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Neoadjuvant Radiotherapy with Capecitabine Plus Bevacizumab for Locally Advanced Lower Rectal Cancer: Results of a Single-institute Phase II Study

KIYOSHI MAEDA[1,2], MASATSUNE SHIBUTANI[2], HIROSHI OTANI[2], TATSUNARI FUKUOKA[2], YASUHITO ISEKI[2], SHINJI MATSUTANI[2], HISASHI NAGAHARA[2], TORU INOUE[1], AKIKO TACHIMORI[1], TAKAFUMI NISHII[1], YOSHITAKA MIKI[3], MASAKO HOSONO[3] and MASAICHI OHIRA[1]

[1]Gastroenterological Surgery, Osaka City General Hospital, Osaka, Japan; Departments of [2]Gastroenterological Surgery and [3]Radiology, Osaka City University Graduate School of Medicine, Osaka, Japan

Abstract. *Background/Aim: A single-arm phase II clinical trial was conducted to evaluate the safety and efficacy of adding bevacizumab to standard capecitabine-based neoadjuvant chemoradiotherapy (CRT) for the treatment of locally advanced rectal cancer (LARC). Patients and Methods: Twenty-five patients were enrolled. Patients received capecitabine-based CRT for 5 weeks and 3 days. Bevacizumab was administered every 2 weeks during CRT. Within 6-10 weeks after completion of CRT, surgery was performed. Results: With regard to CRT-related acute toxicities, most of the adverse events were limited to grade 1. A pathological complete response was obtained in four (16%) patients. In total, six patients (24%) developed postoperative complications. Six out of five (83%) patients healed without the need for surgical intervention. Conclusion: Although acute toxicity during CRT with bevacizumab was minimal and postoperative complications do not seem to increase, the addition of bevacizumab apparently offers no clinically-significant benefit for patients with LARC.*

A number of studies have demonstrated that preoperative radiotherapy significantly reduces the risk of local recurrence in patients with locally advanced rectal cancer (LARC) (1-4). The addition of 5-fluorouracil (5-FU) or capecitabine to preoperative radiotherapy has been shown to improve the pathological complete response (pCR) and down-staging rates compared to radiotherapy alone (5-10). Therefore, preoperative capecitabine-based chemoradiotherapy (CRT) is now a standard treatment for LARC.

The addition to chemotherapy of bevacizumab, a humanized monoclonal antibody against vascular endothelial cell growth factor (VEGF), has been shown to improve survival patients with metastatic colorectal cancer (11-13). Previous studies have demonstrated that the induction of VEGF by radiation contributes to tumor radioresistance and that anti-VEGF treatment can compensate for resistance to radiation (14, 15). Therefore, preoperative CRT plus bevacizumab is considered a promising treatment for LARC, but there have been few studies concerning adequate evidence supporting the efficacy and safety of such regimens.

Regarding the safety of addition of bevacizumab to preoperative CRT, we already carried out a phase I study and concluded that acute toxicity during CRT with the addition of bevacizumab was minimal and easily managed without interruption or attenuation of either capecitabine or radiation dose (16).

The aim of this single-arm phase II study was to evaluate the efficacy of preoperative CRT with capecitabine plus bevacizumab in patients with LARC.

Patients and Methods

This study was approved by the Institutional Review Board at Osaka City University Hospital (Number 2521). Each patient gave their written informed consent prior to any study procedure.

Study design and treatment plan. This study was a nonrandomized, single-institution, phase II trial designed to evaluate the efficacy of neoadjuvant radiotherapy with concurrent capecitabine and bevacizumab in patients with LARC. The primary endpoint was the rate of pCR. Acute toxicity during CRT; postoperative morbidity, and the downstaging rate were also evaluated as secondary endpoints.

