

ORIGINAL RESEARCH ARTICLE

Preoperative chemoradiotherapy using S-1 combined with celecoxib for advanced lower rectal cancer: Phase I/II study

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Abstract:

Objectives: To clarify the safety and efficacy of celecoxib combined with chemoradiotherapy using S-1 for lower rectal cancer. **Methods:** Twenty-one patients with pathologically proven lower rectal adenocarcinoma (cT3-T4, Tx N+, M0) were included in this study. A total dose of 45 Gy was administered in daily fractions of 1.8 Gy. Celecoxib was given orally twice daily with S-1 on the day of irradiation. The dose of celecoxib was set at 400 mg/day. In Phase I, the S-1 dose was started at 80 mg/m²/day; in Phase II, S-1 was administered in the same dose as Phase I. Patients underwent surgery six to eight weeks after completing chemoradiotherapy, followed by six months of postoperative adjuvant chemotherapy. **Results:** The S-1 recommended dose was 80 mg/m²/day. The pathological complete remission rate was 15.8%, the rate of protocol completion was 14.3%, and the rate of adverse events exceeding Grade 3 was 19.0%. Surgery was performed in 19 cases, with a sphincter-sparing rate of 31.6%. Postoperative complications exceeding Grade 3 occurred in 52.4% of cases. The three year overall survival and relapse-free survival rates were 89.3% and 67.0%, respectively. **Conclusions:** We failed to show a synergistic or additive therapeutic effect of preoperative CRT using S-1, combined with celecoxib, for lower advanced rectal cancer beyond CRT using 5 FU or capecitabine alone. The incidence of complications, evidently involving intestinal ischemia, was relatively high. This treatment strategy is not recommended at present.

Keywords:

Rectal cancer, chemoradiation, S-1, celecoxib

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Introduction

In Western countries, preoperative chemoradiotherapy (CRT) is the standard treatment for advanced lower rectal cancer^{1,2)}. Although its effectiveness in reducing local recurrence is widely accepted, its effectiveness in extending the overall survival (OS) remains to be determined. In Japan, the standard treatment for advanced lower rectal cancer is total mesorectal excision (TME) with bilateral pelvic lymph node dissection³⁾. Preoperative CRT is not yet considered a standard treatment.

The National Comprehensive Cancer Network (NCCN) guidelines⁴⁾ recommend 5FU and capecitabine as anti-cancer drugs to be used in preoperative CRT. According to current reports, the pathological complete response (pCR) rate is around 15% with CRT using 5FU or capecitabine^{5,7)}, and several efforts have been made to improve the effect. There are many reports about combining a strong cytotoxic agent, such as oxaliplatin or irinotecan, with 5FU-based CRT⁸⁻¹¹⁾. While some reports indicate improved treatment outcomes, others indicated no additive effect of a strong agent and reported more adverse events, so combining a strong cytotoxic

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agent with preoperative CRT remains controversial. Recently, the notions of providing strong cytotoxic chemotherapy before CRT, known as “induction chemotherapy”^{12,13)} as well as after CRT, known as “consolidation chemotherapy”^{14,15)} have drawn attention for their high clinical and pathological efficacy. The drawback is that patients must undergo a considerably lengthy pre-operative treatment. A treatment method that can achieve a high therapeutic effect, without increasing the risk of adverse events or prolonging the treatment period, is needed.

Celecoxib, a non-steroidal anti-inflammatory drug (NSAID) with a selective inhibitory effect for COX-2, has drawn attention for its anti-neoplasm effect. In familial adenomatous polyposis patients, taking 400 mg celecoxib significantly reduced the number of colorectal polyps¹⁶⁾. Celecoxib was also reported to have a synergistic effect on radiotherapy for malignancy in basic studies¹⁷⁾, and reasonable effects were reported in treatment with 5FU¹⁸⁾ or uracil/tegafur^{19,20)} or capecitabine²¹⁾ in CRT for rectal cancer patients.

