Addition of Bevacizumab to XELOX Induction Therapy Plus Concomitant Capecitabine-Based Chemoradiotherapy in Magnetic Resonance Imaging–Defined Poor-Prognosis Locally Advanced Rectal Cancer: The AVACROSS Study

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ABSTRACT

Background. Concomitant chemoradiotherapy followed by total mesorectal excision is standard treatment for locally advanced rectal cancer. This approach, however, focuses on local disease control and delays systemic treatment. Induction chemotherapy has the advantage of earlier administration of systemic therapy and may improve distant control. The objective of the current study was to assess the efficacy and toxicity of adding bevacizumab to induction chemotherapy followed by preoperative bevacizumab-based chemoradiotherapy in patients with locally advanced rectal cancer.

Patients and Methods. Eligible patients had high-risk rectal adenocarcinoma defined by magnetic resonance imaging criteria. Treatment consisted of four 21-day cycles of bevacizumab (7.5 mg/kg) and XELOX (capecitabine plus oxaliplatin), followed by concomitant radiotherapy (50.4 Gy) plus bevacizumab (5 mg/kg every 2 weeks) and capecitabine (825 mg/m² twice daily on days 1–15). Surgery was scheduled for 6–8 weeks after chemoradiotherapy. The primary endpoint was pathologic complete response (pCR).

Results. Between July 2007 and July 2008, 47 patients

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were recruited. Among 45 patients who underwent surgery, pCR was achieved in 16 patients (36%; 95% confidence interval: 22.29%–51.27%), and an additional 17 patients (38%) had Dworak tumor regression grade 3. R0 resection was performed in 44 patients (98%). Most grade 3/4 adverse events occurred during the induction phase and included diarrhea (11%), asthenia (4%), neu-

tropenia (6%), and thrombocytopenia (4%). Eleven patients (24%) required surgical reintervention.

Conclusions. Addition of bevacizumab to induction chemotherapy and chemoradiotherapy is feasible, with impressive activity and manageable toxicity. However, caution is recommended regarding surgical complications. *The Oncologist* 2011;16:614–620

INTRODUCTION

The current approach for treating patients with locally advanced rectal cancer prioritizes local control over systemic treatment. Preoperative chemoradiotherapy (CRT) is the current standard treatment. This CRT consists of concomitant 5-fluorouracil (5-FU) or capecitabine plus radiotherapy (RT) for 5 weeks, followed by surgery 6–8 weeks later [1, 2]; adjuvant chemotherapy (CT) is administered to some patients after a postoperative recovery period. In many cases, therefore, systemic treatment can be delayed for up to 4 months following the original diagnosis.

Efforts to improve the long-term efficacy of treatment have generally involved the addition of new drugs to the CT backbone or the inclusion of an induction CT regimen prior to the CRT schedule. Several phase I/II clinical trials have shown that similar pathologic complete response (pCR) rates have been achieved when RT is administered with capecitabine either alone or in combination with oxaliplatin or irinotecan [3, 4]. However, induction capecitabine-based CT prior to CRT has proved to be a feasible approach, with pCR rates up to 24% [5–8].

The use of targeted therapies with standard CT regimens has also been investigated in patients with rectal cancer, based on promising results in patients with colorectal cancer in whom the addition of bevacizumab to CT has been shown to improve clinical outcome [9–11]. In the rectal cancer setting, a phase I clinical study of bevacizumab plus standard 5-FU–based CRT demonstrated reductions in tumoral perfusion, vascular volume, microvascular density, interstitial pressure, and viable endothelial cells [12]. The combination of bevacizumab with oxaliplatin and capecitabine, which has demonstrated safety and efficacy in patients with colorectal cancer [11], was active and well tolerated when combined with RT in a phase I study in patients with metastatic or locally advanced rectal adenocarcinoma [13].

The present multicenter phase II study was therefore initiated to assess the efficacy and toxicity of adding bevacizumab to induction CT followed by preoperative bevacizumab-based CRT in patients with locally advanced rectal cancer.