Correspondence to: Kiyoshi Maeda, Department of Gastroenterological Surgery, Osaka City General Hospital, 2-13-22 Miyakojimahondori, Miyakojima-ku, Osaka, 534-0021, Japan. Tel: +81 69291221, e-mail: m1378386@med.osaka-cu.ac.jp

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Patients and eligibility criteria. Eligible patients had to have a histologically verified adenocarcinoma of the rectum with the inferior margin within 5 cm from the anal verge, as assessed by rectosigmoidoscopy. The tumor had to have evidence of T3/T4 disease or any T-stage disease with positive locoregional lymph nodes detected by computed tomography (CT) and magnetic resonance imaging (MRI) of the pelvis. The disease was considered to be resectable at the time of entry in all cases, with no evidence of distant metastases. Other key inclusion criteria were: age 20-75 years; World Health Organization (WHO) performance status of 0-2; adequate organ function, as defined by a leukocyte count of ≥4,000 to ≤12,000/mm^3, a neutrophil count of ≥2,000/mm^3, a platelet count of ≥100,000/mm^3, a hemoglobin level of ≥9 g/dl, a serum bilirubin level of ≤1.5 mg/dl, serum aspartate aminotransferase and alanine aminotransferase levels of ≤100 U/l, a serum creatinine level of ≤1.1 mg/dl (for men) or ≤0.7 mg/dl (for women), and a creatinine clearance of ≥50 ml/min; the ability to ingest food and drugs orally; and no high medical risks.

Chemoradiotherapy. Patients received radiation and capecitabine on Monday through Friday. Bevacizumab was administered at 5 mg/kg intravenously every 2 weeks, on days 1, 15, and 29. Capecitabine was administered twice daily on the days of radiation. Based on the previous phase I dose-finding study, capecitabine was administered at 900 mg/m^2, every 12 h (16).

Radiotherapy was delivered using a 4-field conformal coplanar technique (anteroposterior, posteroanterior, right lateral and left lateral fields) and 6-10 MV photon beams. A total dose of 50.4 Gy was given in 1.8-Gy fractions, five fractions per week, over a total of 5 weeks and 3 days. CT with co-registered positron-emission tomography and MRI was used to delineate the targets. The primary tumor and any involved lymph nodes were defined as the gross tumor volume (GTV). The clinical target volume (CTV) 1 was defined as the GTV of the primary tumor after adding a margin of 2 cm in the cranio-caudal direction and 0.5 cm in the lateral and antero-posterior directions. CTV2 was defined as the GTV of the lymph nodes plus a margin of 0.5 cm. CTV3 was defined as the mesorectum, presacral and internal iliac nodal regions for those with T3 disease, and included the external iliac nodal region when the stage was T4. The planned target volume (PTV) 1 included CTV1, 2 and 3 plus a 1 cm expansion at all borders. This volume was treated with 45 Gy. PTV2 included CTV1 and 2 plus 1 cm of expansion at all borders. A boost of 5.4 Gy was given to PTV2.

During treatment, patients were evaluated bi-weekly. Clinical examinations, complete blood counts and a serum biochemical analysis were performed. Adverse events were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0 (17). The schedule of bevacizumab was modified in the event of grade 2-3 thrombotic, hemorrhagic, proteinuric, hypertensive or allergic adverse events. The drug was withdrawn in the case of grade 4 toxicity, grade 3 toxicity not resolved to grade 1 within 4 weeks, or gastrointestinal perforation.

The dose of capecitabine was also adjusted if adverse events developed. In brief, capecitabine was withheld in cases of grade 2 or greater hand–foot syndrome, grade 3 or greater neutropenia, or gastrointestinal toxic reactions that did not respond to medical treatment. When the toxicity resolved to grade 0-1, treatment was continued at a reduced dose (*i.e.* 900 mg/m^2 to 825 mg/m^2). If there was a second occurrence, capecitabine was discontinued. If toxicity required a dosing delay or interruption of all study drugs for more than 3 weeks, the patient was withdrawn from the study.

Surgery. Within 8-10 weeks after completing chemoradiotherapy, surgery with total mesorectal excision was performed. Postoperative complications were recorded not only during the hospital admission, but also during the first 30 days after discharge. The severity of surgical complications was scored using the Clavien-Dindo classification of surgical complications (18).

In patients achieving a histopathological R0 resection, adjuvant chemotherapy was recommended. The recommended treatment comprised capecitabine at 1,250 mg/m^2 orally twice daily on days 1-14 every 3 weeks for 8 cycles (6 months).

Pathological evaluation. A postoperative, pathological evaluation of the surgical specimen was performed. pCR was defined as the complete disappearance of all tumor cells. The tumor regression grade (TRG) was evaluated by histological regression as: TRG 1: pCR, absence of viable cancer cells in the resected specimen; TRG 2: presence of residual cancer cells; TRG3: predominantly fibrotic changes with few tumor cells; TRG4: very few tumor cells in fibrotic tissue; TRG5, absence of response (19).

