Study Protocol

Preoperative administration of camrelizumab combined with chemotherapy for borderline resectable esophageal squamous cell carcinoma (BRES-1): study protocol of a single-arm, open-label, phase II study

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Background: The prognosis and first-line treatment response of patients with borderline resectable esophageal squamous cell carcinoma (ESCC) are unsatisfactory. We are conducting the borderline resectable esophageal squamous (BRES-1) study to evaluate the safety and efficacy of camrelizumab combined with chemotherapy in patients with borderline resectable ESCC.

Methods: A total of 30 patients with borderline resectable ESCC will be enrolled in the BRES-1 study. These patients will undergo three stages of treatment: neoadjuvant therapy, surgery, and adjuvant therapy. Preoperative therapies will include camrelizumab, cisplatin, and nab-paclitaxel. Preoperative therapies will include camrelizumab, which will be given every 3 weeks for 6 weeks at a dose of 200 mg (baseline weight <50 kg, 3 mg/kg), nab-paclitaxel (130 mg/m^2 on days 1 and 8 of one period with 21 days, a total of two cycles), and cisplatin (75 mg/m^2 on day 1 of one period with 21 days, a total of two cycles). Patients will undergo esophagectomy 3–6 weeks after completing the neoadjuvant treatment. Three weeks after surgery, camrelizumab combined with chemotherapy will continue to be used for two cycles of maintenance therapy. Then, only camrelizumab will be administered for an entire year. The primary endpoint of this study will be pathological complete response (pCR).

Discussion: The BRES-1 trial will evaluate the efficacy and safety of camrelizumab combined with chemotherapy for patients with borderline resectable ESCC. Translational research will explore perioperative complications and drug-related adverse events (AEs).

Trial Registration: ChiCTR, ChiCTR2200056728. Registered 11 February 2022. https://www.chictr.org.cn/index.aspx.

Keywords: Esophageal squamous cell carcinoma (ESCC); chemotherapy; neoadjuvant therapy; immunotherapy; esophagectomy

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Introduction

Esophageal cancer is the seventh most commonly diagnosed cancer and the sixth most common cause of cancer-related mortality worldwide (604,000 new cases and 544,000 deaths in 2020) (1). China has a high incidence of esophageal cancer, and more than 50% of the new cases of esophageal cancer worldwide occur in China. Ninety percent of esophageal cancers are esophageal squamous cell carcinomas (ESCCs) (2). The onset of esophageal cancer is insidious, and most patients who receive treatment are in the middle or late stages of disease with obvious obstruction symptoms that limit surgical treatment.

Currently, the treatment options for esophageal cancer include preoperative neoadjuvant therapy, surgery, and postoperative adjuvant therapy. Many studies have been carried out on the treatment of esophageal cancer. The results of the OEO2 study showed that preoperative neoadjuvant chemotherapy significantly improved the prognosis of patients with esophageal cancer (5-year survival rate of 23%) (3,4). Moreover, the JCOG9204 study demonstrated that postoperative chemotherapy did not significantly improve overall survival (OS) (5). The JCOG9907 study established the therapeutic value of neoadjuvant chemotherapy by comparing the efficiency of preoperative and postoperative chemotherapy (6). The results of both the CROSS study [pathological complete response (pCR) rate, 49%] and the NEOCRTEC5010 trial (median OS time, 100.1 months; pCR rate, 43.5%) showed that neoadjuvant chemoradiotherapy significantly improved OS and the pCR rate in patients with esophageal cancer (7,8). There is evidence that neoadjuvant chemoradiotherapy has a greater pCR rate than neoadjuvant chemoradiotherapy, but satisfactory survival benefits have not been achieved (9-12). The NeoRes1 trial concluded that although chemoradiotherapy increased the pCR rate, it did not translate into a long-term survival advantage [5-year OS and disease-free survival (DFS) were not significantly different], so the authors did not recommend concurrent radiotherapy and neoadjuvant chemotherapy (13).

Advances in research and treatment, for example, immunotherapy, have promoted new opportunities for treating esophageal cancer. Recent data indicate that immunotherapy significantly benefits patients with esophageal cancer. Phase II clinical trials of neoadjuvant immunotherapy are actively underway worldwide. The ESCORT study revealed the excellent efficacy and safety of camrelizumab as a second-line treatment for esophageal cancer (14). The NICE trial made significant progress regarding neoadjuvant immunization and chemotherapy treatment modes (15). The pCR rate of patients included in this study reached 45.4% after neoadjuvant therapy. This excellent result adds new solid evidence for neoadjuvant immunotherapy for esophageal cancer.