PATIENTS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and all of its amendments, and with Spanish laws and regulations, whichever afforded the greater protection to patients. The study was approved by the ethics committee in each of the institutions and all patients provided written informed consent.

Patient Selection

Eligibility criteria included histologically confirmed, locally advanced rectal adenocarcinoma, defined as a tumor with inferior edge ≤ 12 cm from the anal margin, as measured by rectoscopy, with any of the following risk criteria evaluated on pelvic magnetic resonance imaging (MRI): T3 tumor in the inferior third of the rectum; tumor in the middle third of the rectum with an edge located ≤ 2 mm from the circumferential resection margin (CRM); lymph node metastasis (N+) with an edge or margin located ≤ 2 mm from the CRM; tumor or N+ that directly infiltrated the CRM; operable T4 tumor; or any T3N+ disease. N+ disease was defined as any mesorectal lesion/adenopathy meeting at least one of the following criteria: size ≥ 6 mm measured on axial view and considering the diameter as the shorter axis; or any mesorectal lesion/adenopathy with an irregular outline, edge, or margin.

The main exclusion criteria included the following: history of cardiac disease or uncontrolled hypertension; recent or current use of full-dose oral or parenteral anticoagulants or thrombolytic agents (low doses of warfarin were permitted, with an international normalized ratio ≤ 1.5); chronic daily treatment with high-dose aspirin (>325 mg/day); or treatment with nonsteroidal anti-inflammatory drugs.

Study Treatment

Induction treatment was four 3-week cycles of intravenous bevacizumab (7.5 mg/kg) plus XELOX (oxaliplatin 130 mg/m² on day 1, with oral capecitabine 1000 mg/m² twice daily on days 1–15 of the cycle). Patients began CRT 3–6 weeks after the last induction cycle. RT consisted of a total of 45 Gy delivered in 25 daily fractions over 5 weeks (1.8 Gy/d for 5 d/wk), followed by a boost of 5.4 Gy (1.8 Gy/d

for 3 days). Patients received concomitant bevacizumab (5 mg/kg) on day 1 of weeks 1, 3, and 5, plus capecitabine (825 mg/m²) twice daily throughout RT. Total mesorectal excision (TME) was performed 6–8 weeks after the completion of CRT. Postoperative adjuvant CT was administered at the investigators' discretion; four cycles of XELOX was the recommended regimen.

Patient Evaluation

Pretreatment evaluation included a complete medical history and physical examination, hematology, chemistry, coagulation profile, urinalysis, carcinoembryonic antigen, electrocardiogram, thoracic x-ray, abdominal computerized axial tomography, and pelvic MRI. Medical history, physical examination, and laboratory studies were repeated prior to the start of each treatment cycle. Tumor assessments (pelvic MRI) were performed at the end of the induction and CRT phases. After surgery, histologic tumor infiltration (ypT_{yp}N) and grading of regression (assessed using the Dworak scale [14]) were evaluated. All patients were scheduled for a follow-up period of 5 years after surgery.

Patients were evaluated for adverse events during therapy and for 28 days after the last study drug dose. Adverse events were graded according to National Cancer Institute Common Terminology Criteria (version 3.0).

Statistical Considerations

The primary endpoint of the study was pCR rate, assessed using the Dworak scale. The sample size was calculated according to Simon's two-stage design: if the pCR rate was $\leq 5\%$ (π_0), recruitment would end; if the pCR rate was $\geq 21\%$ (π_1), recruitment would continue. Accordingly, assuming $\alpha = 0.05$ and $\beta = 0.1$, 18 patients were required for the first stage and 26 for the second stage.

Other endpoints included percentage of total resections (R0), toxicity, surgical morbidity, local and distance relapse, and disease-free survival (DFS). DFS was calculated from the start of study treatment until disease progression or death from any cause using the Kaplan-Meier method. Analyses were performed using SPSS statistical analysis software (version 17.0; SPSS Inc., Chicago, USA).