Statistical analyses. Preoperative CRT with regimens combining 5-FU or capecitabine has been reported to have a pCR rate of 9-16.9% in patients with LARC (5-10). In the present study, it was assumed that the pCR rate would be 30%, with a minimum activity pCR rate of 10%, an α level of 0.05 (two-sided), and a β level of 0.20. It was estimated that 24 patients would be required. The target number of patients was therefore set at 26, taking excluded patients and dropouts into account.

Results

Patient characteristics. A total of 27 patients were enrolled from August 2013 through August 2017. Two patients were excluded from the study because they refused surgery. The characteristics of the 25 patients are shown in Table I. Seven patients had cT4 disease (28%) and another 20 patients (72%) had cT3 disease. Radiological lymph node metastases were detected in 16 (64%) patients. All patients were evaluable for response and toxicity.

Chemoradiotherapy-related toxicity. The frequency and grade of treatment-related acute toxicities are summarized in Table II. Although one patient experienced grade 2 anal pain, most of the adverse events were limited to grade 1. There was no grade 3 or greater toxicity. Bvacizumab-related toxicity (such as hypertension, thrombosis, proteinuria, or gastrointestinal perforation) was not observed in any of the patients.

No patient needed attenuation or interruption of bevacizumab, capecitabine or radiation. All patients received the scheduled dose of chemoradiotherapy.

Surgery. Surgical resection followed CRT by a median of 8.5 weeks (range=8-10 weeks). The median interval between the final dose of bevacizumab and surgery was 10 weeks (range=9-11weeks). All patients underwent R0 resections (Table III). Out of 25 patients, 24 (96%) patients underwent a laparoscopic procedure. Procedures included abdominoperineal resection

Table I. *Patient characteristics (n=25).*

Characteristic	Value
Age, years	
Median (range)	65 (44-74)
Gender, n	
Male	19
Female	6
ECOG performance status, n	
0	20
1	5
Distance from the anal verge, cm	
Median (range)	3.5 (1-5)
Clinical T-stage	
T3	18
T4	7
Clinical N-stage	
N0	9
N1	6
N2	10
Clinical TNM-stage	
IIA	7
IIB	2
IIIB	11
IIIC	5

Table II. *Adverse events experienced during chemoradiotherapy.*

Toxicity	Grade 1, n (%)	Grade 2, n (%)
Hematological		
Leukocytopenia	14 (56)	0 (0)
Neutropenia	4 (16)	0 (0)
Anemia	2 (8)	0 (0)
Thrombocytopenia	4 (16)	0 (0)
Non-hematological		
Diarrhea	13 (52)	0 (0)
Anorexia	1 (4)	0 (0)
Hand–foot syndrome	2 (8)	0 (0)
Anal pain	7 (28)	1 (4)

Table III. *Surgical approaches and procedures.*

Surgical procedure	n (%)
Surgical approach	
Open	1 (4)
Laparoscopic	24 (96)
Surgical procedure	
Low anterior resection	9 (36)
Proctectomy with colo-anal anastomosis	4 (16)
Abdominoperineal resection	12 (48)

(APR) in 12 (48%) patients and low anterior resection in nine (36%), and proctectomy with colo-anal anastomosis in 4 (16%). The overall rate of sphincter preservation was 52%.

Pathological tumor response. Pathological examination of postoperative specimens revealed no residual cancer neither at the primary tumor (ypT0 or Mandard TRG1) nor lymph nodes (ypN0) in four (16%) patients (Table IV). The pCR rate was, thus, 16%. Histological regression was evaluated as TRG1 in four (16%) patients and TRG2 in eight (32%) patients; marked tumor regression (TRG1 or 2) was, thus, obtained in 12 (48%). In addition, 16 (64%) patients achieved T down-staging, and 13 (52%) patients achieved N down-staging, comprising a combined pathological down-staging rate of 84% (21 out of the 25 patients) (Table V).

Postoperative surgical complications. The postoperative surgical complications are summarized in Table VI. There was no postoperative death. In total, six patients (24%) developed complications. Anastomotic leakage occurred in three (23.1%) out of the 13 patients who underwent sphincter-preserving surgery. Perineal wound dehiscence developed in three (25%) out of the 12 patients who underwent abdominoperitoneal resection. However, all of them healed with conservative treatment without surgical intervention. Re-operation was needed in one patient due to bowel obstruction.

