Study Protocol

A small-scale, exploratory real-world study of nab-paclitaxel combined with oxaliplatin and tegafur in the perioperative treatment of advanced gastric cancer: a study protocol for a real-world clinical trial

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Background: Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is an optimized and improved derivative of paclitaxel with superior efficacy and fewer adverse reactions, and it is widely used in the treatment of advanced gastric cancer. However, there is a paucity of data regarding the safety and efficacy of nab-paclitaxel combined with oxaliplatin (LBP) and tegafur in the treatment of patients with advanced gastric cancer.

Methods: This analysis is a prospective, single-center, open-label, historically controlled real-world study designed to include 10 patients with advanced gastric cancer treated with nab-paclitaxel combined with LBP and tegafur gimeracil oteracil potassium. The primary and main efficacy outcomes are safety indicators, including the incidence of adverse drug reactions and adverse events (AEs), as well as the outliers of laboratory indicators and vital signs. The secondary efficacy outcomes are overall survival (OS), objective response rate (ORR), disease control rate (DCR), and proportion of dose suspensions, dose reductions and discontinuations.

Discussion: Based on the findings of previous studies, we wished to assess the safety and efficacy of nab-paclitaxel combined with LBP and tegafur in the treatment of advanced gastric cancer. The trial requires constant contact and monitoring. The purpose is to determine a superior protocol in terms of patient survival, and pathological and objective response.

Trial Registration: This trial has been registered with the Clinical Trial Registry: NCT05052931 (registration date: 2021/9/12).

Keywords: Nanoparticle albumin-bound paclitaxel (nab-paclitaxel); oxaliplatin (LBP); perioperative treatment; advanced gastric cancer; exploratory real-world study

Submitted Jan 19, 2023. Accepted for publication Apr 17, 2023. Published online Apr 27, 2023.
doi: 10.21037/jgo-23-131
View this article at: https://dx.doi.org/10.21037/jgo-23-131

Introduction

Gastric cancer is the fourth most common malignancy worldwide and ranks second in terms of mortality. Gastric cancer is widespread in China, with the incidence and mortality accounting for 42.6% and 45.0% of the global cases, respectively (1). Patient prognosis is often poor, with multidisciplinary comprehensive treatment mainly centered on surgery, which is currently the only possible cure for gastric cancer (2,3). However, in China, the rate of early diagnosis is less than 10% (4), with the vast majority of patients in an advanced stage at initial diagnosis, resulting in long-term 5-year survival rates hovering around 30% (5). Advanced gastric cancer surgery is difficult and risky, and expanding the scope of surgery does not improve the cure rate. Furthermore, the incidence of postoperative recurrence and metastasis are often high. In recent years, administration of preoperative chemotherapy for locally resectable or potentially resectable advanced gastric cancer has been suggested (6,7). It is hoped that on the premise of ensuring safety, chemotherapy can reduce the primary lesion, improve the R0 resection rate, control micro-metastasis, and reduce postoperative recurrence and metastasis, so as to prolong the overall survival (OS) and disease-free survival (DFS) of the patient (8-10).

Taxanes are active chemicals derived from plants that have antitumor activity. A series of derivatives have been synthesized by structural modification of the active ingredients, including mainly paclitaxel, docetaxel, and taxane skeleton structure derivatives. Some studies focusing on neoadjuvant chemotherapy have shown powerful antitumor efficacy of paclitaxel in gastric cancer. Tsuburaya *et al.* found that among 52 patients with advanced gastric cancer who were treated with intravenous (i.v.) paclitaxel combined with cisplatin (PC regimen), 33 patients (63.5%) reached R0 resection, the pathological response rate (pRR) was 34.6%, and the 3-year survival rate was 41.5% (11). Although taxanes have good antitumor effects, their adverse reactions are also relatively obvious, including allergic reactions, neurotoxicity, bone marrow suppression, cardiovascular toxicity, liver toxicity, and gastrointestinal toxicity (12,13). Continuous research and advancements have resulted in the development of albumin-bound paclitaxel, which not only reduces the incidence of adverse reactions, but also enhances the antitumor efficacy (14). Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is an optimized and improved product of paclitaxel. It is made by nanotechnology and uses the inherent albumin in the human body as a carrier, thereby creating a solvent-free targeted chemotherapeutic drug. This allows the drug to be transported via endocytosis, and therefore more rapidly crosses the endothelial cell layer with greater tissue penetration (15,16). Based on preclinical models, intratumoral delivery and retention resulted in a 33% increase in intratumoral drug concentration (17). Since nab-paclitaxel has higher drug concentration and tumor selectivity, it should therefore afford better efficacy and fewer adverse reactions.

