Informed Consent Form

Title：Comparative Study on the Efficacy of Lobaplatin and Paclitaxel in the Treatment of Advanced Gastric Cancer Patients with D2 Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy

Version: 1.0

Date: 2021.02.09

Organization:

Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Interventions：

D2 surgery + hyperthermic intraperitoneal chemotherapy (paclitaxel/lobaplatin/none) + SOX/XELOX regimen

Dear patient:

We sincerely invite you to participate in the clinical trial named "Comparative Study on the Efficacy of Lobaplatin and Paclitaxel in the Treatment of Advanced Gastric Cancer Patients with D2 Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy". This study was initiated by Pro. Tao of Gastrointestinal Surgery Department, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, and planned to mobilize 231 patients participate in voluntarily.

The following message describe the background, purpose, methods, benefits of research, possible risks or inconveniences that this clinical trial may bring to during the process, and your rights during this trail, etc. Please read carefully before participating in the clinical research. This information 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. If you agree to participate in this clinical trial, please sign in the statement on the bottom of content. This study has been reviewed by the ethics committee of Wuhan Union Hospital.

Research Background

Although the prevalence and mortality of gastric cancer have a gradual decline, the mortality rate of gastric cancer (GC) is still ranked second among all kinds of tumor in the world (736,000 per year). According to the latest data from the National Cancer Registry, the incidence and death of GC cases made up 42.6-45.0% of the global incidence and death in China. Among 183 countries in the world, the incidence rate ranks 5th and the death rate ranks 6th. In 2015, there were about 679,000 new cases of GC in China, including 478,000 men and 201,000 women; and there were approximately 498,000 deaths from GC, including 339,000 men and 159,000 women; the number of morbidities and deaths ranks second among all malignant tumors. Recently, surgical mortality and complications have been reduced with the improvement of diagnosis methods, surgical techniques, perioperative care and treatment for GC. However, GC patients even receive the best treatment options currently considered, the 5-year OS rate is still low (<40% McDonald and Magic trials). For advanced GC, the

recurrence rate of the disease remains high regardless of the country or region. Therefore, in addition to standard R0 resection, D2 lymph node dissection and adjuvant therapy, it is necessary to develop other more effective treatment measures to further reduce the recurrence rate of advanced GC and mortality. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is traditionally used for the treatment of peritoneal cancer combined with cytoreductive surgery (CRS). For the treatment of GC, Kuramot Kuramoto et al. conducted a multi-center clinical trial to evaluate the efficacy of IPC (non-heat peritoneal lavage) for GC patients with positive lavage cytology but no visible peritoneal metastasis. 88 patients were randomly divided into group IPC (N=29) and group IPC combined with intraoperative peritoneal lavage (EIPL) (N=30). Results showed that patients in the IPC+EIPL group have a better overall survival (OS) than surgery alone or IPC group. At present, three small randomized clinical trials evaluating the efficacy of surgery + HIPEC in the treatment of locally advanced GCs have shown that HIPEC is an effective treatment for locally advanced GCs (T3/T4).

Paclitaxel is a broad-spectrum anti-tumor drug that can fight with tumors through multiple anti-cancer mechanisms. The NCCN guidelines regard paclitaxel-based two-drug or three-drug combination as the recommended protocol for advanced GCs. In recent years, paclitaxel has been proved effective in advanced GCs combined with HIPEC, and China clinical expert consensus of HIPEC in GCs has listed it as one of infusion drugs. In the HIPEC-01 clinical trial, paclitaxel was used as a HIPEC infusion drug to compare its safety and efficacy with CRS+ HIPEC. It is expected that the test results will bring more evidence-based evidence.

Platinum drugs are non-specific cell cycle anti-tumor drugs that act on the chemical structure of DNA. Oxaliplatin is unstable in sodium chloride solution. The perfusion fluid generally uses the mixture of glucose or glucose distilled water. However, recent studies have shown that glucose used for intraperitoneal hyperthermic infusion chemotherapy can increase 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, and its perfusion fluid can be normal saline. Wu et al. enrolled 50 patients of GC with peritoneal

metastasis who underwent radical gastrectomy combined with hyperthermic perfusion therapy and used lobaplatin and paclitaxel in a clinical study. The results suggest that this treatment plan can improve OS.

