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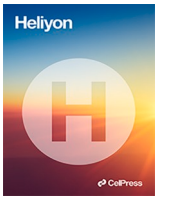

Research article

Evaluation of the efficacy and safety of ramucirumab combined with nab-paclitaxel, lobaplatin, and S-1 in neoadjuvant and conversion therapy for advanced gastric cancer: A study protocol of prospective single-center, randomized controlled and open label clinical trial (RNPLS-01)

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ABSTRACT

Objective: Ramucirumab is a VEGFR2 antagonist. The aim of this trial is to evaluate the efficacy and safety of ramucirumab combined with nab-paclitaxel, lobaplatin and S-1 in neoadjuvant and conversion therapy for advanced gastric cancer.
Methods: and analysis: This study is a prospective single-center, randomized controlled and open label clinical study, enrolling a total of 140 patients with advanced gastric cancer distributed across two distinct cohorts (Cohort A n = 70; Cohort B n = 70). The central focus of the study lies in evaluating the pathological complete response (pCR) of the cancer post-neoadjuvant or conversion therapy. Secondary endpoints encompass the assessment of the R0 resection rate subsequent to the aforementioned therapies, the occurrence of adverse events (AE), progression-free survival (PFS), overall survival (OS), the objective response rate (ORR), the total response rate and its duration, the disease control rate (DCR), and the duration of overall response (DOR).
Ethics: Ethics approval has been obtained from the Ethics Committee at the First Affiliated Hospital (Xijing Hospital) of Air force Military Medical University (KY20232220–F-1).
Trial registration: This trial has been registered at the ClinicalTrials.gov: NCT06169410 (registration date: December 5, 2023).

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1. Introduction

Gastric cancer has become the fifth largest cancer in the world and the fourth leading cause of cancer-related deaths in cash, posing a powerful challenge to the healthcare industry worldwide [1]. Traditional approaches to treating gastric cancer encompass surgery, chemotherapy, radiotherapy, and targeted therapy. In China, a substantial portion of gastric cancer diagnoses occur at advanced stages, precluding the possibility of complete remission. Even among patients with early-stage disease who undergo surgical intervention, a notable proportion experience relapse and distant metastasis, therefore, it leads to a survival rate of less than 10 % in advanced gastric cancer patients within five years [2]. At present, individuals with advanced-stage gastric cancer primarily receive treatment regimens comprising chemotherapy and targeted therapies. Chemotherapy drugs used clinically for advanced gastric cancer include fluorouracil or its derivatives, platinum drugs and paclitaxel drugs. Regarding targeted drug therapy, individuals with gastroesophageal junction adenocarcinoma and HER2-positive gastric cancer can benefit from the utilization of trastuzumab in conjunction with first-line chemotherapy. Furthermore, in cases where patients with advanced gastric experience resistance to second-line chemotherapy agents, the anti-angiogenic tyrosine kinase inhibitor apatinib represents a viable treatment option [3]. Overall, these treatments have limited efficacy in advanced gastric cancer, and data from multiple large-scale clinical studies indicate that the median survival time of advanced gastric cancer patients is only about one year [4].

Inhibiting tumor growth through anti-tumor angiogenesis has been one of the biggest breakthroughs in the development of anti-tumor drugs in the past 20 years. To achieve dilated growth, tumors secrete VEGF, which bind to VEGF receptors, thereby stimulating the generation of new blood vessels. Neovascularization is a key factor in the growth, infiltration, and metastasis of solid tumors, and VEGF as well as VEGFR that play important roles in neovascularization, has become key targets of attention in the development of new anticancer drugs [5]. There are 5 subtypes of VEGF, the main factor of which names VEGF-A, B, C, D, E and VEGF-A. VEGFR can be divided into three subtypes: VEGFR1,2,3 and VEGFR2 are the main of them. When VEGFA, C, D bind to VEGFR2 on tumor endothelial cells, a signaling cascade reaction was initiated to promote endothelial cell proliferation and metastasis along with the increased vascular wall permeability, thereby leading to angiogenesis [6]. Ramucirumab, a recombinant human IgG1 monoclonal antibody, functions as an antagonist of VEGFR2, thereby exerting its therapeutic effects in the treatment of various malignancies [7]. It can specifically bind to the extracellular region of VEGFR2 and block the binding between VEGFR2 and its ligands VEGF-A, C, D, thereby inhibiting the activation of VEGFR2 and its downstream signaling pathways, preventing neovascularization and blocking blood supply to tumor cells, ultimately leads to tumor cell apoptosis [8].