Oxaliplatin (LBP) is a third-generation platinum antitumor drug, which mainly acts through covalent bonding with G and A in DNA bases (Pt-GG and Pt-AG) to form DNA [Pt (II) A2] adducts. This results in intra- and inter-strand cross-links with the DNA, thereby preventing DNA winding and unwinding, as well as transcription and replication processes, and ultimately induce tumor cell apoptosis (18,19). LBP is a combination of lactate and platinum, which has high solubility in water and good stability, and does not require hydration for clinical use. Its anticancer activity is comparable to cisplatin, stronger than carboplatin, and has no cross-resistance with other platinum drugs (20). The average plasma protein binding rate of LBP at 24 hours was only 25%, indicating that the concentration of free LBP in plasma after i.v. administration was high, the tissue distribution was fast, and the concentration in tumor tissue per unit time was high. At the same time, the average urinary excretion rate of LBP in 24 hours was as high as 70%, suggesting that LBP is rapidly cleared by the kidneys, does not accumulate easily in the body, has a short duration of action, and has mild adverse reactions (21). LBP has no obvious nephrotoxicity, ototoxicity, or neurotoxicity, and has significantly less gastrointestinal toxicity (22).

Tegafur gimeracil oteracil potassium is a compound preparation consisting of tegafur, gimeracil, and oteracil potassium. Compared with 5-fluorouracil, tegafur can maintain higher blood drug concentration and improve anticancer activity, significantly reduce drug toxicity, and is convenient to administer. There have multiple reports reliably demonstrating its efficacy and safety in advanced gastric cancer. At the American Society of Clinical Oncology (ASCO) meeting in 2009, Koizumi *et al.* reported phase II study of LBP plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study) (23). A total of 51 patients with unresectable or recurrent advanced gastric cancer were treated with chemotherapy with S-1 and LBP (SOX regimen) to assess for efficacy. In this study, LBP was administered i.v. (100 mg/m^2) on day 1, while S-1 was administered orally [80 mg/m^2/day, twice daily (b.i.d.)] for

14 days followed by a 7-day rest. The schedule was repeated every 3 weeks (Q3W). The response was assessed as PR, stable disease (SD) and progressive disease (PD) in 30, 13, and 5, respectively, of the 51 patients in the efficacy analysis set (three were not assessable). The response rate (RR) was 59% and the disease control rate (DCR; CR + PR + SD) was 84%. The median survival time (MST) was 16.5 months, median progression-free survival (PFS) was 6.5 months, and median TTF was 4.8 months. The results showed that the SOX regimen is workable and exhibits potential efficacy against advanced gastric cancer.

Previous studies have suggested that chemotherapy drugs including taxane, LBP, and tegafur have good efficacy and safety in the treatment of gastric cancer (24-26). While these agents can be used in combination, there is current no relevant data on the combined used of all three chemotherapy drugs. Therefore, to optimize and improve the use of paclitaxel drugs in gastric cancer (27,28), we intend to conduct a clinical trial to assess the efficacy and safety of nab-paclitaxel in combination with LBP and tegafur in advanced gastric cancer.

Methods

Study design

This study is a small sample (n=10) prospective, single-center, open-label, historically controlled exploratory real-world clinical study. The study began on October 1, 2021 and is anticipated to get completion on December 31, 2023.

Inclusion and exclusion criteria

The following primary inclusion criteria were applied: (I) pathological diagnosis of localized advanced gastric adenocarcinoma (cT2Nx-cT4bNx); (II) patients aged 18–75 years old; (III) Eastern Cooperative Oncology Group (ECOG) score ≤1; (IV) patient has not received any previous antitumor treatment; (V) abdominal surgery in patients with grade 3 or above is anticipated to be tolerable; (VI) when the subject's baseline routine blood and biochemical indicators are satisfactory, the routine blood and biochemical examination criteria satisfies the following: white blood cell (WBC) count >4.0×10^9/L, absolute neutrophil count (ANC) ≥1.5×10^9/L, hemoglobin (Hb) ≥80 g/L, platelet (PLT) count ≥100×10^9/L, total bilirubin (TBIL) ≤1.5× upper limit of normal (ULN), alanine transaminase (ALT) and aspartate aminotransferase (AST) <2.5× ULN, ALT and AST <5× ULN for patients suffering from liver metastases, and blood urea nitrogen (BUN) and creatinine (Cr) ≤1.5× ULN or endogenous Cr clearance ≥50 mL/min (Cockcroft-Gault formula); (VII) no concomitant tumors; (VIII) the participants willingly agree to take part in the study and follow-up, and complete the informed consent form in a timely manner; and (IX) the patient's estimated life span is ≥6 months.

