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Preoperative Radiation Therapy with Concurrent Capecitabine, Bevacizumab and Erlotinib for Rectal Cancer: A Phase I Trial

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Summary

This phase I trial evaluated preoperative radiotherapy with concurrent capecitabine, bevacizumab and erlotinib for rectal cancer. Eighteen patients were evaluable. Treatment was well tolerated, and the maximum tolerated dose (MTD) was not reached. One patient had grade 3 acute toxicity and 3 patients had grade 3 post-operative complications. 44% of patients had pathologic complete response. The 3-year disease-free survival rate was 94%.

Objectives—The goal of this phase I trial was to determine the maximum tolerated dose (MTD) of concurrent capecitabine, bevacizumab and erlotinib with preoperative radiation therapy for rectal cancer.

Methods/Materials—Patients with clinical stage II-III rectal adenocarcinoma, within 12 cm from the anal verge, were treated in 4 escalating dose levels, using the continual reassessment method. Patients received preoperative radiation therapy with concurrent bevacizumab (5 mg/kg intravenously every 2 weeks), erlotinib and capecitabine. Capecitabine dose was increased from 650 mg/m² to 825 mg/m² orally twice daily on the days of radiation therapy; erlotinib dose was increased from 50 mg orally daily in weeks 1–3, to 50 mg daily in weeks 1–6, to 100 mg daily in weeks 1–6. Patients underwent surgery at least 9 weeks after the last dose of bevacizumab.

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Results—Nineteen patients were enrolled, and 18 patients were considered evaluable. No patient had grade 4 acute toxicity and 1 patient had grade 3 acute toxicity (hypertension). The MTD was not reached. All 18 evaluable patients underwent surgery, with low anterior resection in 7 (39%), proctectomy with coloanal anastomosis in 4 (22%), posterior pelvic exenteration in 1 (6%), and abdominoperineal resection in 6 (33%) patients. Of the 18 patients, 8 (44%) had pathologic complete response, and 1 had complete response of the primary tumor with positive nodes. Three patients (17%) had grade 3 post-operative complications (ileus, small bowel obstruction and infection). With a median follow-up of 34 months, 1 patient developed distant metastasis, and no patient had local recurrence or death. The 3-year disease-free survival was 94%.

Conclusions—The combination of preoperative radiation therapy with concurrent capecitabine, bevacizumab and erlotinib was well tolerated. The pathologic complete response rate appears promising and may warrant further investigation.

INTRODUCTION

Preoperative radiation therapy with concurrent fluoropyrimidine has been widely accepted as a standard of care for stage II and III rectal cancer^{1,2}. A recent update from the German Intergroup trial showed that preoperative chemoradiation reduced 10-year local relapse rates compared to postoperative chemoradiation³. Randomized trials have also shown that preoperative radiation with concurrent 5-fluorouracil (5-FU) improves local control and pathologic complete response rates, compared to preoperative long course radiation alone^{4,5}.

Preoperative radiation with concurrent 5-FU or its oral prodrug, capecitabine yields pathologic complete response (pathCR) rates of around 10–20%^{1,2,4–6}. Improving the pathCR rate could potentially improve local control and sphincter preservation rates. Moreover, since patients with pathCR show improved long-term oncologic outcomes, an increase in the pathCR rate could potentially lead to an improvement in overall oncologic outcomes^{7,8}. Many clinical trials have evaluated the addition of other chemotherapeutic and biologic agents to fluoropyrimidine-based chemoradiation in an effort to increase the pathCR rate. Three randomized trials have shown that the addition of concurrent oxaliplatin to capecitabine or 5-FU does not increase the pathCR rate^{6,9,10}. Phase II trials have reported that the addition of concurrent bevacizumab to chemoradiation results in pathCR rates of 16–32%^{11–16}. Other prospective trials have shown that the addition of cetuximab to chemoradiation does not improve and may even impair pathologic response, with reported pathCR rates of 5–9%^{17–20}.

Our hypothesis was that simultaneous targeting of the vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) pathways, in combination with chemoradiation, would improve pathCR rates in patients with rectal cancer. We evaluated the addition of bevacizumab, a fully humanized monoclonal antibody against VEGF-A, and erlotinib, an oral EGFR tyrosine kinase inhibitor, to capecitabine-based chemoradiation. The primary objective of this phase I trial was to determine the maximum tolerated dose (MTD) of concurrent capecitabine, bevacizumab, and erlotinib with preoperative radiation therapy

for the neoadjuvant treatment of rectal cancer. Secondary objectives included determining the rates of pathCR and disease-free survival (DFS).