Approved by the FDA and EMA in 2011–2012, ramucirumab is authorized for treating gastric and primary liver cancer [9–12]. In April 2014, the FDA issued approval for the standalone application of ramucirumab in treating advanced or metastatic gastric cancer and gastric esophageal junction adenocarcinoma in patients who have experienced disease progression after receiving fluorouracil or platinum-based chemotherapy protocols. Notably, ramucirumab marked a significant milestone as the first-line biological therapy approved specifically for gastric cancer [13]. This regulatory decision was informed by the compelling results of two pivotal clinical trials, namely the REGARD trial (NCT00917384) and the RAINBOW trial (NCT01170663), which demonstrated the efficacy of ramucirumab in the management of advanced or metastatic gastric cancer and gastric esophageal junction adenocarcinoma [14]. The RAINBOW trial, a multinational initiative conducted across various centers, utilized a randomized, double-blind, placebo-controlled phase III methodology to assess the safety and effectiveness of the combination of ramucirumab and paclitaxel compared to paclitaxel alone in a group of 665 individuals with advanced gastric cancer who had undergone prior treatment. The outcomes of this investigation indicated that individuals who were administered the combination of ramucirumab and paclitaxel achieved a median overall survival (OS) of 9.63 m, whereas those in the paclitaxel monotherapy group had a median OS of 7.36 months. In addition, the median PFS of paclitaxel monotherapy was 2.86 months, while combination therapy was 1.54 months higher, reaching 4.40 months. The median TTP for monotherapy is only 4.4 months, while combination therapy can reach 5.5 months. The ORR for monotherapy is 16 %, while the ORR for combination therapy is 28 %. ($P = 0.0001$). The disparities in OS and PFS among the groups were statistically notable, highlighting the efficacy of ramucirumab in treating patients with advanced gastric cancer. A comprehensive network meta-analysis of 33 randomized controlled trials. The purpose is to determine which treatment plan is optimal for resectable cancer patients, assessing the effects of various preoperative, postoperative, and perioperative treatments on overall survival [15]. The study's results demonstrate a notable survival benefit for four specific interventions compared to surgery alone: preoperative chemoradiotherapy, postoperative chemotherapy, perioperative chemotherapy, and postoperative chemoradiotherapy. However, the analysis did not reveal any statistically significant distinctions in overall survival among above indicators. Hence, further investigations are warranted to ascertain the most efficacious treatment strategy for these patients. Currently, there is a lack of research on monoclonal ramucirumab in neoadjuvant transformation therapy for advanced gastric cancer patients. The phase II/III trial evaluating the efficacy of ramucirumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma did not demonstrate a significant difference in pathological response rates [16]. However, the addition of ramucirumab notably boosted R0-resection rates (96 % vs. 82 %, $P = 0.009$) and exhibited a tendency towards enhanced disease-free survival, with no significant impact on overall survival. The escalation in severe postoperative complications prompted the suspension of patient recruitment with Siewert type I tumors due to safety concerns. The study also documented an increase in non-surgical severe adverse events with the combination therapy. Further investigation is essential to assess the impact, including survival outcomes, of integrating ramucirumab into chemotherapies as neoadjuvant conversion therapy for gastric cancer. The purpose of this clinical study is to explore and evaluate the safety and effectiveness of adding ramucirumab to the neoadjuvant and conversion therapy regimen of nab-paclitaxel, lobaplatin, and S-1 for patients.

2. Methods and analysis

2.1. Study design

This research is a prospective study carried out a single-center, utilizing randomization and an open-label approach, with two distinct groups. The particular arrangement is outlined as follows: For Cohort A, individuals diagnosed with advanced gastric or gastroesophageal junction adenocarcinoma will receive neoadjuvant treatment involving nab-paclitaxel, lobaplatin, S-1, and ramucirumab, in contrast to nab-paclitaxel, lobaplatin, and S-1.Cohort B consists of patients with advanced gastric cancer who are initially unresectable or not candidates for radical surgery (R0 resection), and they will receive conversion therapy with nab-paclitaxel, lobaplatin, S-1, and ramuciruma compared with nab-paclitaxel, lobaplatin, and S-1.