Patients with the following conditions are excluded from the study: (I) previous history of other malignancies, except for cured basal cell carcinoma of the skin and carcinoma *in situ* of the cervix; (II) patients with positive human epidermal growth factor receptor 2 (HER2) test results who accept antitumor therapy including herceptin therapy and other antitumor drugs, including China Food and Drug Administration (CFDA) modern traditional Chinese medicine preparations approved or marketed for antitumor therapy, chemotherapy, molecular targeted therapy, hormone therapy, immunotherapy, biological therapy, or radiation therapy, etc.; (III) microsatellite instability (MSI) patients should be excluded; (IV) pregnant or lactating women in the reproductive period without taking effective contraceptive measures or those who have reproductive requirements during the antitumor treatment; (V) patients with serious, uncontrolled medical conditions or infections, active hepatitis B virus (HBV) or hepatitis C virus (HCV), or those diagnosed with chronic bowel disease or short bowel syndrome; (VI) patients with significant dysfunction of the blood, kidney, metabolic, gastrointestinal, or endocrine systems;; (VII) patients with other contraindications to surgery, including those with significant diseases such as atrial fibrillation, angina pectoris, compensated heart or lung, etc.; (VIII) patients prone to gastrointestinal bleeding and/or coagulation dysfunction [international normalized ratio (INR) >1.5]; (IX) patients with peripheral neuropathy and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 2 or above; (X) patients who are allergic to nab-paclitaxel components, or to LBP, tegafur, or contrast medium, as well as any other preparation components in this protocol. The investigators shall determine if particular patients are not suitable to for this protocol.

The dropping out standards are as follows: (I) the subject rejects the informed consent form and requests to be withdrawn from the study; and (II) if the drug is not tolerated even after lowering the dose to the lowest possible dose.

The terminating study criteria are as follows: (I) the subject dies or is lost to follow-up; (II) it is determined

that the procedures may cause unexpected, significant, or unacceptable risk to the subject; (III) the study drug treatment is confirmed to be ineffective; and (IV) the existing efficacy results support early termination of the study.

Dosage regimen

The experimental group will be given 3 cycles of neoadjuvant chemotherapy (a treatment cycle is 21 days), which includes injections of nab-paclitaxel [100 mg/m^2, day (D)1, Q3W], LBP (85 mg/m^2, D1, Q3W), and tegafur gimeracil oteracil potassium (40–60 mg/m^2), followed by surgery, and a further 6 cycles of adjuvant chemotherapy at 3 to 4 cycles post-surgery. Patient vital signs, laboratory examinations, imaging examinations, adverse event (AE) records, and other data of the patients in this group were complete during the medication period.

Dosing interruption and dose adjustment

Since this study is a real-world study, it does not require dosing interruptions and dose adjustment schedules for nab-paclitaxel and platinum.

Planned sample size

This study will include 10 patients with advanced gastric cancer who will receive nab-paclitaxel along with LBP and tegafur gimeracil oteracil potassium as the experimental group. For the control group, the study will retrospectively examine 10 patients with advanced gastric cancer who previously received docetaxel combined with LBP and tegafur gimeracil oteracil potassium in our center.

Main indicators and research endpoints

Safety indicators

The following safety indicators will be assessed: (I) AEs, including type, incidence, classification (judged according to the NCI-CTCAE v5.0 standard), severity, duration, and correlation with the test drugs; (II) the outliers of laboratory indicators, including incidence, classification (according to NCI-CTCAE v5.0 standard), duration, etc.; (III) vital signs, including blood pressure, pulse, respiratory frequency, electrocardiogram, and Karnofsky performance status (KPS) or ECOG performance status score, etc.

During the clinical trial, once a serious adverse reaction occurs, the investigators should provide a serious AE (SAE) report within 1 day, and submit it to the ethics committee, the higher authorities, and the sponsor. The content should include all details, measures taken, and results of the SAEs.

Secondary efficacy indicators

Efficacy indicators

Four efficacy indicators will be evaluated. OS is defined as the period from random grouping to death due to various reasons, and is an intention-to-treat (ITT) population.

The objective response rate (ORR) is defined as the decrease in the volume of the tumor to a predetermined value and the proportion of patients who can maintain the minimum time limit requirements, including cases with complete response (CR) and partial response (PR). The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 is used to assess the objective tumor remission by an Independent Review Committee. Subjects must have measurable tumor lesions at baseline, and the efficacy evaluation criteria are set out for CR, PR, SD, and PD. Subjects who drop out will be assessed based on the date of the last follow-up. For patients withdrawing the study, but who have not yet achieved PD, tumor assessment will be obtained and documented during follow-up. Patients who died prior to data analysis will be assessed based on the last recorded visit.