Borderline resectable esophageal carcinoma (BREC) is defined as a tumor with suspected invasion of adjacent organs (such as the aorta, trachea or vertebrae) that is not definitively diagnosed as cT4b. The optimal treatment strategy for patients with BREC remains to be determined. We have designed a single-arm, open-label phase II trial to evaluate the efficacy and safety of camrelizumab combined with chemotherapy for treating BREC patients. We present this article in accordance with the SPIRIT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1851/rc).

Methods

Trial design

This is a single-center, single-arm, and open-label prospective phase II study of patients with BRECs on imaging. This study was initiated in December 2020. The first subject was enrolled in February 2021. Participants are still being recruited for the study, and the study is expected to be completed in February 2025.

Endpoints of the study

The primary endpoint of this study will be the pCR rate to neoadjuvant therapy in patients with borderline resectable ESCC. A pCR will be recorded when a surgical resection specimen contains no viable tumor cells (ypT0N0M0).

The secondary endpoints will be (I) major pathological response (MPR), which will be recorded when 10% or fewer viable tumor cells are observed in the surgical resection specimen (16); (II) OS and DFS; and (III) the conversion rate of surgery and R0 resection rate. R0 resection will be defined as a negative proximal, distal, or circumferential resection margin (17,18). The quality of life and nutritional status of patients will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and EORTC QLQ EC questionnaire (OES18) (19,20).

The safety evaluation will include any adverse events (AEs) associated with neoadjuvant therapy and perioperative

complications. Safety assessment results mainly refer to AEs related to neoadjuvant therapy, including immune-associated pneumonia, allergic rash, atrial fibrillation, anemia, leukopenia, thrombocytopenia, nausea, vomiting, and diarrhea, which will be recorded along with the time of occurrence, severity, relationship with the study drug, duration, action taken and outcome. Postoperative complications include anastomotic leakage, recurrent laryngeal nerve injury, atelectasis, pleural effusion, and arrhythmia. Postoperative complications will be reported and classified based on the Clavien-Dindo system (21).

Pathological evaluation

Pathological reports will describe tumor size, the extent of tumor invasion, resection margin, overall number of positive lymph nodes dissected, grade of tumor regression, and stage of differentiation. Postoperative pathological staging will be defined according to the American Joint Committee on Cancer criteria for esophageal cancer (8^{th} edition) (22). Pathological reactions will be graded according to the College of American Pathologists (CAP) criteria and evaluated in all resected specimens (23). To assess and grade the response of esophageal tumors, the extent of residual disease will be classified into the following four categories: grade 0, no residual cancer cells (pCR); grade 1, single cells or small groups of cancer cells; grade 2, residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells; and grade 3, extensive residual cancer with no apparent tumor regression.

Sample size calculation

This study will be a differential trial, and pCR will be used as the primary endpoint. Pass15 software will be used to calculate the sample size with a two-sided significance level of 5% and 80% test efficiency. Assuming that the pCR associated with anti-programmed cell death 1 (PD-1) treatment combined with preoperative chemotherapy is 28% (24), the sample size will be 27 patients. To account for an expected drop-out rate of approximately 10%, we aim to enroll 30 patients.

Eligibility criteria

Patients with BREC (with suspected involvement of peripheral organs but not definitive cT4b tumors) will be enrolled in this study. Positive programmed cell death ligand 1 (PD-L1) expression will not be mandatory for enrollment. The detailed inclusion criteria are as follows:

- Histologically confirmed ESCC, with BREC;
- Thoracic or abdominal esophageal carcinoma and metastasis to lymph nodes confined to regional lymph nodes (Japanese Classification of Esophageal Cancer, 11^{th} edition) (25);
- Age ranging from 18 to 70 years;
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1;
- Expected survival time of more than 12 weeks;
- Normal major organ function met the following criteria:
  - (I) Routine biological tests:
    - Hemoglobin (HB) ≥90 g/L;
    - Absolute neutrophil count (ANC) ≥1.5×10^9/L;
    - Platelet (PLT) ≥80×10^9/L;
  - (II) Biochemical tests:
    - Albumin (ALB) ≥30 g/L;
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 upper limit of normal (ULN); if there are liver metastases, ALT and AST ≤5 ULN;
    - Total bilirubin (TBIL) ≤1.5 ULN;
    - Creatinine (Cr) ≤1.5 ULN or Cr clearance (CCr) ≥60 mL/min;
- Evaluation by echocardiogram: left ventricular ejection fraction (LVEF) ≥50%;
- Voluntary patient enrollment in the study and signed informed consent with good compliance and follow-up.