Table IV. *Pathological response to chemoradiation.*

Tumor regression grade	n (%)
1	4 (16)
2	8 (32)
3	7 (28)
4	6 (24)
5	0 (0)

Discussion

Preoperative radiotherapy with concurrent 5-FU or capecitabine the risk of local recurrence and remains a standard treatment in patients with LARC. Previous studies about standard treatment using CRT with 5-FU or capecitabine demonstrated pCR rates of 8% to 16.9% (5-10). An achievement of pCR and a negative surgical resected margin correlate with a lower local recurrence and improved prognosis.

Although many studies have demonstrated that the addition of bevacizumab to chemotherapy prolongs the survival of patient with metastatic colorectal cancer (11-13), the efficacy and safety of adding neoadjuvant bevacizumab to CRT were unclear. Several previous studies have evaluated preoperative

Table V. *Distribution of patients by postoperative pathological ypT-stage and ypN-stage compared with pretreatment cT-stage and cN-stage.*

	ypT0	ypT1	ypT2	ypT3	ypT4	ypN0	ypN1	ypN2
cT3	4	1	4	9	–	–	–	–
cT4	–	–	4	3	–	–	–	–
cN0	–	–	–	–	–	8	1	–
cN1	–	–	–	–	–	5	–	–
cN2	–	–	–	–	–	7	1	3

Table VI. *Postoperative surgical complications experienced by patients (including duplicates).*

Surgical complication	Grade, n		
	I	II, IIIa	IIIb
Perineal wound infection	3	–	–
Anastomotic leakage	3	–	–
Bowel obstruction	–	–	1

CRT with capecitabine plus bevacizumab in patients with LARC (20-23). In these studies, it was reported that although most of the adverse events during CRT were mild, 9-10% of patients could not complete the treatment due to grade 3 or greater severe adverse events (*e.g.* diarrhea, neutropenia, leukocytopenia and anal pain). In our study, the adverse events that occurred during CRT were limited to grade 1-2. All patients completed the scheduled dose of CRT without severe toxicity. Bevacizumab-related toxicity, such as hypertension, thrombosis, proteinuria and gastrointestinal perforation did not occur in our patient. One of the reasons why severe toxicity was not observed in our study may have been the weekday-on/weekend-off administration of capecitabine. In most of the previous studies, capecitabine was administered continuously during CRT. The weekday-on/weekend-off schedule is a standard regimen used for preoperative CRT for rectal cancer. Pentheroudakis *et al.* (24) and Ngan *et al.* (25) also reported that the rates of adverse events were lower for the weekday-on/weekend-off schedule compared with those in patients on the continuous schedule.

Regarding efficacy, some previous studies reported that the addition of bevacizumab increased the pCR rate. A pCR rate of 32% was reported by Crane *et al.* (20) and 25% by Resh *et al.* (21). However, in subsequent phase II studies, pCR rates were 13.3% to 16% (26-28), and we also obtained a pCR rate of 16%, which was similar to the rates reported in the studies using standard CRT with 5-FU or capecitabine without bevacizumab. Therefore, in terms of pCR, no obvious benefit seems to be obtained from the addition of bevacizumab.

Regarding postoperative complications, wound complications are well-recognized risks after CRT. The frequency of wound complications in our study was relatively high (25%, 3/12) in the patients who underwent APR. However, the rate was similar to that reported for standard CRT without bevacizumab (5-11). Swellengrebel *et al.* studied 138 patients with LARC who underwent APR after preoperative CRT, and reported that surgical perineal wound complications were observed in 37% of patients and surgical intervention was required in 21.7% of the patients (29). In our study, the occurrence rate of perineal wound complications was also high, however, all patients healed without surgical intervention. Therefore, our study suggests that the addition of bevacizumab does not seem to be related to an increased risk of wound complications.

Long-term effects of this regimen with bevacizumab cannot be judged from this trial. Willet *et al.* reported that both overall and disease-free survival tended to be higher in patients with standard CRT with bevacizumab and suggested that adding bevacizumab may have a potential role in improving survival (20). Long-term follow-up results on survival and on local control are needed to determine the potential impact of adding bevacizumab to preoperative standard CRT.

In conclusion, acute toxicity during CRT with bevacizumab was minimal and postoperative complications did not seem to increase, however, in terms of the pCR rate, the addition of bevacizumab to capecitabine-based CRT apparently offers no clinically obvious improvement in patients with LARC.

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