The DCR is the percentage of patients with the best overall response (BOR) according to RECIST 1.1, including those who have achieved CR, PR, and SD.

The proportion of dose suspensions, dose reductions, and discontinuations due to drug-related toxicity will also be assessed.

Data collection and observation indicators

See the test flow chart for details (*Table 1*).

Follow-up

Follow-up of the periods of screening and enrollment

The screening period commences from signing of the informed consent forms and ends with enrollment or exclusion. Subjects must have full disclosure of the study and sign the form before proceeding to screening of specified procedures. The relevant data from laboratory examinations and imaging evaluations, which were performed for routine clinical care prior to signing the informed consent form, can be used if it occurred within the specified window period.

Informed consent forms need to be signed at least

Table 1 Test flow table

Visit window	Screening period		Treatment period (±3 days)			Adjuvant therapy		Study completion/ withdrawal [28] (±7 days)	Safety follow-up [29] (±7 days)	Survival follow-up [30] (±7 days)
	D14–D1	D7–D1	C1	C2	1 week before surgery (±3 days)	C3	C4–C6			
Signing informed consent [1]	√									
Demographic data	√									
Previous medical history [2]	√									
ECOG score [3]		√	√	√	√	√	√	√	√	
Vital signs [4]		√	√	√	√	√	√	√	√	
Physical examination [5]		√	√	√	√	√	√	√	√	
Routine blood tests [6]		√	√	√	√	√	√	√	√	
Routine urine tests [7]		√	√	√	√	√	√	√	√	
Blood biochemistry [8]		√	√	√	√	√	√	√	√	
Fecal occult blood [9]		√	√	√	√	√	√	√	√	
Thyroid function [10]		√	√	√	√	√	√	√	√	
Blood coagulation function [11]		√	√	√	√	√	√	√	√	
Evaluation of liver and kidney function [12]		√	√	√	√	√	√	√	√	
Pregnancy test [13]	√									
Virological examination [14]	√							√		
12-lead electrocardiogram [15]		√	√	√	√	√	√	√	√	
Tumor imaging examination [16]	√				√	√	√	√	√	
Nab-paclitaxel dosing [17]			√	√		√	√			
LBP dosing [18]			√	√		√	√			
Dosing of oral tegafur gimeracil oteracil potassium [19]			√	√		√	√			
Surgery [20]					√					
Tumor marker [21]		√	√	√	√	√	√	√	√	
Pathological evaluation [22]	√						√			
AE [23]	√	√	√	√	√	√	√	√	√	√
Combined medication/concomitant therapy [24]	√	√	√	√	√	√	√	√	√	√
NRS [25]	√				√	√	√	√	√	
Nutritional status assessment [26]		√	√	√	√	√	√	√	√	
Follow-up of survival information and antitumor therapy [27]										√

In addition to the inspection items and time points listed in the table, the researcher can add visits and other inspection items at any time according to actual needs, and the inspection results shall be filled using the eCRF "unplanned visits" form. The time window for this study plan is ±3 days, except where noted. [1]–[30]: see Appendix 1 for specific information. D, day; C, cycle; ECOG, Eastern Cooperative Oncology Group; LBP, oxaliplatin; AE, adverse event; NRS, nutritional risk screening; eCRF, electronic case report form.

14 days prior to treatment. Data related to patient demographics, infectious disease screening [HBV, HCV, syphilis, acquired immunodeficiency syndrome (AIDS)], and tumor lesion imaging examination [computed tomography (CT) or magnetic resonance imaging (MRI)] will be collated. A pregnancy test (applicable to women of child-bearing age), past disease history, past medication history, history of drug allergy, history of tobacco and alcohol, pathological assessment, nutritional risk screening (NRS), history of AEs and drug combinations must be obtained. Within a week before starting drug therapy, ECOG scores, vital signs, physical examination, routine blood tests, routine urine tests, blood biochemistry, fecal occult blood tests, thyroid function, coagulation function, evaluation of liver and kidney function, 12-lead electrocardiogram, tumor markers, AEs, concomitant medication, and nutritional status assessment should be completed, and the criteria of inclusion and exclusion will be checked.