METHODS

Eligibility

The study included patients with stage II-III (T3-4 and/or node-positive) rectal adenocarcinoma, based on endorectal ultrasound (EUS) and/or pelvic magnetic resonance (MR) imaging. The tumor had to be within 12 cm of the anal verge, and there had to be no evidence of distant metastasis on chest CT, and abdomen-pelvic CT or MR. The study included patients with age of at least 18, and Eastern Cooperative Oncology Group (ECOG) performance status 0–1. Other inclusion criteria were hemoglobin ≥ 9 g/dL, absolute neutrophil count $\geq 1500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, total bilirubin <2 mg/dL, blood urea nitrogen ≤ 30 mg/dL, creatinine ≤ 1.5 mg/dL, and creatinine clearance ≥ 30 mL/minute.

Exclusion criteria were inadequately controlled hypertension, recent history of myocardial infarction or unstable angina, class II or greater congestive heart failure, unstable symptomatic arrhythmia, class II or greater peripheral vascular disease, history of stroke or transient ischemic attack, history of hypertensive crisis or hypertensive encephalopathy, history of aortic aneurysm or aortic dissection, recent history of peripheral arterial thrombosis, proteinuria or significantly impaired renal function, impaired hepatic function, coagulopathy, serious and uncontrolled infection, non-healing wound, ulcer or bone fracture, and recent abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess. Patients with prior pelvic radiation therapy, chemotherapy, VEGF or EGFR-directed therapy, or recent surgical procedure were also excluded.

Treatment

Patients were treated in four escalating dose levels, in cohorts of 2 patients, using the continual reassessment method, with a target dose-limiting toxicity (DLT) rate of 25% at the MTD ²¹. Table 1 shows the doses of capecitabine, bevacizumab, and erlotinib in the four dose levels. Capecitabine was given only on the days of radiation, with the dose increased from 650 mg/m² orally twice daily in dose level 1, to 825 mg/m² orally twice daily in dose levels 2–4. In all dose levels, patients were given bevacizumab 5 mg/kg intravenously every two weeks, starting with the first week of radiation. The erlotinib dose was increased from 50 mg orally daily given only in the first three weeks of radiation (dose levels 1–2), to 50 mg orally daily given throughout the radiation course (dose level 3), to 100 mg orally daily given throughout (dose level 4). All patients were treated with a radiation dose of 45 Gy in 25 fractions to the pelvis, and 50.4 Gy in 28 fractions to the primary rectal tumor. Patients underwent surgical resection with a minimum interval of 9 weeks after the last dose of bevacizumab. Following surgery, patients were given adjuvant chemotherapy, with the regimen at the discretion of the treating medical oncologist.

Assessment of Toxicity and Outcomes

Acute toxicity was assessed during and within 4 weeks after chemoradiation. Patients were seen on a weekly basis during chemoradiation and for a follow up visit 4 weeks after

completion of chemoradiation. Information on post-operative toxicity and complications was recorded in electronic hospital records by surgical collaborators. Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0²². Grade 3 or higher acute toxicity was considered to be DLT.

Pathologic response was determined by gastrointestinal pathologists at our institution. After surgery and adjuvant chemotherapy, patients were seen for follow-up every 3–4 months for the first year, and every 4–6 months thereafter. Patients underwent CT of the chest, abdomen and pelvis within 6 months after completion of adjuvant chemotherapy, and every 6 months thereafter. DFS was measured from the date of surgery and was estimated by Kaplan-Meier methods²³.

RESULTS

Patient and Treatment Characteristics

Nineteen patients were enrolled in the study. Of these, one withdrew early because of insurance reasons; this patient was considered non-evaluable and has not been included in our analysis. Patient characteristics are shown in Table 2. Of the 18 evaluable patients, 9 underwent EUS, 8 underwent EUS and MR, and 1 underwent only MR for staging. The clinical T category was T3 in 17 and T4 in 1 patient. Fourteen patients had clinically node-positive disease. The median distance of the inferior extent of the tumor from the anal verge was 4.5 cm.