There is no prospective randomized controlled clinical study on the choice of lobaplatin and paclitaxel in HIPEC of advanced GC patients in the nation. Based on the widely use of HIPEC among prevention and treatment of peritoneal cancer after surgery in the early stage，we carried out a prospective, single-center, randomized controlled clinical trial to explore the efficacy, perioperative safety and immune status evaluation of different infusion drugs in D2 surgery combined with HIPEC in the treatment of advanced GC patients. Further, this study provides clinical evidence for the clinical development of the best comprehensive treatment plan.

Research Purpose:

Primary purpose: To compare the OS rate and the survival rate without peritoneal metastasis of paclitaxel and lobaplatin using for GCs with D2+HIPEC+ SOX/XELOX regimen. Observation period is 3 years

Secondary purpose: the incidence of postoperative adverse reactions (refer to CTCAE5.0 (including blood routine, liver and kidney function, patient's reaction to HIPEC, adverse events)

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 paclitaxel, 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.D2 surgical resection of GC

Operation method: open surgery or laparoscopic surgery

The steps are as follows: anesthesia → blood collection → abdominal cavity exploration and evaluation → intraoperative drawing in accordance with the admission criteria → preoperative abdominal lavage → standard D2 surgical resection → removal of cancer, adjacent and normal tissue specimens → surgery area requires photo for evidence (Proved to be D2 surgery) → Postoperative abdominal lavage. During the abdominal cavity exploration, “assessment of lesion area”, “assessment of tumor size” and “intraoperative staging” should be carried out, and according to whether the patient has peritoneal cancer or not, the experimental group and control group can be determined.

(1) Surgical resection range: the distance between the gastric resection margin of the localized GC and the tumor should be more than 3-4cm, and the distance between invasive GC should be more than 5cm. For esophageal gastric junction cancer, the resection margin of the esophagus should be more than 3cm from the tumor. Frozen pathological biopsy should be performed when necessary. For tumors that invade the pyloric duct, the distance between the duodenal resection margin and the tumor should be more than 3 cm. Remove enough lymph nodes according to the staging method of GC.

(2) The principle of tumor-free operation: first ligate veins and arteries at the root of the blood vessel, and at the same time sweep the lymph nodes, then separate and resect the specimen. The operation should be gentle, more sharp separation and less blunt separation. The tumor could not be directly touched to avoid the damage to the lymph nodes which can cause cancer cells to spread and local implantation. The serosal layer can be protected by covering method or applying various glues

（3）protect the incision when removing the specimen to prevent the incision from planting tumor cells.

（4）Intraoperative cytology

Before and after the resection of the primary cancer, rinse the attachment area of the primary cancer with more than 1000ml of normal saline, collect more than 500ml of rinsing solution, and send it to the pathology department for centrifugation at 1000g ,10min. Collect nucleated cell smears for HE staining microscopy. We get two chief physicians and above pathologists using HE staining method to detect tumor cells. When two pathologists dispute the conclusion, consult the deputy chief physician and above pathologists to confirm the diagnosis.

（5）Abdominal lavage after the operation: After the operation, lavage of the abdominal cavity should be performed to remove free cancer cells in the abdominal cavity as much as possible. The lavage fluid should be normal saline.

（6）After the operation is completed, take photos or videos for archive. Photo or video must cover the following organizations:

Distal subtotal gastrectomy: show the left gastro-omental artery ligation point, common hepatic artery, proper hepatic artery, left gastric artery ligation point, left and right gastric vein ligation point, proximal splenic artery, right sub-pyloric artery and vein ligation point, naked proximal minor curve side

Proximal gastrectomy: show the left gastric artery ligation point and coronary vein stump, common hepatic artery, proximal splenic artery, celiac artery trunk, and splenic hilum.

Total gastrectomy: show the ligation point of the left gastric artery and vein, the ligation points of the right gastric artery and vein, the common hepatic artery, the abdominal trunk, the splenic artery, the splenic artery, the proper hepatic artery, the right gastroepiploic artery and vein ligation point, and the sub-pyloric artery vein.

（7）Complete the collection of pathological tissue samples, peripheral blood samples and lavage fluid samples during the operation, and take photos of each sample for archiving.