Follow-up during treatment

The treatment period begins with the subject's first dose and ends with discontinuation of study treatment. The first study medication should be as close as possible to the time when the screening period check is completed to confirm that it meets the inclusion and exclusion criteria, and the longest time from randomization is 3 days. Routine blood, routine urine, blood biochemistry, fecal occult blood, thyroid function, coagulation function, liver and kidney function, tumor markers, 12-lead electrocardiogram, etc. should be performed before each cycle of medication, within 1 week before surgery, and before each cycle of adjuvant therapy. Routine pre-medication examinations and periodic imaging examinations for efficacy assessment, recording AEs and concomitant medication should be performed throughout the administration period.

Follow-up at the end of treatment

At the completion of treatment, the following examinations should be performed: ECOG score, vital signs, physical examination, routine blood, routine urine, blood biochemistry, fecal occult blood, thyroid function, coagulation function, liver renal function, virological examination, tumor imaging examination (CT or MRI), tumor markers, AEs, concomitant medication, NRS and nutritional status assessment.

Follow-up of safety and efficacy indicators

All subjects will be followed up every 30 days after the last treatment until 90 days after the last dose. The first safety follow-up includes the following inspection items: ECOG score, vital signs, physical examination, routine blood, routine urine, blood biochemistry, fecal occult blood, thyroid function, coagulation function, liver renal function, tumor imaging examination (CT or MRI), tumor markers, AEs, concomitant medication, NRS and nutritional status assessment. The second and third safety visits can be telephone visits and only information related to survival, concomitant medications/concomitant treatments, and AEs will need to be collated.

Statistical analysis program

The mean, standard deviation, median, maximum value, and minimum value will be used to summarize the measurement results. Count data will be summarized by frequency and percentage. Time-event data will be analyzed using the Kaplan-Meier method to estimate the survival rate and plot the survival curve. All data analysis will be programmed and calculated using the SPSS software. Statistical analyses will be two-way tests. A P value ≤ 0.05 will be considered statistically significant, and a 95% confidence interval (CI) will be adopted.

The complete analysis set will be used to assess baseline data, and the full analysis set (FAS) and the per-protocol set (PPS) will be used to examine all effectiveness indicators; the security analysis set will be based on the safety analysis set.

For efficacy analysis, the evaluation indicators are R0 resection rate, 3-year OS rate, pathologic CR (pCR) rate, ORR of the tumor, and DFS.

Fort safety analysis, AEs will be assessed by NCI-CTCAE v5.0. The analysis of AEs will be based on the full treatment analysis set, and the incidence of adverse reactions will be calculated in groups. The relative frequency and frequency of adverse reactions will be listed by system, the percentage will be calculated, and then detailed lists of various AE cases will be documented, including items in the following lists: (I) description of drug exposure; (II) statistics of the incidence and the severity of AEs, any SAEs, and any causal relationship with the study drug; (III) descriptive statistics of the vital signs, laboratory test values, electrocardiogram, and changes relative to baseline levels of the subjects at each follow-up point, and the statistics of the data deviating from the reference range; and (IV) classified statistics of combined medication and concomitant therapy.

Definition of the statistical analysis of the data

For the FAS, based on the principle of ITT analysis, the efficacy analysis will be performed on all patients who receive drug treatment and who take the drug at least once. For the case data form which the whole treatment process could not be observed, the last observation data is carried forward to the final result of the study (LOCF).

For the PPS, all patients who meet the inclusion criteria, achieve good compliance without taking illegal drugs during the study period, and complete the specific contents of the case report form will be included. No imputation will be performed for missing data. Statistical analyses of the FAS and PPS will be performed concurrently with the analysis of drug efficacy.

For the safety analysis set, among all recruited cases, all the patients who use the study drug at least once with post-medication safety records will be enlisted in the safety analysis set. This dataset will be applied to safety analysis.

Ethics and dissemination

This study has received approval from the Ethics Committee of the First Affiliated Hospital of the Fourth Military Medical University (Xijing Hospital) (No. KY20212102-C-1). Before enrolling subjects in the study, the investigator is obliged to offer each candidate, or his or her legal representative, with a clear and detailed description of the study's goals, processes, and potential benefits and dangers, as well as collect signed consent forms. The present study protocol is developed on the basis of the Recommendations for Intervention Trials Statement. The patients enrolled are informed of having the right to withdraw from the process at any time, and informed consent will be saved as clinical research files. During the research period, the subject's individual privacy and data confidentiality are key protection objectives. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data management

The case report forms will be filled out by Clinical Research Coordinator (CRC), and data collection and processing will be performed after the review of the completed case report form. Investigators should ensure data authenticity and accuracy and replace the names by codes aimed at protecting patient privacy. The principal investigator and statistical analyst will verify and confirm the statistics before fixing them. After this time, the determined data file should not be altered.