Of the 18 patients, 2 were enrolled in dose level 1, 4 in dose level 2, 4 in dose level 3, and 8 in dose level 4. Patients underwent computed tomography (CT) based simulation for radiation therapy planning. Fifteen patients were treated in a prone position, using a belly board device for bowel displacement, with a 3-field technique (PA and right and left laterals) and a dose of 45 Gy in 25 fractions to the pelvis, followed by a boost (right and left laterals) with an additional 5.4 Gy in 3 fractions to the rectal tumor, involved nodes and adjacent pelvic and presacral regions. The remaining 3 patients were treated with intensity modulated radiation therapy in order to cover the inguinal regions, with a dose of 45 Gy in 25 fractions to the pelvis and inguinal regions, and a sequential boost of 5.4 Gy in 3 fractions to the rectal tumor; suspicious inguinal nodes were given an integrated boost of 60–63 Gy in 2 of these patients.

All patients underwent surgery with total mesorectal excision (TME). The median interval between completion of chemoradiation and surgery was 8.2 weeks (range 7.3–14.6 weeks); this interval was less than 10 weeks in all but one patient. The specific surgical procedures were low anterior resection in 7 (39%), proctectomy with coloanal anastomosis in 4 (22%), posterior pelvic exenteration in 1 (6%) and abdominoperineal resection in 6 (33%) patients. Hence, 11 (61%) patients had sphincter preservation. All patients undergoing sphincter preservation underwent temporary diverting ileostomy. All patients received adjuvant chemotherapy, with an oxaliplatin-based regimen in 17 patients, and single agent capecitabine in 1 patient.

Toxicity

Seventeen patients developed grade 2 acute toxicity (Table 3). One patient, at dose level 2, developed grade 3 hypertension. No patient developed any other grade 3 or 4 acute toxicity. Based on prespecified guidelines, capecitabine was stopped early or given at a reduced dose in 3 patients with grade 2 acute toxicity (1 in dose level 2, 2 in dose level 4); erlotinib was also stopped early in one of these patients. The MTD was not reached. Based on the continual reassessment model, the posterior probability of DLT at the highest dose level was 0.15.

Three patients developed grade 3 post-operative complications: ileus, small bowel obstruction with pelvic abscess, and cellulitis. In addition, 3 patients developed grade 2 post-operative complications: pelvic abscess (N=2) and anal fissure (N=1).

Pathologic Response

Of the 18 patients, 8 (44%) had pathCR (Table 4). The percentage of patients with pathCR was 50% in each of dose levels 1–3, and 38% in dose level 4. In addition to the 8 patients with pathCR, 1 patient had a complete response at the primary site with pathologically involved lymph nodes, and 8 patients had 10% viable tumor in the pathologic specimen. Thus, 17 (94%) patients had either pathologic complete response or complete response of the primary tumor or 10% viable tumor in the surgical specimen. The yp T and N categories were T0N0 (N=8), T0N1 (N=1), T1N0 (N=1), T2N0 (N=3), T2N1 (N=1), T3N0 (N=1), T3N1 (N=2), and T3N2 (N=1). Down-staging of the T category was seen in 15 (83%) patients.

Oncologic Outcomes

The median follow-up interval was 34 (range 20–64) months from the date of surgery. There were no deaths or local recurrences. One patient developed a single pulmonary metastasis 9 months after surgery for rectal cancer and underwent a wedge resection for the metastasis. No other patient developed metastasis. The 3-year estimated DFS rate was 94%.

DISCUSSION

In this phase I trial, the combination of preoperative radiation therapy with concurrent capecitabine, bevacizumab and erlotinib was well tolerated, with relatively low rates of acute and post-operative toxicity. While the MTD was not reached, the highest dose level in this study could potentially be used for future studies. The pathologic response rate appears impressive, with 44% of patients having pathCR. The 3-year DFS rate of 94% also appears promising.

This phase I trial has its limitations. The trial was originally designed as a phase I/II trial, but was closed early because of withdrawal of financial support. Given the small number of patients, it is difficult to draw firm conclusions regarding the pathCR or DFS rates for this combination of preoperative therapy. Moreover, the primary endpoint for the phase I portion of the trial was MTD and toxicity, and not the pathCR rate. Nevertheless, the results from this trial are intriguing, and represent among the highest reported rates of pathologic

response. Further studies will be necessary to confirm the rates of pathCR and DFS with this regimen.

