Anlotinib Combined with SOX Regimen (S1 [Tegafur, Gimeracil and Oteracil Porassium Capsules] + oxaliplatin) in Treating Stage IV Gastric Cancer: a Single-Armed and Single-Centered Clinical Trial

Informed consent

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Dear Madam / Sir,

Hello!

You will be invited to participate in a single-arm, single-center clinical study of anlotinib hydrochloride combined with the SOX regimen (tigio + oxaliplatin) in the treatment of stage IV gastric cancer. It is important that you understand the specifics of this research before agreeing to participate in it. Whether or not to participate in this study depends entirely on your personal wishes, and your treatment will not be affected if you do not participate in this study.

Introduction

Gastric cancer is currently the fourth most common malignancy worldwide with the second highest mortality rate [1]. There are 952,000 new cases in the world every year, with 73.5% in Asia and 47% in China. The most recent analytic data in 2012 [2] revealed that the incidence of gastric cancer in China ranked the second most common (36.21/100,000), and the mortality rate was the third highest (25.88/100,000). In addition to the high incidence rate and recurrence rate, the most important reason for the high mortality rate of gastric cancer is that most patients have late-stage disease when they are diagnosed. However, chemotherapy has very limited therapeutic effect on advanced gastric cancer [3]. In addition, advanced gastric cancer usually cannot be treated surgically due to invasion of the pancreas encircling large blood vessels or distant metastasis. Moreover, about

50% of localized lesions cannot be radically resected, and the surgical cure rate is still low. At present, chemotherapy and targeted therapy are the main treatments for advanced gastric cancer[4]. Compared to optimal supportive care, standardized chemotherapy and targeted therapy prolong survival relieve clinical symptoms and improve quality of life [5].

In recent years, molecular targeted therapy has been highly effective with low toxicity in treating cancers such as breast, colorectal, thyroid and non-small cell lung cancers, and its combination with chemotherapy for advanced cancer has become a popular research topic[6-11]. There is currently no standardized therapeutic option for advanced gastric cancer, and the treatment protocol varies globally. A large-scale retrospective study shows that patient baseline status is a single independent factor affecting survival rate among patients with late-stage gastric cancer[12]. In addition, distant metastatic sites (especially peritoneum and liver), two or more metastases, and low protein levels are risk factors for poor prognosis [12].

Protein Tyrosine Kinase (PTK) signaling pathway is involved in the proliferation, differentiation, and migration of tumor cells[13]. Interfering with or blocking the tyrosine kinase pathway can be used to influence the growth of tumor cells. Therefore, screening for PTK inhibitors has become a new method for discovering anti-tumor drugs. Anlotinib hydrochloride is a multi-targeted receptor tyrosine kinase inhibitor that targets angiogenesis-related kinases such as vascular endothelial growth factor receptors 1, 2, and 3 (VEGFR1/2/3), fibroblast

growth factor receptors 1, 2, and 3 (FGFR1/2/3), and other tumor-associated kinases involved in cell proliferation[14]. These tumor-associated kinases such as platelet-derived growth factor alpha/beta (PDGFRα/β), c-Kit, and RET are significantly inhibited by anlotinib[15]. And the angiogenesis kinase inhibition spectrum (e.g. Met, FGFR1/2/3) is broader[16]. Anlotinib hydrochloride also has significant inhibitory activities against some kinase targets that are under investigation such as Aurora-B, colony-stimulating factor 1 receptor, and discoidin domain receptor 1[17]. Moreover, anlotinib hydrochloride has significant inhibitory activity against multiple kinase mutants such as PDGFRα, c-Kit, c-Met, and epidermal growth factor receptor and the inhibitory activity against mutants is even stronger than that of the wild-type[18]. Therefore, the efficacy and safety of anti-angiogenic drugs (e.g., anlotinib hydrochloride) combined with chemotherapy for advanced gastric cancer are worth exploring and researching to provide more evidence and guidance for clinical practice.

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Inclusion and exclusion criteria

The inclusion criteria were as follows. 1) The patients provided written

informed consent form to participate in the study. 2) Patients were diagnosed with stage IV gastric adenocarcinoma by biopsy/pathology (any T, N, M1, with extra-gastric measurable lesions [RECIST 1.1 criteria] including unresectable locally advanced tumors, advanced tumors by R1 or R2 resection, and recurrence or metastasis status post R0 resection. 3) Patients were 18 years of age or older with an Eastern Cooperative Oncology Group performance status score of 0 to 2 points. 4) Functions of the major organs met the following criteria within 7 days before treatment :routine examination standard (without blood transfusion within 14 days): hemoglobin ≥ 90g/L, absolute neutrophil count ≥ 1.5 × 109/L, platelet (PLT) ≥ 80 × 109/L; and chemistry panel test met the following criteria: total bilirubin (TBIL) ≤ 1.5 times the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5x ULN or if complicated with liver metastasis then ALT and AST ≤ 5x ULN, serum creatinine ≤ 1.5x ULN or creatinine clearance ≥ 60mL/min. 5) Women of childbearing age agreed to use contraceptives (e.g., intrauterine devices, contraceptives, or condoms) during the study period and within the first 6 months after the study; had a negative serum or urine pregnancy test 7 days prior to study enrollment, and were non-lactating patients. Male candidates agreed to use contraception during the study period and within the first 6 months after the study.