Discussion

Gastric cancer is a common malignant tumor of the digestive tract, and its incidence and mortality rate are among the top of all malignant tumors. At present, D2 surgery is the standard surgical method for advanced gastric cancer, but most patients (more than 70%) present with advanced gastric cancer, and surgery such as expanding the scope of lymph node dissection combined with organ resection can no longer bring more benefits to patients (29). Therefore, it is particularly important to reduce the stage of tumors through neoadjuvant chemotherapy and combine surgery for the comprehensive treatment of locally advanced gastric cancer to improve the R0 resection rate and improve OS. The traditional first-line SOX regimen, namely LBP and S-1 combination, is mostly used for perioperative or postoperative maintenance treatment of gastric cancer, which can significantly improve prognosis and improve OS (23). The combination of paclitaxel and pyrimidines can be used for the comprehensive treatment of unresectable locally advanced gastric cancer (30). However, some people still have disease progression after receiving the above treatment, and the effectiveness rate of neoadjuvant chemotherapy still needs to be improved.

The three-drug combination regimen docetaxel, cisplatin, and 5-fluorouracil (DCF) and modified DCF (mDCF) can be applied to patients with advanced metastatic gastric cancer in good physical condition and with large tumor burden. Although the three-drug regimen DCF reached the research endpoint in the phase III study, but the high toxicity limited its clinical application (31). Although the same paclitaxel, docetaxel and albumin paclitaxel are inhibiting tumor cell growth by inducing and promoting microtubule assembly, polymerization, and stabilization of microtubules, interfering with microtubule rearrangement, resulting in mitotic arrest, but albumin paclitaxel uses human blood albumin as a carrier and no longer needs to use toxic co-solvents (such as polyethylene castor oil), so at the time of infusion, hormones are no longer needed for pretreatment. Previous clinical study data show that the response rate and OS data of nab-paclitaxel regimen are not inferior to other taxanes regimens (32). Therefore, nab-paclitaxel is expected to make the combination of three drugs play a greater role in neoadjuvant therapy of locally

advanced gastric cancer. There are no reported data on albumin-bound paclitaxel combined with LBP and tegafur in combination with neoadjuvant chemotherapy for locally advanced gastric cancer. Therefore, we would like to explore the safety and efficacy of the combination of three drugs in the field of neoadjuvant chemotherapy for locally advanced gastric cancer, and use a more potent regimen for patients in neoadjuvant therapy, in order to achieve the purpose of lowering tumor stage, improving R0 resection rate and improving OS, and reducing postoperative complications caused by expanding the scope of lymph node dissection or combined organ resection. So we designed this study.

But our design still has certain limitations. We wanted to explore the safety of albumin-bound paclitaxel in combination with LBP and tegafur for neoadjuvant chemotherapy for locally advanced gastric cancer, and to further explore the effectiveness of the regimen once its safety has been demonstrated. The setting of the sample size limits the authoritative conclusions of this study to some extent. Although the setting of the control group is not mandatory, if the three-drug combination neoadjuvant chemotherapy and the two-drug combination can be directly statistically compared, or compared with other types of taxane, it can show the improvement effect of a specific chemotherapy drug on drug safety.

In conclusion, in neoadjuvant chemotherapy for locally advanced gastric cancer, albumin-bound paclitaxel combined with LBP and tegafur regimen is used in advance for neoadjuvant therapy of locally advanced gastric cancer. To investigate the safety and efficacy of albumin paclitaxel combined with LBP and tegafur in neoadjuvant chemotherapy for locally advanced gastric cancer, so as to control tumor progression as soon as possible, reduce tumor stage, improve R0 resection rate and improve OS.

Acknowledgments

Funding: This work was supported by grants from the Key Clinical High Tech Project of Xijing Hospital (No. XJZT19Z26), the National Key Research and Development Program of China (No. 2020YFE0202200), and the Key Research and Development Project of Shaanxi Province (No. 2022ZDLSF03-04).

Footnote

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-131/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-131/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethical approval has been obtained from the Ethics Committee at the First Affiliated Hospital of the Fourth Military Medical University (Xijing Hospital) (No. KY20212102-C-1). Informed consent will be obtained from all study participants. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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(English Language Editor: J. Teoh)

Cite this article as: Zheng J, Wang S, Xu G, Wang J, Wang Y, Luo J, Wang Y, Yang J. A small-scale, exploratory real-world study of nab-paclitaxel combined with oxaliplatin and tegafur in the perioperative treatment of advanced gastric cancer: a study protocol for a real-world clinical trial. J Gastrointest Oncol 2023;14(2):1131-1140. doi: 10.21037/jgo-23-131

Appendix 1

[1] Written informed consent signed by the subject or legal representative/independent witness must be obtained before screening.