RESULTS

Patients and Treatment

Between July 2007 and July 2008, 47 patients were entered into the study. Baseline patient characteristics are summarized in Table 1. All patients completed the first cycle of induction CT; 94%, 89%, and 85% completed the second, third, and final cycles, respectively. Most patients under-

Table 1. Clinical characteristics at baseline ($n = 47$)

Characteristic	Value
Median age, years (range)	58.5 (51–65)
Median Karnofsky performance status, % (range)	90 (90–100)
Sex, n (%)	
Male	33 (70)
Female	14 (30)
Risk group, ^a n (%)	
1	12 (26)
2	3 (6)
3	4 (9)
4	3 (6)
5	3 (6)
6	22 (47)
TNM stage, n (%)	
T3N0	5 (11)
T3N1	22 (47)
T3N2	14 (30)
T4N0	2 (4)
T4N1	2 (4)
T4N2	2 (4)

^aRisk group was determined by pelvic magnetic resonance imaging as follows: Group 1: T3 tumor in the inferior third of rectum; group 2: tumor in the middle third of rectum, edge ≤ 2 mm from circumferential resection margin (CRM; threatened CRM); group 3: N+, edge or margin located ≤ 2 mm from CRM (threatened CRM); group 4: tumor or N+ directly infiltrating the CRM; group 5: tumor T4 (operable); group 6: any T3N+.

went concomitant CRT, with 85% completing the first and second cycles and 83% completing the third cycle. Among the 45 patients (96%) who proceeded to surgery, 39 (87%) had received the planned treatment. The remaining 6 patients (13%) underwent surgery without completing the scheduled treatment: 2 patients had only one induction cycle; 3 patients had 2 or 3 induction cycles followed by RT but no concomitant CT; and 1 patient did not receive the last concomitant CT cycle.

Treatment Efficacy

Of the 45 patients who underwent surgery, 16 patients (36%; 95% confidence interval [CI]: 22.29%–51.27%) had a pCR in the primary tumor and lymph nodes, whereas an additional 17 patients (38%) achieved grade 3 tumor regressions (Table 2). Absence of residual tumor (R0) was achieved in all except 1 patient, who had received only one induction CT cycle and had microscopic residual disease (R1). In general, patients who were unable to complete

Table 2. Histologic tumor regression grade and infiltrating status (ypTypN) after surgery (*n* = 45)

	No. patients (%)
Tumor regression grade ^a	
0	1 (2)
1	3 (7)
2	6 (13)
3	17 (38)
4	16 (36)
Not determined	2 (4)
ypTypN	
T0N0	16 (36)
T1N0	6 (13)
T2N0	9 (20)
T3N0	7 (16)
T3N1	7 (16)

^aGrade 0: no regression; grade 1: dominant tumor mass with obvious fibrosis and/or vasculopathy; grade 2: predominantly fibrotic changes with few tumor cells or groups (easy to find); grade 3: very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; grade 4: no tumor cells, only fibrotic mass (total regression or response).

treatment as planned did not achieve a satisfactory response. Among the 39 patients who completed preoperative treatment plus the 1 patient who received all but the fourth induction cycle, 83% attained Dworak tumor regression grade (TRG) 3 or 4 responses.

After a mean follow-up of 32 months, 38 patients continued to be free of any sign of disease. Five patients had metastatic progression, including the only patient in the study group to have had local failure, the patient with R1 surgery. Three patients had died, two as a result of metastatic disease and another with a second neoplasm of the larynx. One patient was lost to follow-up, without evidence of disease, at 11 months.

Toxicity

Adverse events observed in this study are summarized in Table 3. During the induction phase, the most frequent grade 3/4 adverse events were diarrhea (11%), asthenia (4%), neutropenia (6%), and thrombocytopenia (4%). Moreover, two patients died because of sudden death or diabetic ketoacidosis. During the CRT phase, grade 3 adverse events were lymphopenia (2.5%), rectal tenesmus (2.5%), and hypertriglyceridemia (2.5%). No grade 4 adverse events or deaths were reported during CRT.

