incapacity or other reasons, or the subject is a minor, it shall be signed by the guardian.

Guardian’s Signature: Date: Year Month Day

Relationship with subjects:

Reasons why the subject cannot sign the informed consent form:

Researcher's Statement

I have accurately informed the subjects of the contents of the informed consent form and answered their questions, and the subjects voluntarily participated in this clinical study.

Investigator’s signature: Date: Year Month Day