[2] Medical history: including tumor history (tumor diagnosis, surgery, radiotherapy, drug treatment) and history of other comorbidities and drug allergies.

[3] ECOG score: assessments are made within 7 days before the first administration, before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during the safety follow-up.

[4] Vital signs: includes blood pressure, pulse, body temperature, and respiratory rate; time points of testing are within 7 days before the screening period (within 7 days before the first dose), before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during safety follow-up; tests can be added at any time if there are any associated discomfort symptoms.

[5] Physical examination: time points of testing are within 7 days before the screening period (within 7 days before the first dose), before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during safety follow-up; comprehensive physical examinations, including general condition, head and face, neck, skin, lymph nodes, eyes, otolaryngology, oral cavity, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system, mental status, and other examinations; targeted physical examination are carried out on condition that there are clinical indications.

[6] Routine blood tests: testing items include red blood cell count, Hb, PLT count, WBC count, neutrophil count, lymphocyte count; testing time points are within 7 days before the first dose, before dose on the first day of each week during the study period (if tests are completed in the screening period within 7 days before the first dose the test, there is no need to test again for the first dose), within 1 week before surgery, before each cycle of adjuvant therapy, completing study treatment, withdrawing from the study treatment, and during safety follow-up; if there are any related discomfort symptoms, tests can be added at any time. If the subject performed the tests within the specified window period of the study, it is not necessary to repeat the test during the screening period.

[7] Routine urine tests: includes WBCs, red blood cells, and urine protein; tests are done within 7 days before the first administration, before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during safety follow-up; if there are any related discomfort symptoms, tests can be added at any time. If the urine protein is ≥2+, 24-hour urine protein quantitative determination should be added.

[8] Blood biochemistry: includes ALT, AST, γ-glutamyl transferase (GGT), TBIL, direct bilirubin, alkaline phosphatase (AKP), BUN or urea (preferably BUN), total protein, albumin, Cr, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-. Tests are conducted within 7 days before the first administration, before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during safety follow-up. If there are any related discomfort symptoms, tests can be added at any time.

[9] Fecal occult blood tests: tests are performed within 7 days before the first administration, before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during safety follow-up. If there are any related discomfort symptoms, tests can be added at any time.

[10] Thyroid function: testing items included thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). Tests are performed within 7 days before the first administration, before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during safety follow-up. If there are any related discomfort symptoms, tests can be added at any time.

[11] Blood coagulation function: testing items included activated partial thromboplastin time (APTT), prothrombin (PT), fibrinogen (FIB), and INR. Tests are done within 7 days before the first administration, before each cycle of medication,

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within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during safety follow-up. If there are any related discomfort symptoms, tests can be added at any time.

[12] Evaluation of liver and kidney function: evaluations are made within 7 days before the first administration, before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during safety follow-up.

[13] Pregnancy test: applicable to women, serum pregnancy tests can be used during the screening period, and urine pregnancy tests can be used at other time points. Tests are done within 14 days prior to the first dose, upon completion/withdrawal of study treatment, and one assessment at the first visit during the safety follow-up.

[14] Virological examination: hepatitis B surface antigen (HBsAg; if positive, HBV-DNA needs to be tested), hepatitis B surface antibody (HBs-Ab), hepatitis B e-antigen (HBe-Ag), hepatitis B e-antibody (HBe-Ab), hepatitis B core-antibody (HBc-Ab), and HCV-Ab (if positive, HCV-DNA needs to be tested), and human immunodeficiency virus (HIV)-Ab. Tests are done within 14 days before the first dose.

[15] 12-lead electrocardiogram: tests are conducted within 7 days before the first administration, before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, when completing study treatment, withdrawing from study treatment, and during safety follow-up. If there are any related discomfort symptoms, tests can be added at any time.

[16] Tumor imaging examination: including chest X-ray, CT scan of the neck, chest, and abdomen, gastroscope and abdominal B-ultra sonography examination; MRI, positron emission tomography (PET)-CT, bone scan, brain magnetic resonance, and other tests can be selected to be perform when other imaging examinations identify problems or patients experience symptoms in the corresponding sites.

