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Phase II Trial of Neoadjuvant Chemotherapy using Triplet without Radiotherapy for Borderline Resectable Advanced Rectal Cancer in Japan (NEUTRAL Trial)

Kinuko Nagayoshi[1], Shuntaro Nagai[1], Yoshihiko Sadakari[1], Hayato Fujita[1], Kenji Tsuchihashi[2], Tatsuya Manabe[3], Yoshitaka Tanabe[4], Takashi Ueki[5], Eishi Baba[6] and Masafumi Nakamura[1*]

[1]Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[2]Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[3]Department of Surgery, Faculty of Medicine, Saga University, Saga, Japan

[4]Department of Surgery, Kitakyushu Municipal Medical Center, Fukuoka, Japan

[5]Department of Surgery, Hamanomachi Hospital, Kitakyushu, Japan

[6]Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

[*]Corresponding author: Masafumi Nakamura, Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, Tel: +81-92-642-5441; Fax: +81-92-642-5458; E-mail: mnaka@surg1.med.kyushu-u.ac.jp

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Abstract

We are conducting a multicenter phase II prospective study to evaluate the safety and efficacy of neoadjuvant chemotherapy using FOLFOXIRI without radiotherapy for patients with borderline resectable locally advanced rectal cancer. The primary endpoint is complete resection (R0) rate. R0 rate is evaluated as the absence of residual tumor after surgery, as determined by macroscopic and microscopic findings. Secondary endpoints are: completion rate of scheduled treatment, objective response rate, rate of early tumor shrinkage, pathological response rate, down-staging rate, overall survival, disease-free survival, local recurrence rate, sphincter-preserving rate, state of conducting adjuvant chemotherapy, adverse events defined by Common Terminology Criteria for Adverse Events version 3.0 and postoperative complication. Thirty patients are required for this study.

Objective

A multicenter phase II prospective study to evaluate the safety and efficacy of neoadjuvant chemotherapy using FOLFOXIRI without radiotherapy for patients with borderline resectable locally advanced rectal cancer.

Keywords: Chemotherapy; radiotherapy; rectal cancer

Introduction

Total mesorectal excision (TME) is established as a standard procedure for rectal cancer that can achieve lower local recurrence rates compared to conventional surgery [1]. However, locally advanced rectal cancer often occupies the narrow pelvic space and invades surrounding organs, resulting in macroscopic or microscopic residual tumor of the resected margin that causes local recurrence. Borderline resectable rectal cancer, defined as locally advanced rectal cancer of stage cT4 and/or cN2/3 based on thin-sliced magnetic resonance imaging (MRI) assessment, has been recognized as high risk for local recurrence and poor survival [2-4]. Thus, effective adjuvant therapy for prevention of local recurrence is greatly needed and has been and assessed in treatment of locally advanced rectal cancers, such as borderline resectable cancer. In Western countries, neoadjuvant radiotherapy (NRT) and neoadjuvant chemoradiotherapy (NCRT) followed by TME is a standard treatment for stage II/III locally advanced rectal cancer [5]. NCRT significantly reduces local recurrence, although the survival benefit remains unclear [6-8]. In Japan, NRT and NCRT are not commonly used because of a lack of radiotherapy-specialized facilities and radiation oncologists compared with Western countries. Additionally, a previous study conducted in Japan revealed that extended lymphadenectomy, including lateral pelvic lymph node dissection following TME for advanced lower rectal cancer, could reduce local recurrence and improve survival rate [9]. Because of this, a treatment strategy of surgery followed by adjuvant chemotherapy is widely used in Japan. However, NRT or NCRT as neoadjuvant therapy is being used at a limited number of facilities in Japan.