3. Hyperthermic intraperitoneal chemotherapy（HIPEC）（Take paclitaxel drug group as an example）

The location of the drainage tube: The two drainage tubes with the tube opening in the upper abdomen are used as perfusion tubes. The tube openings are placed under the left side of the diaphragm and the liver and kidney recesses. After HIPEC is completed, the left side of the diaphragm can be used as a postoperative abdominal drainage tube. Two drainage tubes with nozzles located in the lower abdomen are used as outflow tubes, and the nozzles are placed on both sides of the pelvic floor. Each drainage tube is generally placed on the plane of the anterior axillary line, and the perfusion tube should be placed near the tumor as much as possible, while the outflow tube should be placed away from the tumor area.

Temperature setting: 43±1.0℃.

Perfusion time: 60min.

Dosage of perfusion fluid: The principle of perfusion fluid is to fill the abdominal cavity and unblocked circulation.

The choice of perfusion fluid: physiological saline.

Drug selection and dosage: Paclitaxel 75mg/m2.

Timing of treatment: intraoperatively

Treatment course: the first time after surgery, the second time 48h after first time.

Intraoperative medication: give intravenous sedatives during treatment when the patient is intolerant, adjust the dose according to the patient's response, and give fluids according to the monitoring of vital signs.

Cytological examination: Before and after the resection of the primary cancer, rinse the attachment area of the primary cancer with more than 1000ml of normal saline, collect more than 500ml of rinsing solution, and send it to the pathology department for centrifugation at 1000g ,10min. Collect nucleated cell smears for HE staining microscopy. We arrange two chief physicians and above pathologists using HE staining method to detect tumor cells.

When two pathologists dispute the conclusion, consult the deputy chief physician and above pathologists to confirm the diagnosis.

Immunological examination: After HIPEC, collect patient blood samples and 5mL the above-mentioned flushing fluid samples for immunological indicators such as CD3, CD4 and CD8 lymphocyte population; IL-2, 4, 8, 10, etc.

Intraoperative monitoring: During HIPEC treatment, monitor blood pressure, body temperature, pulse, urine output, respiration, blood oxygen saturation, whether the perfusion tube is blocked and whether the outflow is smooth. If there is profuse sweating, if the heart rate is faster than 100 beats/minute etc. It is necessary to strengthen fluids after eliminating the cause of hypovolemia. If abnormalities such as breathing and blood oxygen saturation occur, pay attention to the number of anesthetics and perfusion fluid, and stop treatment if necessary.

Judgment of postoperative complications: whether there is bleeding, infection, peritonitis, anastomotic leakage, intestinal obstruction, intestinal perforation, intestinal necrosis, death and other complications in the abdominal cavity (refer to CTCAE v5.0) and unplanned secondary operations;

4.Postoperative systemic adjuvant chemotherapy regimen (SOX/XELOX regimen)

After 4-6 weeks of the operation, the patient recovered, and 8 cycles of postoperative systemic adjuvant chemotherapy were then started. The chemotherapy regimen uses SOX/XELOX regimen.

SOX regimen: Oxaliplatin 130mg/m2 IV d1+ Tegafur capsules: For those with body surface area <1.25m2, 40mg/time, 2 times/d; for those with 1.25m2≤body surface area <1.5m2, 60mg/time, 2 times /d; For those with body surface area ≥1.5m2, 60mg/time, 2 times/d, d1-14, q3w, 4-8 cycles.

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

Eight cycle chemotherapy monitoring: Laboratory tests were performed 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-glutamyl transferase 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).

5.1.2 Dosage and administration method

1）Administration method: intraperitoneal hyperthermic perfusion (HIPEC)

2）Drugs and dosage

Drug group 1: Paclitaxel 75mg/m2

Drug group 2: Lobaplatin 50mg/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 HIPEC interval was no less than 24 hours, 43 degrees, and 60 minutes. The expected number of participants in this study is 231. 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 5 years after the end of the clinical study.

Research process and duration: September 15, 2020 to September 15, 2024

Possible benefits:

Participating in this study, you will receive the most commonly used treatment options for advanced GC 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 paclitaxel 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 GC 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 GC 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, paclitaxel, 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: SOX, 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 Wuhan 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. patients voluntarily participate 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 XXX (name of investigator or related personnel) at (phone number).

Subject statement

I have read this informed consent form carefully. I 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