Lower anterior resection and abdominoperineal resec-

tion were performed in 30 (67%) and 14 (31%) patients, respectively, and other procedures were performed in another patient. Sphincter preservation was not achieved in 18 patients (40%). Twenty-six patients (58%) experienced at least one postoperative complication. The complications experienced by these patients were wound infection (10 events), intra-abdominal infections (7 events), anastomotic leak (5 events), stoma complications (2 events), and other complications (10 events). Eleven patients (24%) required repeat surgery possibly as a result of study procedures, although seven of these patients had a previously permanent colostomy or protection ileostomy.

These complications were generally due to suture failures: six patients had secondary pelvic abscesses that resolved with drainage, four patients required an ileostomy/colostomy, and one patient had suppurative peritonitis.

DISCUSSION

Preoperative CRT with fluoropyrimidines followed by TME is preferred over postoperative CRT for patients with locally advanced rectal cancer because of good overall compliance rates, improved local control, reduced toxicity, and an increased rate of sphincter preservation in patients with low-lying tumors [15]. The addition of active drugs to the preoperative regimen does not, however, greatly improve the efficacy of treatment [3]. Indeed, two randomized studies have confirmed that the addition of oxaliplatin to fluoropyrimidine-based CRT increased toxicity but did not significantly improve local control rates [16, 17], although there appeared to be a lower rate of patients with metastases at surgery in the oxaliplatin group in the STAR study [16]. Promising results have, however, been reported for induction CT, which has the potential advantage of delivering effective therapy early in the course of disease while the tumor is intact and the patient's performance status is good. This approach can result in better tumor shrinkage compared with classic preoperative chemoradiotherapy and can also enhance treatment exposure to micrometastatic disease [6]. Chau and colleagues treated patients with high-risk rectal cancer with capecitabine and oxaliplatin followed by synchronous CRT and TME [5]. They observed a pCR rate of 24%, with residual microscopic disease in 48% of patients, no progression during the induction phase, symptomatic improvement shortly after commencing treatment, and downstaging in 76% of patients [5]. A pCR rate of 20% was later reported for this regimen in an expanded patient group [7]. In a randomized comparison of induction versus adjuvant capecitabine–oxaliplatin, however, no difference in clinical outcomes was observed between the two treatment regimens, although the induction regimen had a more favorable safety profile [6].

Table 3. Adverse events reported during induction chemotherapy and concomitant chemoradiotherapy

Adverse event	No. of patients (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Induction treatment (<i>n</i> = 47)					
Anorexia	5 (11)	2 (4)	1 (2)	0 (0)	8 (17)
Elevated aspartate aminotransferase	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)
Asthenia	10 (21)	10 (21)	2 (4)	0 (0)	22 (47)
Elevated bilirubin levels	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)
Diarrhea	6 (13)	4 (8.5)	5 (11)	0 (0)	15 (32)
Arterial hypertension	3 (6)	1 (2)	1 (2)	0 (0)	5 (11)
Mucositis	8 (17)	3 (6)	0 (0)	0 (0)	11 (23)
Peripheral neuropathy	13 (28)	2 (4)	1 (2)	0 (0)	16 (34)
Neutropenia	2 (4)	0 (0)	3 (6)	0 (0)	5 (11)
Thrombocytopenia	3 (6)	0 (0)	1 (2)	1 (2)	5 (11)
Hand-foot syndrome	2 (4)	5 (11)	0 (0)	0 (0)	7 (15)
Deep vein thrombosis	0 (0)	1 (2)	1 (2)	0 (0)	2 (4)
Vomiting	9 (19)	5 (11)	1 (2)	0 (0)	15 (32)
Concomitant chemoradiotherapy (<i>n</i> = 40)					
Anemia	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)
Lymphopenia	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)
Asthenia	5 (13)	3 (8)	0 (0)	0 (0)	8 (20)
Cystitis	4 (10)	1 (3)	0 (0)	0 (0)	5 (13)
Diarrhea	3 (8)	4 (10)	0 (0)	0 (0)	7 (18)
Skin reaction	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)
Hemorrhage	0 (0)	1 (3)	0 (0)	0 (0)	1 (3)
Arterial hypertension	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)
Hypertriglyceridemia	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)
Nausea	4 (10)	0 (0)	0 (0)	0 (0)	4 (10)
Neuropathy	2 (5)	0 (0)	0 (0)	0 (0)	2 (5)
Rectal tenesmus	2 (5)	0 (0)	1 (3)	0 (0)	3 (8)
Rectitis	0 (0)	1 (3)	0 (0)	0 (0)	1 (3)