The oral fluoropyrimidine S-1, an anti-cancer drug invented in Japan, is designed to improve 5-FU's antitumor activity while reducing gastrointestinal toxicity²²⁾. Gimeracil, a dehydropyrimidine dehydrogenase (DPD) inhibitor, is reported to have a radio sensitizing property when combined with S-1²³⁾, and there have been several reports of CRT using S-1 for rectal cancer mainly from Japan²⁴⁻²⁶⁾.

Given the above-mentioned findings, we conducted a Phase I/II study of CRT, using S-1 combined with celecoxib, for advanced lower rectal cancer. The aim was to clarify the recommended dose of S-1 in this treatment and to assess the clinical effect. The primary objectives of the Phase I study were to determine the recommended S-1 dose for the Phase II study. In the Phase II study, the primary objective was the pCR rate, and the secondary objectives were the rate of completeness of protocol treatment, clinical response, relapse-free survival (RFS), OS, rate and degree of adverse events, and the anal sphincter preservation rate.

Methods

Eligibility criteria

Patients with histopathologically proven, locally advanced, lower rectal adenocarcinoma (cT3-T4, Tx N+, M0) were eligible to participate in this study. Additional eligibility criteria were as follows: no prior systemic chemotherapy or pelvic radiotherapy, over 20 years of age, Eastern Cooperative Oncology Group performance status ≤ 1 , expected to live for at least three months, no severe organ failure (defined as a leukocyte count $\geq 4,000/\text{mm}^3$ and $\leq 12,000/\text{mm}^3$, a neutrophil count $\geq 2,000/\text{mm}^3$, a platelet count $\geq 100,000/\text{mm}^3$, a hemoglobin level ≥ 9.0 g/dl, serum aspartate aminotransferase and alanine aminotransferase ≤ 100 U/L, a serum

bilirubin level ≤ 1.5 mg/dl, and a creatinine clearance ≥ 60 ml/min), the ability to ingest food orally, and written informed consent provided.

This study was approved by the institute review board of the Chiba University School of Medicine.

Radiotherapy

A total dose of 45 Gy was delivered in daily fractions of 1.8 Gy, five days a week for five weeks, using a 3- or 4-field box technique. Patients were irradiated using a linear accelerator over 10 MV. The gross tumor volume included the main tumor and swelling lymph nodes and, if the tumor invaded adjacent organs, the invaded area. The clinical target volume included the gross tumor volume, mesorectum, and regional lymphatics, including the perirectal, pre-sacral space, internal iliac, and obturator lymphatics. The planning target volume was located 1 cm outside the clinical target volume. According to these definitions, the treatment fields were set as follows: The superior border was placed at L5-S1, and the inferior border was placed 3-4 cm below the lower edge of the tumor. The lateral borders were at least 1.5 cm lateral to the widest bony margin of the true pelvic wall, the anterior border was the most posterior aspect of the symphysis pubis, and the posterior border was the most posterior aspect of the sacrum.

S-1 chemotherapy and celecoxib administration

S-1 was given orally, after breakfast and dinner, twice daily on the day of irradiation. The S-1 dose was assigned based on the body surface area. Dose-limiting toxicity (DLT) was defined as severe hematologic toxicity (leukopenia, neutropenia, and thrombocytopenia) of Grade 4, or non-hematological toxicity (excluding fatigue and appetite loss) of Grade 3 or more, according to the National Cancer Institute Common Terminology Criteria for Adverse Event version 4.0 or a delay in S-1 administration for 14 days or more because of toxicity.

The initial dose of S-1 was set at 80 mg/m²/day (level 1). The maximum tolerable dose (MTD) was defined as the dose that produced DLT in at least three of six patients. If DLT occurred in three or more of six patients, the dose was decreased to 60 mg/m²/day (level 0). The dose immediately below the MTD was considered the requested dose (RD) for Phase II studies. If DLT occurred in two or fewer of the six patients, Level 1 was considered the RD.

Patients were given 400 mg/day of celecoxib with S-1 on the day of irradiation.

Dose escalation was not allowed for S-1 or celecoxib.