The exclusion criteria were as follows. 1) Patients who were previously treated with anlotinib. 2) Patients who were previously treated with VEGFR-tyrosine kinase inhibitors such as sunitinib, sorafenib, famitinib, apatinib,

and regorafenib. 3) Patients currently suffering from or who previously had other malignant tumors within 5 years, except cervical cancer in situ, non-melanoma skin cancer, and superficial bladder tumors (Ta [non-invasive tumor], Tis [in situ carcinoma] and T1 (tumor-infiltrating basement membrane]). 4) Patients received systemic anti-tumor therapy including cytotoxic therapy, signal transduction inhibitors, and immunotherapy 4 weeks prior to enrollment or during the study or who were treated with mitomycin C in the 6 weeks before study. Patients received extended-filed radiation therapy in the 4 weeks before enrollment or involved field radiation therapy in the 2 weeks prior to enrollment. 5) Patients with unresolved toxic effects above Grade 1 Common Terminology Criteria for Adverse Events(CTCAE) (4.0) due to prior treatment, but not including alopecia and oxaliplatin-induced neurotoxicity that was lower than Grade two. 6) Patients with any sign or history of hemorrhage, regardless of severity, with any bleeding or bleeding episodes ≥ CTCAE Grade 3 within 4 weeks prior to enrollment; or with unhealed wounds, ulcers, or fractures. Patients with a clear possibility of gastrointestinal bleeding, including the following conditions: local active ulcer lesions, and fecal occult blood 2+; patients with a history of melena, hematemesis, fecal occult blood 1+ in the past 2 months, and patients with gastric tumor primary lesions without surgically resection, and considered to be at high risk of having gastrointestinal bleeding by main research staff. 7) Medical conditions that affected ability to take oral medication (e.g., inability to swallow, chronic diarrhea). 8) Patients with pleural effusion or ascites, causing respiratory

symptoms (≥CTCAE Grade 2 dyspnea (level 2 dyspnea refers to shortness of breath during low-intensity physical activity, affecting instrumental activities of daily living). 9) Patients with any of the following severe and/or uncontrolled diseases: taking one antihypertensive medication but still having unsatisfactory blood pressure (systolic blood pressure ≥150 mmHg, diastolic blood pressure ≥100 mmHg); suffering from Grade 1 or above myocardial ischemia or myocardial infarction, malignant arrhythmia (including QTC ≥ 480ms) and ≥ Grade 2 congestive heart failure according to New York Heart Association classification; active or uncontrolled severe infection (≥ CTCAE Grade 2 infection); cirrhosis, decompensated liver disease, or active hepatitis; renal failure requiring hemodialysis or peritoneal dialysis; history of immunodeficiency including HIV-positive or other acquired, congenital immunodeficiency diseases, or a history of organ transplantation; poorly controlled diabetes (fasting blood glucose [FBG] >10mmol/L); urinalysis indicating urine protein ≥ ++ and confirmed >1.0 gof 24-h urine protein; seizures that require treatment; history of psychotic medication abuse and are unable to quit; mental disorder; brain metastases with neurological symptoms or symptoms controlled for less than 2 months. 10) Patients who had major surgical treatment, open biopsy, or significant traumatic injury within 28 days before enrollment. 11) Arterial/venous thrombosis caused events that occurred within 6 months such as cerebrovascular accidents (including transient ischemic attacks), deep vein thrombosis, and pulmonary embolism. 12) Patients who participated in other clinical trials of anti-tumor

medications or are undergoing other clinical trials within 4 weeks.

The dropping out criteria were if chemotherapy or experimental drug treatments other than the presenting protocol was used during the trial.

The terminating study criteria were as follows: 1) Progressive disease (PD) will be determined based on efficacy evaluation criteria or considered by tumour markers, blood test and image test including enhanced CT or MRI of the chest, abdomen, and pelvis. 2) Grade 3 or higher malignant pleural effusion or pneumothorax occurred according to the National Cancer Institute(NCI) CTCAE4.0 grading standard. 3) Interim analysis showed that the medications lacked efficacy. 4) The researchers/study clinicians considered that the treatment should be terminated from the perspective of the best benefit of the patient. 5) Intolerable adverse reactions or serious adverse events were confirmed by the investigators. 6) Patients with poor compliance and those taking medications other than 80% to 120% of the dose. 7) Patients who voluntarily withdrew informed consent. 8) Patients who used other anti-tumor drugs (e.g., chemotherapy, targeted therapy, or biological agents) that affect efficacy judgment. 9) Patients with unexpected pregnancy. 10) Death of the patient.