2.2. Inclusion and exclusion criteria

The eligibility criteria for participant inclusion in this investigation encompass the following parameters: 1) Patients with stage III or IV (cT3-4N + M0-1) gastric cancer, encompassing those initially deemed unresectable or challenging for R0 resection. Group A consists of individuals identified with advanced gastric or gastroesophageal junction adenocarcinoma through cytological or histopathological examination, necessitating pre-surgery neoadjuvant treatment to lower the chances of recurrence and metastasis. In comparison, Group B encompasses patients diagnosed with either advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma initially deemed inoperable or difficult for complete resection based on cytological or histopathological findings, requiring pre-surgery conversion therapy to facilitate potential surgical interventions. 2) Individuals between the ages of 18 and 75 who have an Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or lower are eligible to participate in the study; 3) Patients should not have received any prior anti-cancer therapies, such as surgery, radiation, chemotherapy, targeted treatment, or immunotherapy; 4) Prior to treatment, organ and bone marrow functions should meet specific criteria within a week, including hemoglobin(>80 g/L), absolute neutrophil count(>1.5 × 109/L), platelet count(>100 × 109/L), no recent blood transfusions, total bilirubin levels within 1.5 times the upper normal limit (ULN), alanine aminotransferase and aspartate aminotransferase within 2.5× ULN (or up to 5× ULN with liver metastasis), serum creatinine within 1.5× ULN or creatinine clearance equal to or greater than 50 mL/min, urinary protein less than 2+, and activated partial thromboplastin time and international standardized ratio below 1.5 × ULN; 5) Patients are anticipated to have a life expectancy exceeding 6 months; 6) Individuals must have the ability and willingness to give written informed consent for their participation in the research. The criteria for exclusion were specified as follows: 1) Excluding patients with a history of various malignant tumors, skin basal cell carcinoma and cervical carcinoma in the past; 2) Patients positive for HER-2 who choose to undergo Herceptin treatment; HER2-negative status was identified by an Immunohistochemistry (IHC) score of 0 or 1+, or a score of 2+ lacking Fluorescence in Situ Hybridization (FISH) amplification. HER-2 positive patients opting for Herceptin therapy; HER2-negative classification encompassed individuals with an IHC score of 0 or 1+, or those with a score of 2+ but lacking Fluorescence in Situ Hybridization (FISH) amplification. 3) Women who are pregnant, nursing, of childbearing age without efficient contraception, or desiring fertility during the study period; Women who are pregnant or breastfeeding, in their reproductive years without adequate contraceptive methods, or those with fertility aspirations throughout the research duration; 4) Patients excluded from participation included those with severe uncontrolled internal illnesses, infections, chronic gastrointestinal conditions, or compromised bowel function. Additionally, individuals with significant organ dysfunction such as heart, lung, liver, and kidney impairment, as well as severe metabolic disturbances affecting drug metabolism, were ineligible. Patients at risk of gastrointestinal bleeding or with abnormal coagulation function (INR>1.5) were also excluded. Furthermore, individuals with ongoing HBV or HCV infections and those experiencing peripheral neuropathy at NCT-CTCAE Level 2 or higher were not eligible for the study. The study objectives encompass: 1) Unacceptable adverse responses or significant adverse incidents verified by the investigators; 2) After considering from the perspective of maximizing patient benefits, the researcher/clinical physician decides to terminate treatment; 3) Voluntary withdrawal of informed consent by patients; 4) Patients dropped out; 5) Patient fatality.

2.3. Dosage regimen

The medication cycle for patients in both experimental groups is three weeks, with the first two weeks of administration and a one week pause in between. At the beginning of each cycle, ramucirumab (8 mg/kg), lobaplatin (30 mg/m^2), and nab-paclitaxel (100 mg/m^2) are administered intravenously, along with oral administration of S-1. The dosage is determined by body surface area (<1.25 m^2 - 40 mg; 1.25–1.5 m^2 - 50 mg; >1.5 m^2 - 60 mg). The patients in the control group, except for those who did not receive infusion of ramucirumab, had the same dosage and medication cycle as the experimental group.