Patients who do not meet the above inclusion criteria will be excluded. Additional exclusion criteria are as follows:

- Hypersensitivity or metabolic disorder to paclitaxel and cisplatin;
- Presence of brain metastases;
- Presence of any active autoimmune disease or a history of autoimmune disease (such as but not limited to autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, and hyperthyroidism), and presence of asthma requiring medical intervention with bronchodilators, (patients with asthma with complete remission in childhood and without any intervention in adulthood will not be included);
- Current use of immunosuppressants or systemic hormone therapy for immunosuppression purposes (dose >10 mg/d of prednisone or other equivalent hormones) and continued use within 2 weeks before enrollment;

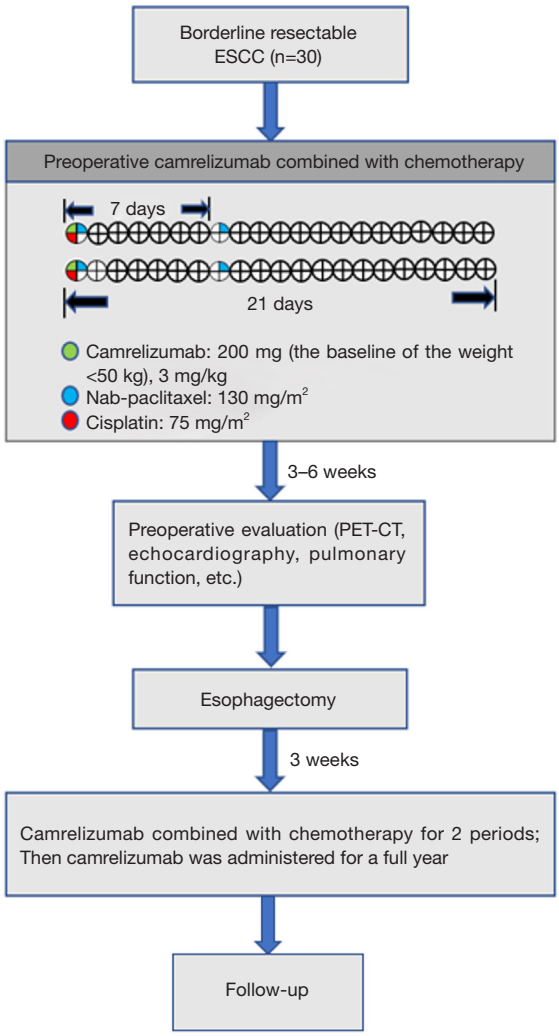

Figure 1 Flowchart of preoperative camrelizumab combined with chemotherapy for borderline resectable ESCC. ESCC, esophageal squamous cell carcinoma; PET-CT, positron emission tomography-computed tomography.

- The presence of any severe or uncontrolled disease, including poor blood pressure control (systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100 mmHg); grade I or higher myocardial ischemia or infarction, arrhythmias (including QT interval ≥480 ms), and grade I cardiac insufficiency;

❖ Active or uncontrolled severe infection;
❖ Liver diseases such as decompensated liver disease, active hepatitis B, and active hepatitis C;
❖ Urine protein ≥ ++ by routine urine test and confirmed 24-hour urine protein level greater than 1 gram;
❖ Women who are pregnant or breastfeeding;
❖ Presence of other malignancies within 5 years (except cured basal cell carcinoma of the skin and carcinoma in situ of the cervix);
❖ A history of psychotropic drug abuse without cessation or the presence of mental disorders;
❖ Participation in other drug clinical trials within 4 weeks.

Baseline evaluation

Before enrollment and the initiation of neoadjuvant therapy, a baseline assessment will be scheduled for each patient to stage the disease and exclude brain metastases and any other exclusion-related factors. The evaluation will include physical examination, upper gastrointestinal (GI) endoscopy, tumor biopsy (if not previously examined), endoscopic ultrasonography, positron emission tomography (PET)-computed tomography (CT), enhanced chest CT, routine blood tests, pulmonary function, electrocardiogram, and echocardiography.

Neoadjuvant treatment

Preoperative treatment will consist of immunotherapy and chemotherapy (*Figure 1*). Camrelizumab at a dose of 200 mg will be given every 3 weeks for 6 weeks. For patients weighing less than 50 kg, camrelizumab will be administered at 3 mg/kg. Two cycles of chemotherapy will be administered and will include cisplatin (75 mg/m^2 on day 1 of each 21-day cycle) and nab-paclitaxel (130 mg/m^2 on days 1 and 8 of each 21-day cycle).