In recent years, anticancer chemotherapy for the treatment of colorectal cancer has undergone beneficial developments; and mean survival rates for unresectable and recurrent colorectal cancer have significantly improved over the last ten years. Use of chemotherapy combined with an appropriate monoclonal antibody has become a standard in the initial treatment for metastatic colorectal cancer [10-13]. Several studies have demonstrated improved survival and tumor response rate using a triplet regimen with bevacizumab compared with a doublet regimen and bevacizumab in metastatic settings [14-16]. The randomized phase III TRIBE study showed that treatment with fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) plus bevacizumab significantly improved progression-free survival (12.1 months versus 9.7 months, respectively; HR, 0.75, p=0.003) and the rate of metastatic tumor resection (65% versus 53%, respectively, p=0.006); and demonstrated improvement in overall survival (29.8 months versus 25.8 months, respectively; HR, 0.80,

p=0.03) compared with results using fluorouracil, leucovorin and irinotecan (FOLFIRI) plus bevacizumab in a previous phase III trial. Additionally, treatment with FOLFOXIRI had an acceptable toxicity profile [15,17]. Sub-group analysis suggested that the benefit from FOLFOXIRI plus bevacizumab was consistent regardless of molecular status of RAS and BRAF [15]. In the phase II OLIVIA trial, overall resection rate was significantly increased in the FOLFOXIRI plus bevacizumab arm compared with modified regimen using fluorouracil, leucovorin and oxaliplatin (mFOLFOX6) plus bevacizumab arm (61% versus 49%, respectively) in patients with initially unresectable colorectal liver metastases. This led to an improved R0 resection rate of metastatic tumors (81% versus 62%, respectively) and progression-free survival (18.6 months versus 11.5 months, respectively; hazard ratio: 0.43) [16]. These results suggest that a strong treatment, such as a triplet regimen with bevacizumab, may represent a new treatment option aimed at converting unresectable cancer to curative resection by reducing the size of metastatic tumors in colorectal cancer patients; and that this treatment strategy could be used for treating primary tumors.

In contrast to local recurrence, distant recurrence after curative surgery strongly influences the prognosis of stage II/III rectal cancer [18]. Adjuvant chemotherapy has been demonstrated to improve long-term disease-free survival rates in patients with resected stage II/III colorectal cancer. This treatment could eradicate micrometastases and reduce distant metastases, resulting in improved outcomes. A neoadjuvant strategy using intensive systemic chemotherapy that is effective for tumor shrinkage may contribute to reduction of both local and distant recurrence after surgery. A triplet regimen combined with bevacizumab is suggested to result in both better tumor response rates and resection rates than a doublet regimen combined with bevacizumab [16] or a triplet regimen without bevacizumab [19] for treatment of metastatic liver tumors. However, a previous study aimed at volume reduction of primary tumor (N-SOG 03) using a doublet regimen plus bevacizumab for locally advanced rectal cancer showed that bevacizumab increased adverse effects and severe postoperative complications such as perforation, delayed wound healing and anastomotic leakage [20]. Adding bevacizumab to the treatment regimen as neoadjuvant therapy for primary tumors requires further careful investigation. Thus, we considered that an intensified neoadjuvant chemotherapy using a triplet regimen without bevacizumab; which is expected to both decrease local recurrence through tumor reduction, similar NRT or NCRT, and prevent micro metastases resulting from distant metastases; could be performed safely in the perioperative period for primary tumors. This treatment may give a survival benefit, considering there would be no risk of complications induced by radiotherapy such as sexual and voiding dysfunctions, intestinal and defecation problems and secondary carcinogenesis. We designed the present study to confirm the safety and efficacy of neoadjuvant FOLFOXIRI therapy without radiotherapy for borderline resectable rectal cancer.

The institutional review board of each participating center approved the study protocol.

This study was registered at the UMIN Clinical Trial Registry as UMIN 000032871

Study protocol

Purpose

This study is designed to assess the safety and efficacy of neoadjuvant chemotherapy using FOLFOXIRI without radiotherapy for borderline resectable advanced rectal cancer.

Study setting

The study is a multi-institutional prospective phase II study.

Endpoints

The primary endpoint is complete resection (R0) rate. R0 rate is evaluated as the rate at which treatment results in the complete absence of any residual tumor after surgery, as determined by macroscopic and microscopic findings.

Secondary endpoints are completion rate of scheduled treatment, objective response rate, rate of early tumor shrinkage, pathological response rate, down-staging rate, overall survival, disease-free survival, local recurrence rate, sphincter-preserving rate, state of conducting adjuvant chemotherapy, adverse events defined by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and postoperative complications.

Eligibility criteria

Inclusion criteria: The primary tumor is staged according to the eighth edition of TNM Classification of Malignant Tumors [21].

Histologically proven adenocarcinoma of the rectum.