2.4. Sample size calculation

The sample size estimation was conducted using the PASS 11.0 software. The primary efficacy endpoint in this study is the rate of pCR. It was reported that the pCR rates of preoperative neoadjuvant chemotherapy and conversion therapy of advanced gastric cancer patients were approximately 4.8–10 %, therefore the pCR rate of the control group is estimated to be 10 %. It was also reported that the pCR rate of advanced cancer patients receiving a combination of chemotherapy and targeted therapy is around 20 %, therefore the pCR rate of the experimental group is estimated to be 20 %. After the selection criteria are determined, patients who meet the selection criteria will be randomly assigned to the experimental group and control group in a 1:1 ratio We set unilateral 0.025 as the testing level

and the confidence level is set as 80 %. After calculated by PASS11.0 software, the sample size for each group is estimated as 58 cases and the total sample size is estimated as 116 cases. Within the study, Cohort A will consist of 58 participants, evenly divided with 29 individuals in both the experimental and control groups. Similarly, Cohort B will also enroll 58 participants with the same distribution. Accounting for a predetermined dropout rate of 20 %, the final target enrollment is set at 140 cases. Consequently, each cohort will aim to enroll 70 cases, with an equal distribution of 35 patients in the experimental group and 35 patients in the control group. SAS software was used to generate a randomized table of participants using block randomization method. During the trial, the random numbers will be selected in order of screening numbers, and the corresponding envelopes will be opened based on the random numbers to obtain the grouping results.

2.5. Blind method

Although this trial was designed as open label, other independent researchers who conducted the imaging evaluation will be in a blinded state in the imaging evaluation phase for reducing the evaluator bias.

2.6. Efficacy assessment indicators

The main effectiveness evaluation is the pCR of the tumor subsequent to neoadjuvant or transformation therapy, evaluated through pathological response grading (TRG) as a marker of tumor regression according to the patient's postoperative pathological findings. Supplementary effectiveness indicators encompass the rate of complete R0 resection following therapy, occurrences of AE, PFS, OS, ORR, overall response rate and duration, rate of DCR, and length of DOR. For patients without disease progression or death at analysis, the last tumor assessment date serves as the cutoff. Patients lost to follow-up are documented by days based on the last follow-up time, while survivors at data analysis are recorded using their last follow-up while alive.

PFS is the time from ramucirumab initiation to disease progression or death, per RECIST v1.1. OS is from enrollment to any cause of death. ORR is the total response rate (partial + complete response) assessed by RECIST 1.1 criteria. DCR is the percentage of CR, PR, and SD. DOR is from first objective remission to disease progression or death, per RECIST v1.1. The safety measure includes adverse events and the occurrence of adverse drug reactions post-administration. Adverse events pertain to negative medical incidents during clinical trials following patient medication intake. This study will encompass adverse events irrespective of their link to the treatment, from patient consent signing until a month post-treatment completion. Adverse events will be categorized and documented throughout the study and follow-up period in accordance with NCI CTCAE (version 5.0). Assessment of toxicity will consider severity, causality, grading, and actions taken regarding experimental treatment. All adverse events, such as drug-related reactions, peripheral neuropathy, bone marrow suppression, and liver or kidney dysfunction, will be recorded and evaluated.

2.7. Data collection and observation indicators

All participants will undergo a thorough clinical and laboratory assessment encompassing tumor size, quality of life, survival duration, and hematological and biochemical parameters. Baseline information, including gender, age, contact details, comprehensive medical, medication, and drug allergy histories, ECOG performance status, BMI, blood cell counts, liver and kidney function tests, will be documented. CT/MRI will be performed on the patient's chest, abdomen, and pelvis within 21 days before treatment. PET examination will not be performed as a routine imaging assessment. Suspected lesions will be evaluated through imaging examinations, and there may be some adverse reactions during treatment, such as nausea, vomiting, diarrhea, and abdominal discomfort. The efficacy evaluation is every three cycles.

2.8. Follow-up

Treatment follow-up: Each treatment cycle occurs every 21 days. After every 3 cycles, ultrasound gastroscopy and imaging tests (enhanced CT or MRI of the chest, abdomen, and pelvis) will assess tumor progression.