For chemotherapy-related AEs during neoadjuvant therapy, clinical observation, dose adjustment, suspension of chemotherapy and symptomatic treatment will be carried out based on the type and severity of the AEs and a discussion among multidisciplinary experts. Dose adjustment of camrelizumab will not be recommended as a response to immune-related AEs. After the completion of neoadjuvant therapy, physical examination, routine blood tests, enhanced chest CT, PET-CT, echocardiography, pulmonary function assessment, and electrocardiogram will be performed to reassess the disease status and rule out any surgical contraindications.

Surgery

Surgery will be arranged 3 to 6 weeks after the completion

of neoadjuvant therapy. Surgical procedures will include open or minimally invasive esophagectomy (video-assisted or robot-assisted esophagectomy) with two- or three-field lymphadenectomy. McKeown esophagectomy will be performed for each patient.

Adjuvant treatment

Three weeks after surgery, two 21-day cycles of maintenance therapy will be continued with camrelizumab combined with chemotherapy. Then, maintenance treatment will be continued with camrelizumab (every 2 weeks) for an entire year.

Follow-up

Postoperative follow-up will be arranged according to the National Comprehensive Cancer Network (NCCN) guidelines for esophageal cancer (26). Follow-up visits will be performed by the study center every 3 months during the first year and every 6 months thereafter until death or the end of the study. Chest CT is required for all patients and the following parameters will be recorded during the follow-up period: survival, time to disease progression or death, other oncologic treatments, and serious AEs (SAEs) occurring during the study.

AEs

AEs are defined as any adverse medical event that occurs in a subject or clinical trial subject after receiving a drug or treatment regimen but are not necessarily causally related to the treatment. SAEs will refer to medical circumstances that require hospitalization or prolonged hospitalization, disability, affect workability, endanger life or death, or lead to congenital malformations during clinical trials. All events (AEs and SAEs) will be recorded from the time of signing the consent form to 30 days after the last use of the drug.

In this study, we will record all AEs and their severity, duration, treatment measures, and outcomes. We will follow up on these AEs regularly until the patients return to normal or the study ends.

Statistical analysis

Descriptive statistics (proportions with 95% confidence intervals) will be used to summarize the endpoints of pCR, MPR, the conversion rate of surgery, and the R0 resection rate. AEs and perioperative complications will be analyzed using multivariate logistic regression. *T*-tests for two independent samples will be used to determine whether there is a difference in quality-of-life scores between patients before and after treatment. A two-sided significance level of 5% will be used.

Ethics approval for the research

The study will be conducted following the protocol, legal and regulatory requirements, and the general principles outlined in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Council for Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki (as revised in 2013). The study has been reviewed and approved by the Ethics Committee of Zhengzhou University School of Medicine (No. L2021-Y079-008). All patients enrolled and their families provided written informed consent. Participants recruited in the future will also be required to provide informed consent.

Data access statement

Jiangsu Hengrui Medicine Co., Ltd. and Shijiazhuang Pharmaceutical Company will provide the data supporting this study's findings. Subject to specific criteria, conditions, and exceptions, they may also provide access to related individual deidentified participant data. By obeying the current laws and regulations, they take great precautions to ensure the privacy of their clinical trial participants.

Discussion

Neoadjuvant therapy for esophageal cancer mainly includes neoadjuvant chemoradiotherapy, neoadjuvant chemotherapy, neoadjuvant immunotherapy combined with chemoradiotherapy, and neoadjuvant immunotherapy combined with chemotherapy. The exploration of neoadjuvant therapy modes is ongoing. As early as 2002, the OEO2 study confirmed the significant advantage of neoadjuvant chemotherapy for the long-term survival of esophageal cancer patients (3). The JCOG9024 study and the JCOG9907 study further established the role of neoadjuvant chemotherapy in esophageal cancer (5,6). In recent years, with the findings of the CROSS study and

the 5010 study, the status of neoadjuvant radiotherapy combined with chemotherapy for esophageal cancer has dramatically improved; it has become the standard neoadjuvant treatment for esophageal cancer and has been included in esophageal cancer treatment guidelines (7,8).

The NeoRes1 study further explored whether adding radiotherapy to neoadjuvant chemotherapy could improve patients' long-term survival (13). Although neoadjuvant chemoradiotherapy improved the pCR rate compared with that of neoadjuvant chemotherapy, this improvement did not translate to a benefit in long-term survival. In addition, the preferred population for radiotherapy does not include all patients. For example, in patients with multisite or even extensive lymph node metastasis, the radiation area is too large, which may increase the incidence of radiation-related complications. In addition, radiotherapy can lead to fatal complications such as esophagotracheal or aortic fistulas in patients with tumors invading the trachea or thoracic aorta. Furthermore, studies such as the CALGB-9781 study and the CROSS study showed that there was still a high risk of distant recurrence and metastasis after neoadjuvant chemoradiotherapy (7,27). These results indicate that the intensity of systematic treatment is insufficient to cure this disease. All these factors suggest that neoadjuvant chemoradiotherapy may have certain defects, or in some selective populations, the treatment mode of neoadjuvant chemoradiotherapy may not be ideal.