Surgery and post-operative adjuvant chemotherapy

Patients underwent surgical resection six to eight weeks after completing chemoradiation. No anti-cancer treatment occurred between chemoradiation and surgery. The surgical

Table 1. Patients Characteristics.

		Number
Age, median (range)		68 (46-88)
Gender	Male	12
	Female	9
Tumor stage	cT2	1
	cT3	14
	cT4	6
Nodal status	cN0	7
	cN1	7
	cN2	7
Tumor size, median (range) (mm)		45 (24-94)
Distance from anal verge (cm)	<5cm	13
	5-10cm	8
Histologic differentiation	Well	11
	Moderate	7
	Poor/mucinous	3

techniques included low anterior resection, abdominoperineal resection, and Hartmann's procedure using TME or tumor-specific ME. In low anterior resection, the construction of a covering stoma was allowed. Lateral pelvic lymph node dissection was omitted when lymph node metastases were not suspected in the lateral pelvic region before CRT. We diagnosed lateral pelvic lymph node metastasis if one of these criteria were met: short axis over 5 mm, high accumulation in positron emission tomography, or high intensity in diffusion weighted magnetic resonance imaging.

Post-operative adjuvant chemotherapy was scheduled for 8-12 weeks after surgery. Four courses of S-1 for 28 days were given at 6-week intervals or 8 courses of S-1 for 14 days were given at 3-week intervals.

The response assessment

The response was assessed both clinically and pathologically. The clinical tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1²⁷. The degree of tumor shrinkage was assessed using computed tomography or pelvic magnetic resonance imaging (MRI). These examinations were performed four weeks after patients completed chemoradiation. The pathological response was graded in accordance with the Japanese Classification of Colorectal Carcinoma 8th edition²⁸ as follows: Grade 0 means no treatment response, Grade 1a means less than one third of the cancer tissue has necrosis or degeneration, Grade 1b means one third to less than two thirds of the cancer tissue has necrosis or degeneration, Grade 2 means more than two thirds of the cancer tissue has necrosis or degeneration, and Grade 3 means complete pathological remission. Down-staging was determined by comparing pretreatment clinical TNM stage with postoperative histopathologic TNM stage.

Statistical analyses

The RFS and OS were assessed by Kaplan-Meier method. Phase II's primary objective was determining the pCR rate of CRT with S-1 and celecoxib. Based on the current literature data, we anticipated a 30% objective pCR rate. The planned sample size was 20 patients, which was calculated by the Southwest Oncology Group's two-stage attained design based on a 30% target pCR rate and a 10% minimum pCR rate with an α error of 0.1 and β error of 0.2.

Results

Patients

From July 2013 to June 2016, 21 patients were enrolled in this Phase I/II study. The patients and tumor characteristics at baseline are listed in Table 1. The first six patients were enrolled in Phase I and treated with the RD; their data were also included in Phase II.

Dose setting

In the Phase I study, S-1 was started at 80 mg/m²/person (Level 1), and only one patient suffered DLT (CTCAE Grade 3 diarrhea), so Level 1 was considered the RD. All six patients in the Phase I study were treated at the Level 1 dose and included in Phase II.

Safety and compliance with chemoradiation

The patient with DLT in Phase I was forced to interrupt S-1 and celecoxib administration. Among the 15 patients included in Phase II, two administrations were interrupted for skin rash, one declined to continue the protocol, and one required a dose reduction for S-1 due to prolonged diarrhea of CTCAE Grade 2. Ultimately, 16 patients (76.2%) completed CRT at the RD. In the interrupted cases, Celecoxib was stopped simultaneously with S-1. Although one patient in Phase I had to interrupt the radiation dose at 41.4 Gy due to severe diarrhea, the remaining 20 patients completed therapy with 45 Gy radiation. Adverse events (AEs) during CRT are shown in Table 2. AEs exceeding Grade 3 occurred in 4 patients (19.0%) and no patients suffered from Grade 4 AEs.

Regarding the clinical response according to RECIST, PR was achieved in 16 cases, and the response rate was 76.2%. There were no PD cases.