Safety monitoring: The safety monitoring phase spans from the commencement of treatment to 90 days post the final dose. It primarily involves gathering patient blood test results and adverse event data. In case of unplanned follow-up necessitated by adverse events, details regarding type, timing, severity, and management of adverse reactions will be documented. Patients experiencing unresolved adverse effects will receive close monitoring and treatment until they reach NCI CTCAE V5.0 first-degree recovery or full resolution. Survival monitoring: Survival assessments will occur once every 3 cycles until patients' decease, with the cause and date of death recorded for OS calculation. The survival follow-up primarily focuses on tracking disease progression (date of progression) and subsequent anti-tumor therapies until the patient's passing. Follow-up evaluations will include blood tests, tumor markers (serum AFP, CEA, CA19-9, CA125), and imaging tests (enhanced CT or MRI of the chest, abdomen, and pelvis) to collect and analyze survival status. Long-term post-treatment monitoring: Patients will undergo follow-ups every 3 months during the first and second-year post-medication completion, every 6 months ($\pm$14 days) in the third to fifth years, and annually thereafter to gather survival data and any relevant subsequent examination findings. The trial will conclude once the median follow-up period extends to 36 months.

2.9. Definition of the analytical dataset

Full Analysis Set: Following the intention-to-treat (ITT) principle, efficacy analysis includes all patients who underwent drug

treatment and administered the drug at least once. In instances where the entire treatment process was not observed, the last observation data will be extrapolated to the final study outcome (LOCF) Per Protocol Set: This set comprises cases that adhere to the study protocol, demonstrate good compliance, refrain from consuming prohibited medications during the study period, and fulfill the required content in the case report form. Safety Analysis Set: The safety analysis set will include all participants who have been administered the study medication at least once and have documented safety profiles post-medication. This specific dataset will be utilized for conducting safety analyses throughout the study.

2.10. Data management

The researcher completes the case report form, following which data entry and management activities are conducted upon reviewing the form. Researchers must verify the data's accuracy. Subsequently, the principal researchers and statistical analysts will finalize the data after confirming its correctness. Once locked, the data file will remain unaltered. To safeguard patient privacy, codes will substitute the patient's names. Key investigators, data administrators, statisticians, and auditors will select the dataset for analysis.

2.11. Statistics

Statistical analyses will utilize SAS 9.4 or a more recent version. The data will be described statistically using either the mean $\pm$ standard deviation or median (range). Frequency and percentage will represent counting data, with group differences compared using chi-square tests. Survival rates for time-event data will be estimated using Kaplan-Meier, and intergroup differences will be assessed with the log-rank test. Survival curves will also be generated. All statistical tests will be two-sided, with statistical significance defined as a P value ≤ 0.05, and a 95 % confidence interval will be employed. For the main efficacy indicator pCR, the Clopper Pearson method will be used to calculate the 95 % CI of each group's rates and the Miettienen Nurminen method will be used to calculate the 95 % CI of the inter group (experimental group-control group) rate difference. If the lower limit of the 95 % CI of the rate difference is greater than 0, it indicates that the experimental group is superior to the control group.

For adverse events, statistical descriptions will be made using the number of occurrences and incidence rate. The cumulative occurrence rate of serious adverse events will be calculated. For the severity of adverse events, if the same patient experiences the same adverse event multiple times, the most severe one will be included in the analysis; if different adverse events occur in the same patient, the most severe adverse event will be included in the analysis.

The analysis of adverse events will be based on the safe treatment analysis set, and data analysis will be included but not be limited to calculating the incidence and frequency of adverse reactions by grouping. A detailed list of patients with various adverse events will provide.

3. Ethics statement

Ethics approval has been obtained from the Ethics Committee at the First Affiliated Hospital (Xijing Hospital) of Air force Military Medical University (KY20232220–F-1). The investigator must thoroughly explain the study's purpose, procedures, potential advantages, and risks to each potential participant or their legal representative to secure signed informed consent forms before enrollment. Participants will be notified of their prerogative to discontinue participation in the study at any juncture, ensuring the preservation of their personal privacy and the confidentiality of their data throughout the research process. Explicit written consent will be mandatory for all participants, with a guarantee of the confidentiality of their personal information. This trial is registered on ClinicalTrials.gov: NCT06169410 (registration date: December 5, 2023).

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Juan Wang: Writing – original draft. **Guanghui Xu:** Investigation. **Shushang Liu:** Investigation. **Yuxuan Ma:** Investigation. **Shu Wang:** Investigation. **Mengbin Li:** Investigation. **Yan Zhao:** Investigation. **Haoyuan Wang:** Investigation. **Yuhao Wang:** Investigation. **Chaosheng Peng:** Conceptualization. **Huade Huo:** Investigation. **Haolin Li:** Investigation. **Gang Ji:** Conceptualization. **Jianjun Yang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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