Study design

This study was a single-armed and single-centered clinical study.

Dosage regimen

Anlotinib hydrochloride capsules were taken orally (before breakfast) once a day, 12mg each time, 2 weeks on and 1 week off; S1 40mg in the morning and 60mg at night, 2 weeks on and 1 week off; oxaliplatin 130 mg/m 2 IV drip d1, 3 weeks a cycle. Patients with disease control (complete response [CR] + partial response [PR] + stable disease [SD]) who could tolerate adverse reactions continued to take medication for 1 year, and did not take any other type of anti-tumor therapy until disease progression had occurred. Patients were evaluated every 6 weeks (2 cycles). Treatment were stopped when the investigators concluded that the patients were no longer good candidates to continue the presenting regimen or when the efficacy evaluation deemed disease to be progressing.

Research process

In order to determine your eligibility for the study (screening), you need to cooperate to complete the following: before starting treatment, the doctor will collect your medical history and basic information (including name, gender, age, contact number, ECOG score, BMI, previous treatment history , Surgery history, etc.), you need to complete the following tests: ECG, chest and abdomen CT, blood, urine, fecal routine (including fecal occult blood), blood biochemistry (ALT, AST, TBil, DBil, IBil, BUN, Cr), Electrolytes (K +, Na +, CL-, Ca2 +), coagulation function tests (PT, APTT, TT, Fbg, D-dimer, INR), serum CEA, CA199. If you are a woman of childbearing age, a pregnancy test is also required

to rule out the possibility of pregnancy.

During the study period, you will receive regular tests (hematuria, liver and kidney function, electrolytes, etc.). These tests are routine tests during chemotherapy and will not increase your extra burden. Follow-up at the end of each cycle: the main examination items include blood, urine, fecal routine, liver and kidney function and electrolytes. An electrocardiogram examination (with special attention to QTc) and blood, urine, stool routine test, blood biochemistry, and coagulation tests are performed at the end of each cycle. If symptoms such as anterior chest pain and palpitations appear, myocardial enzymes (CK, CK-MB) and troponin should be checked. If neutrophils are $\leqslant 1 \times 109$ / L or platelets are $\leqslant 50 \times 109$ / L, supportive care should be given, and dose adjustment or delayed medication if necessary. If urinary protein ++ or above occurs during the medication, the urinary protein quantification should be measured within 24 hours within one week. Efficacy evaluation was performed every 2 cycles (CT / MRI + serum CEA, CA199 detection). Thyroid function (T3, T4, FT3, FT4, TSH) was checked every 2 cycles.

During the entire study period, please cooperate fully with your doctor to tell the doctor what happened and answer the doctor's questions truthfully. We will record all adverse events from the day you sign this informed consent to 30 days after the last dose. You started the post-treatment follow-up period after the last use of the study drug, and we hope you continue to cooperate with our follow-up.

Confidentiality and privacy authorization

Your health information is protected by relevant Chinese laws. By signing this informed consent, you agree to the research doctor and research center personnel to collect, use, and share your health information data. Your initials will be provided to the researcher after being assigned a code as research data.

Your medical records (studies medical records / CRFs, test sheets, etc.) will be kept intact at the hospital you visit. The doctor will record the test results on your medical record. Researchers, ethics committees, and drug regulatory agencies will be allowed to access your medical records. Any public report on the results of this research will not disclose your personal identity and your personal privacy will be protected by us.

Voluntary participation / complete or partial withdrawal from the study

Participation in this research is entirely yours. You can choose not to participate in this research, you can also opt out at any time, and your medical treatment and rights will not be affected by this and will not be discriminated by medical staff.

Informed consent · Agreement Signature Page

The doctor in charge of the research or the relevant researcher has orally informed me about the research and I have read the written information.

I had ample opportunity to discuss the above research and ask questions.

I agree to participate in this study and understand that my participation in the study is completely voluntary and will cooperate fully with my doctor.

I understand that I can withdraw from the study at any time and that my withdrawal will not affect my future medical treatment.

By signing this informed consent, I agree that my personal information data, including my medical information data, will be used in the manner described above.

I know I will get a copy of this informed consent.

Patient name:

Patient's Signature:_____Signature Date: _____

contact number:_____

or

Signature of legal representative: _____Date of signature: _____

(Only when the subject is incapacitated)

The relationship with the patient is: _____Phone: _____

Researcher's Signature: _____ Signature Date: _____

contact number:_____