Surgery and post-operative complications

Surgical resection was performed in 19 patients, and two rejected surgery. In the patients who received surgery, 6 had their anal sphincter preserved, 11 underwent abdominoperineal resection, and two underwent Hartmann's procedure (anal sphincter preservation rate: 31.6%). Eight patients underwent surgery with laparoscopic assistance. In the histo-

Table 2. Major Adverse Events of CRT.

	Grade 1	Grade 2	Grade 3
Nausea	0	1	0
Diarrhea	1	2	1
Appetite loss	0	0	1
Stomatitis	1	0	0
Gastritis	1	0	0
Leukocytopenia	6	5	1
Neutropenia	3	4	2
Anemia	6	7	2
Skin rash	0	2	0
Dermatitis radiation	16	5	0

Table 3. Postoperative Complications Exceeding Grade 2 in Clavien-Dindo Classification.

	Grade 2	Grade 3a	Grade 3b
Wound infection	1	0	0
Enterocolitis	1	0	0
Lymphocele	0	1	0
Pelvic infection	1	3	0
Anastomotic leakage	0	4	0
Melena	0	1	0
Stoma necrosis	0	0	1
Lymph leakage	0	0	1
Neurogenic bladder	1	0	0
Incarceration of groin hernia	0	0	1

logical evaluation, two patients had positive surgical margins, and pathological complete resection was carried out in 17 patients (89.5%). Three patients showed Grade 3, eight patients showed Grade 2, three patients showed Grade 1b, and five patients showed Grade 1a. The pCR rate was 15.8%. Down-staging of T stage occurred in 10 patients (52.6%), and down-staging of stage grouping occurred in four patients (21.1%).

Post-operative complications are shown in Table 3. Post-operative complications exceeding Grade 3 in the Clavien-Dindo classification occurred in 11 patients (52.4%). Anastomotic leakage occurred in four of the six patients with anastomosis.

Post-operative adjuvant chemotherapy

Post-operative adjuvant chemotherapy was successfully performed in seven patients; three were given S-1 according to the protocol dose. Two patients were forced to stop due to AEs, one needed to change the drug due to a skin rash, and one received Capox treatment (capecitabine plus oxaliplatin) at the attending physician’s decision due to a positive surgical margin. Twelve patients could not receive adjuvant chemotherapy, and only three patients were able to complete the protocol from CRT to post-operative chemo-

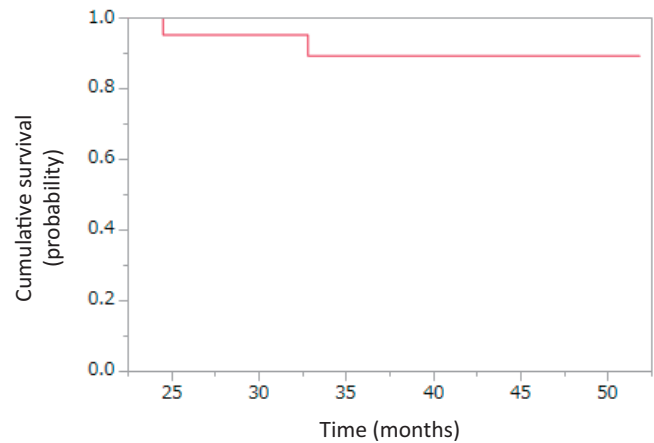


Figure 1. Kaplan-Meier plot for overall survival.

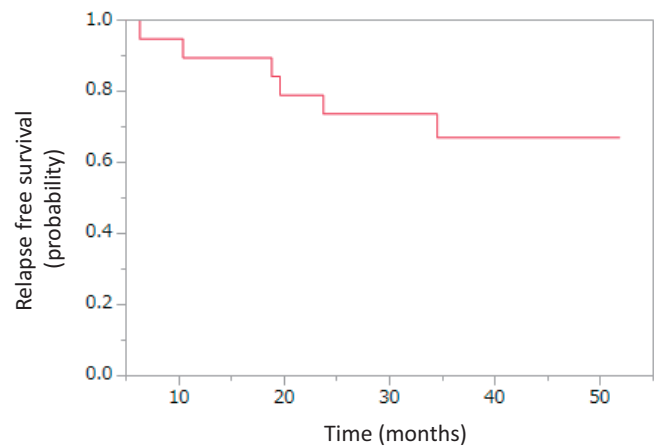


Figure 2. Kaplan-Meier plot for relapse-free survival in patients performed surgical resection.

therapy (protocol complete rate 14.3%).