In the present study, the addition of bevacizumab to a similar CRT regimen in patients with MRI-defined poor prognosis resulted in a pCR rate of 36%, with an additional 51% of patients having residual microscopic disease (TRG 2 or 3). Although comparisons between studies must be made with caution, these findings appear to be very promising. A retrospective review of neoadjuvant CT and RT regimens in patients who had not been selected according to MRI criteria reported a median ypCR result of 23% [18]; in randomized studies, pCR rates of 8%–26% have been reported [19–21]. Others have reported promising results following the addition of bevacizumab to standard preoperative CRT. Willett and colleagues reported a pCR rate of 16%, and an additional 72% of patients who had only microscopic foci remaining after treatment with bevacizumab and 5-FU plus RT in a phase I/II study in patients with T3/T4 tumors [22].

In a phase II study in patients with T3/4, N1, or recurrent disease, administration of capecitabine and bevacizumab concomitant with preoperative RT resulted in a pCR rate of 32% and a microscopic residual disease rate of 24% [23]. A slightly lower pCR rate of 24% was observed in a phase II study of patients with T3/4N0 or T1-4N1-3 rectal cancer who received induction CT comprising only two cycles of 5-FU/LV + oxaliplatin (FOLFOX6) plus bevacizumab, followed by concomitant RT plus FOLFOX and bevacizumab [24].

Studies have shown a positive correlation between response to treatment and DFS [18, 20, 25]. In the study by Rodell and colleagues, complete regression (TRG 4) was associated with longer DFS, better local and lymph node con-

tol, and reduced risk of distant metastases [20]. Poor tumor regression (TRG 0 or 1) was associated with adverse pathologic features such as more advanced ypT categories and a higher incidence of nodal involvement and was predictive of an unfavorable outcome [20]. TRG alone is not a definitive indicator, however; well-established histopathologic factors such as ypT and ypN staging are also relevant prognostic factors [26]. As ypCR (ypT0N0) after neoadjuvant therapy [18] and ypT0-2 [27] are considered indicators of good prognosis, nearly 70% of patients in the present study with ypT0-2 after surgery may be considered to have a favorable prognosis.

Overall, the adverse-event profile of the present treatment regimen was as expected. However, special attention needs to be paid to the sudden death suffered by one patient during the induction phase; this may have been a result of cardiac effects of capecitabine [28] and/or bevacizumab [29]. In a previous study of capecitabine-based induction CT, two deaths attributed to cardiac toxicity occurred during the induction CT phase, leading to a protocol amendment and the subsequent exclusion of patients with a recent history of clinically significant cardiac problems [5]. Moreover, the rate of postsurgical complications was not negligible in the present study; most were associated with wound-healing complications and 24% of patients required further surgery. Intestinal deviation at the time of initial surgery did not appear to have a protective effect against suture failures. However, the relationship between these wound-healing complications and bevacizumab is unclear, as the median time from the last dose of bevacizumab to surgery

was 2 months, which is longer than the half-life of bevacizumab [30].

CONCLUSIONS

The results of this study suggest that adding bevacizumab to induction CT and concomitant CRT is a feasible and active approach to treating patients with MRI-defined, poor-prognosis, locally advanced rectal cancer. This regimen does not increase the toxicity burden of the induction and concomitant treatment, although some postoperative complications were observed. Further studies are required to define the exact contribution of bevacizumab to these results and to assess the impact that induction CT and concomitant CRT have on the outcome of treatment.

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