Immunotherapy is a promising new treatment option for esophageal cancer. Perioperative data from many phase II clinical studies related to neoadjuvant immunotherapy are emerging. The PALACE study (pCR rate, 55.6%) and the NICE study (pCR rate, 45.4%) suggest a significant advantage of immunotherapy combination regimens in neoadjuvant therapy for esophageal cancer (15,28). Based on the currently reported data of neoadjuvant immunotherapy for esophageal cancer, the pCR rates vary from 19% to 55.6%, with inevitable fluctuations in different treatment regimens. These differences are mainly reflected in the following aspects: (I) the treatment mode of neoadjuvant therapy (neoadjuvant immunotherapy combined with radiotherapy and chemotherapy, neoadjuvant immunotherapy combined with targeted therapy or chemotherapy, neoadjuvant immunotherapy combined with chemotherapy, etc.) and (II) the chemotherapy regimen, which can differ from one clinical study to another. Immunotherapy drugs also differed between studies. Finally, the baseline status of the patients included in each study varied. In addition, Osorio *et al.* showed that the GI tract is one of the most responsive organ systems to immunotherapy (29). The results. This indicates that the esophagus may have a high immunotherapy response rate.

Several preclinical trials have demonstrated synergistic effects between immunotherapy and chemotherapy (30-32). Conventional chemotherapy can lead to DNA damage in tumor cells, increasing the presentation of tumor-associated antigens and promoting the recruitment of antigen-presenting cells (33,34). It may also lead to the destruction of the original immune cells and to T-cell remodeling, which helps reshape the immune response of T cells to malignant tumors (32). PD-1 is a coinhibitory receptor that is highly expressed on several immune cells including activated T cells, B lymphocytes, and natural killer cells. PD-L1 is one of its ligands. The binding of PD-1 to PD-L1 inhibits the activation of T cells around tumors (35,36). PD-1/PD-L1 immune checkpoint inhibitors (ICIs) are a new approach to treating esophageal cancer. The results of animal experiments showed that the survival time of mice treated with neoadjuvant immunotherapy was longer than that of mice treated with adjuvant immunotherapy (37). This finding suggested that neoadjuvant immunotherapy is superior in comparison. After immunotherapy, significant T-cell mobilization occurs in the tumor-draining lymph nodes. The removal of lymph nodes in the drainage area will terminate the lymphocyte invasion of the tumor. At the same time, surgical stress and anesthesia can support a state of immunosuppression in the body, increasing the risk of tumor recurrence and metastasis (38). Surprisingly, a study on adjuvant immunotherapy (CheckMate577) for esophageal cancer treatment has reached its primary endpoint (39). The findings confirm the effectiveness of adjuvant therapy at the clinical level. Therefore, we can conclude that neoadjuvant immunotherapy plays a more critical role than adjuvant therapy. In this clinical study, neoadjuvant and adjuvant immunotherapies will be included in the research protocol.

Based on the above considerations, immunotherapy combined with chemotherapy may have certain advantages in selected patients. This study aims to explore the safety and efficacy of immunotherapy combined with chemotherapy for the treatment of BRECs.

Strengths and limitations

The response to neoadjuvant immunochemotherapy has not been shown to be inferior to the response to concurrent chemoradiotherapy. The proposed trial will provide insights

into a new treatment option for patients with BREC that will overcome the complications caused by radiotherapy. Therefore, this study will be limited to patients with BREC. Long-term follow-up data on immunotherapy for esophageal cancer patients will be collected. However, due to the specific features of the patients in this study, the results of tumor staging for a given tumor may differ among clinicians, and the difficulty of diagnosis is considered one of the limitations of this study.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1851/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1851/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1851/coif). J.L. reports that this study was funded by the Jiangsu Hengrui Medicine Co., Ltd. The other 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. The study will be conducted following the protocol, legal and regulatory requirements, and the general principles outlined in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Council for Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki (as revised in 2013). The study has been reviewed and approved by the Ethics Committee of Zhengzhou University School of Medicine (No. L2021-Y079-008). All patients enrolled and their families provided written informed consent. Participants recruited in the future will also be required to provide informed consent.

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