The RFS, OS, and local control

The median follow-up period was 39.5 months, and the three-year-OS of all cases was 89.3%. (Figure 1) In patients who underwent surgical resection, the three-year-RFS was 67.0%. (Figure 2). Six patients developed relapse, one had local recurrence, five developed metastases to the lung and one developed metastasis to the para aortic lymph node. The three-year local control rate was 94.7%.

Discussions

In this Phase I/II trial, patients were given a combination of celecoxib and S-1, which is frequently used in CRT for rectal cancer in Japan. This combination therapy for rectal cancer is being reported here for the first time. In Phase I, DLT occurred in only one of six cases, and the RD of S-1 was determined to be 80 mg/m²/day. In Phase II, the pCR rate, which was the primary endpoint of this study, was

15.8%, indicating no additional effect of celecoxib. This unfavorable result may have been due to the low completion rate of CRT at the RD. Among the five cases of discontinuation, two were forced to cease CRT due to diarrhea, two due to skin rash, and one due to rejection. Jakobsen et al.¹⁹⁾ reported that more than half the patients who underwent CRT with tegafur/uracil and celecoxib suffered from skin rash, probably because of drug interactions. In the present study, skin rashes were rarer than was previously reported, but the influence of the interaction of S-1 and celecoxib on AEs could not be denied.

The three-year OS and RFS was 89.3% and 67.0% respectively, which also failed to prove the additive effect of celecoxib on CRT. One reason for these unfavorable results may have been the very low completion rate (14.3%) of the protocol regimen including adjuvant chemotherapy. Among the 19 patients who underwent surgery, 12 could not receive adjuvant chemotherapy, half because of prolonged postoperative complications. Four of the six patients with anastomoses suffered from anastomotic leakage, and one suffered from stoma necrosis; these results indicate intestinal blood flow disturbance. Of note, several complications seemed to have been caused by intestinal ischemia. There were some reports of adverse effects of COX-2 inhibitory drugs to intestinal anastomoses. Burton et al.²⁹⁾ reported in their meta-analysis that the anastomotic leakage rate did not differ significantly between patients using NSAID perioperatively and those not using NSAID. However, Reinsinger et al.³⁰⁾ reported that COX-2 knock-out mice and diclofenac-treated mice had significantly higher anastomotic leakage rates than normal mice, and they insisted on the importance of COX-2 in intestinal repair. COX-2 was also reported to play an important role in angiogenesis. Celecoxib may have caused the intestinal ischemic events in this study, which may have prevented the protocol regimen from being completed, thereby giving unfavorable results.

In the present study, the anal sphincter preservation rate was 31.6%, which was lower than in other reports of CRT for rectal cancer⁸⁻¹⁰⁾. The distal spread of the tumor cells was reported to remain in some cases, even though the tumor had been flattened³¹⁾. Therefore, the resecting range was not reduced from that assumed before CRT at our institution. Furthermore, the anal function was impaired by nerve damage from irradiation after CRT^{32,33)}, so we strongly recommend against anal preservation in cases requiring very low levels of anastomoses near the anal verge after CRT. These strategies may have led to the very low anal preservation rate.

The limitation of this study is the small number of patients involved, as this study was conducted at a single institution. If this treatment could be tested in more cases, different results might be obtained.

In conclusion, we failed to show a synergistic or additive

therapeutic effect of pre-operative CRT using S-1 combined with celecoxib for lower advanced rectal cancer beyond CRT using 5 FU or capecitabine alone, and the incidence of complications evidently involving intestinal ischemia was relatively high. This treatment strategy is not recommended at present.

Conflicts of Interest

There are no conflicts of interest.

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