- ❖ During the screening period, the tumor evaluation can be up to 4 weeks before the first use of the study drug, and the imaging examination results obtained before signing the informed consent can be used for the tumor evaluation in the screening period as long as they meet the requirements of RECIST 1.1.
- ❖ During the study treatment period, imaging examinations are performed once in the first two cycles or before surgery, and imaging examinations are performed every 9 weeks thereafter. Imaging examinations should be performed in a timely manner (±4 weeks, if the previous examination time was within 4 weeks of the termination of treatment, reexaminations are not required when leaving the group). Imaging conditions should be the same as the baseline (including scan slice thickness, contrast agent, etc.). The allowable window period for imaging studies is ±7 days, and unscheduled imaging studies can be performed when disease progression is suspected (such as worsening symptoms).
- ❖ During safety follow-up and survival follow-up, subjects without imaging progression should still have imaging assessments at the same frequency if possible, until disease progression or initiation of other antitumor therapy.
- ❖ In addition to disease progression confirmed by imaging, subjects who discontinue study treatment for other reasons should also undergo imaging examinations at the frequency specified in the protocol as much as possible until documented disease progression, initiation of new antitumor therapy, or death.

[17] Administration of nab-paclitaxel: 100 mg/m^2, administered on the first day of each cycle, repeated Q3W, 2 cycles of neoadjuvant therapy before surgery and 6 cycles after surgery.

[18] LBP: 85 mg/m^2, administered on the first day of each cycle, repeated Q3W, 2 cycles of neoadjuvant therapy before surgery and 6 cycles after surgery.

[19] Tegafur gimeracil oteracil potassium: one treatment cycle includes 40–60 mg/m2 tegafur, orally, twice a day, after breakfast and dinner, for 14 consecutive days, followed by 7 days off; repeated Q3W.

[20] Surgery: within 3 to 6 weeks after the end of the last treatment, the investigator should decide whether to perform surgery according to the specific condition and the patient's informed preference.

[21] Tumor marker: assessed within 7 days before the first dose, before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, completion/exit of study treatment, and during safety follow-up.

[22] Pathological evaluation: pathological diagnosis and evaluations are performed within 60 days before the first administration and after gastric cancer resection, respectively.

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[23] AEs: the evaluation time commences from signing the informed consent form until the 30th day after the last medication; after that, only the concomitant medication of AEs related to the study drug will be recorded. If the patient starts a new antitumor therapy during the AE collection period, only AEs related to the study drug will be collected after the new antitumor treatment.

[24] Combined medication: all combined medication and concomitant therapy from 14 days before signing the informed consent form to the last safety follow-up will be recorded; after that, only concomitant medications for AEs related to the study drug will be recorded. Any SAE or AEs of special interest (AESI) related to the study drug should be recorded until the end of the AE.

[25] NRS: NRS assessment of patients will be conducted using the NRS 2002 scale within 14 days before the first dose, within 1 week before surgery, before each cycle of adjuvant therapy, upon completion/exit of study treatment, and during safety follow-up.

[26] Nutritional status assessment: the nutritional status of patients will be assessed using the Patient-Generated Subjective Global Assessment (PG-SGA) scale within 7 days before the first dose, before each cycle of medication, within 1 week before surgery, before each cycle of adjuvant therapy, upon completion/exit of study treatment, and during safety follow-up.

[27] Survival information and antitumor treatment follow-up: the safety assessment and AE follow-up should be continued after the 90-day safety follow-up till death or the subjects are lost to follow-up or termination of the study. Meanwhile the concomitant treatment of patients should be recorded. The subjects themselves, their family members or local physicians will be contacted once every 3 months by telephone to collect information on survival (date of death and cause of death) and after the end of study treatment (including treatment received). The situation of each survival follow-up should be recorded in detail into the follow-up table. Follow-up will be conducted every 3 months (±7 days) in the 1st to 2nd years, and every 6 months (±14 days) in the 3rd to 5th years. After that, follow-up will be conducted once a year to collect survival information and follow-up treatment information.

[28] Study completion/withdrawal: if the 12-lead electrocardiogram, routine laboratory tests (including routine blood routine, urine routine, blood biochemistry, blood electrolytes, coagulation function, thyroid function, fecal occult blood, and virology tests), and the results of the subject's self-assessment are completed within 7 days prior to withdrawal from treatment, these tests do not need to be performed again at the visit.

[29] Safety follow-up: all subjects are required to be followed up in the research center at 30 days after the last medication (if the visit of withdrawal from the study treatment was completed, the visit is changed to telephone follow-up). The telephone follow-up is used to obtain safety information (including AE outcomes, new-onset SAEs, and AEs of special concern).

[30] Survival follow-up: after the safety follow-up period, the subjects enter the survival follow-up period until the subjects die, are lost to follow-up, withdrew their informed consent, or the sponsor terminates the study. During this period, the follow-up will be conducted every 3 months in the 1st to 2nd years, every 6 months in the 3rd to 5th years, and once every year thereafter to collect survival information and follow-up.

https://dx.doi.org/10.21037/jgo-23-131