Borderline resectable locally advanced rectal cancer fulfilled at least at least one of the following criteria detected by enhanced abdominal computed tomography (CT) or enhanced pelvic magnetic resonance imaging (MRI) [19]: (i) cT4a with circumferential resection margin <1 mm, (ii) cT4b, (iii) cN2/3, (iv) metastases of internal iliac lymph nodes, (v) metastases of obturator lymph nodes (metastatic lymph node is confirmed as ≥5mm in a minor axis).

Tumor with inferior edge located below peritoneal reflection determined by enema examination.

UGT1A1*1/*28 genotypes as follows: UGT1A1 *1/*1 or UGT1A1*28/*1 or UGT1A1*6/*1.

Without history of previous chemotherapy or radiotherapy for rectal cancer.

Performance status (PS) 0–1.

Age ranging between 20 and 74.

Adequate organ function that simultaneously satisfied the following conditions within 14 days before registration: (i) WBC ≥3,000/mm3 to ≤12,000/mm3, (ii) Neutrophil count ≥1,500/mm3, (iii) Platelet count ≥100,000/mm3, (iv) Serum bilirubin ≤2.0 mg/dL, (v) AST ≤100 IU/L, (vi) ALT ≤100 IU/L, (vii) Serum creatinine ≤1.3 mg/dL.

Written informed consent prior to registration.

Exclusion criteria: Synchronous distant metastases.

No history of treatment using blood products within 14 days prior to registration.

Cancerous ascites necessary for treatment.

Active infection.

A synchronous or metachronous active malignancy.

Past history of peripheral neuropathy greater than Grade 1 or severe drug-induced allergy.

Serious co-morbidities such as pulmonary fibrosis or interstitial pneumonia, poorly controlled diabetes mellitus, severe cardiovascular disease or another serious medical condition.

Pregnancy or breastfeeding.

Treatment Methods

Neoadjuvant chemotherapy

Patients receive six cycles of FOLFOXIRI regimen. FOLFOXIRI regimen is as follows: (i) oxaliplatin 85 mg/m^2, irinotecan 165 mg/m^2 and folinic acid 200 mg/m^2 by intravenous bolus infusion on day 1 every 2 weeks, (ii) 5-fluorouracil 3200 mg/m^2 as a 48 h continuous infusion on day 1 every 2 weeks. After neoadjuvant chemotherapy, the primary tumor is reevaluated with enhanced chest and abdominal CT and enhanced pelvic MRI to determine if it is resectable.

Surgery

TME with D3 lymph node dissection is scheduled between 2 and 8 weeks after the completion of chemotherapy. A tumor located at or below the peritoneal reflection is an indication for lateral pelvic lymph node dissection [5]. Combined resection of other organs is allowed as necessary for R0 resection. Laparoscopic surgery is permissible in this trial.

Follow-up schedule

The participants will be followed-up every 3 months until 5 years after the completion of the protocol treatment according to the surveillance schedule described in the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines [5]. Adjuvant chemotherapy will be conducted depend on disease stage.

Study Design and Statistical Methods

The present trial is a phase II trial to evaluate the efficacy and safety of combined treatment of neoadjuvant chemotherapy and radical surgery for borderline resectable locally advanced rectal cancer. In the N-SOG 03 study, the R0 rate of patients with neoadjuvant chemotherapy consisting of capecitabine, oxaliplatin and bevacizumab followed by surgery was 90% (19). Therefore, the primary hypothesis is that an R0 rate of 90% is achievable using a FOLFOXIRI treatment regimen equivalent to a doublet regimen combined with bevacizumab. In this phase II trial, the planned sample size is 30 patients, which was calculated using Southwest Oncology Group's two-stage attained design based on a target p R0 rate of 90% and a minimum R0 rate of 70%, with an alpha error of 0.05 and a beta error of 0.20. Assuming a dropout or ineligibility rate of 10%, the target number of enrolled patients was determined to be 30 patients.

Participating Institutions

Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University; Department of Medicine and Bio systemic Science, Graduate School of Medical Sciences, Kyushu University; Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University; Department of Surgery, Hamanomachi Hospital; Department of Surgery, Kitakyushu Municipal Medical Center; Department of Surgery, Faculty of Medicine, Saga University.

Conflict of Interest statement

None declared.

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