Previous trials with bevacizumab have shown pathCR rates of 16–32%, while trials with cetuximab have shown pathCR rates of 5–9%^{11–20}. The much higher pathologic response rate seen in this trial suggests that dual targeting of the VEGF and EGFR pathways may have a synergistic effect on chemoradiation. There is prior evidence supporting the combination of bevacizumab and erlotinib in colorectal cancer; a randomized trial has shown that maintenance therapy with bevacizumab and erlotinib improves progression-free survival, compared to maintenance therapy with bevacizumab alone in patients with metastatic colorectal cancer²⁴. The role of erlotinib appeared to be independent of KRAS status in that trial²⁵.

Previous trials with concurrent bevacizumab and preoperative radiotherapy have reported high rates of surgical complications^{11–15}. In contrast, in this trial only 3 (17%) patients developed grade 3 and 2 developed grade 2 post-operative complications. We hypothesize that the minimum 9 week interval between the last dose of bevacizumab and surgery may have helped ameliorate surgical complications.

It is possible that the extended interval between chemoradiation and surgery may have increased the rate of pathologic response in this trial. In a recent phase II trial evaluating the optimal interval between chemoradiation and surgery, patients with an average 6 week interval had 18% pathCR, while those with an average 11 week interval had 25% pathCR²⁶. In the current trial, the median interval between chemoradiation and surgery was around 8 weeks, with almost all patients undergoing surgery within 10 weeks of completing chemoradiation. Hence, it is unlikely that the high rates of pathCR were solely due to the interval between chemoradiation and surgery.

A major limitation of this study is the lack of pretreatment KRAS testing, and other biomarker or correlative studies. However, given the small number of patients in this trial, it would be difficult to derive meaningful conclusions from biomarker or correlative studies. Also, the very high rate of complete and near-complete pathologic response would make it difficult to determine clinical or biologic predictors of response. Future studies are warranted on biologic and genomic determinants of response to chemoradiation in rectal cancer patients, with the ultimate goal being biomarker-driven studies of targeted therapies.

The current standard of preoperative fluoropyrimidine-based chemoradiation followed by total mesorectal excision for rectal cancer results in excellent local control; the German Intergroup trial recently reported 10-year local relapse rates of only 7.1% in the preoperative chemoradiation arm³. Hence, it would likely be difficult to further improve local control by enhancing radiosensitization. However, enhanced radiosensitization may improve pathologic response, which could have potential benefits for rectal cancer. Studies have shown that patients with pathCR have improved oncologic outcomes^{7, 8}. Increasing the pathologic response could potentially improve long-term disease control and survival. Indeed, the high DFS rate in this trial is consistent with previous reports correlating pathologic response and long-term outcomes. Moreover, increased pathologic response may lead to enhanced

sphincter preservation in patients with low rectal cancers. Increased pathologic response may even allow us to pursue studies on local excision or watchful waiting in a greater proportion of patients ^{27–30}.

In conclusion, this phase I trial showed that the combination of preoperative radiation therapy with concurrent capecitabine, bevacizumab and erlotinib was well tolerated with a low rate of acute toxicity and a relatively low rate of post-operative complications. Moreover, this regimen led to high rates of pathologic response and DFS. Dual targeting of the VEGF and EGFR pathways could potentially have a synergistic effect on radiosensitization. Further clinical and correlative studies may be warranted on the combination of preoperative radiotherapy with concurrent capecitabine, bevacizumab and erlotinib for rectal cancer.

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Table 1

Dose Levels

Dose Level	Number of Patients	Capecitabine*	Bevacizumab	Erlotinib
1	2	650 mg/m ² , twice daily	5 mg/kg q 2 wks X 3	50 mg daily, wks 1–3
2	4	825 mg/m ² , twice daily	5 mg/kg q 2 wks X 3	50 mg daily, wks 1–3
3	4	825 mg/m ² , twice daily	5 mg/kg q 2 wks X 3	50 mg daily, wks 1–6
4	8	825 mg/m ² , twice daily	5 mg/kg q 2 wks X 3	100 mg daily, wks 1–6

* Given only on days of radiation

Table 2

Patient Characteristics

Characteristic	Number of Patients (%) or Median (Range)
Age (years)	48 (26–60) years
Gender	
Male	10 (56%)
Female	8 (44%)
Clinical Stage	
T3N0	3 (17%)
T3N1	13 (72%)
T3N2	1 (6%)
T4N0	1 (6%)
Grade	
Moderately differentiated	17 (94%)
Poorly differentiated	1 (6%)
Distance from Anal Verge (cm)	4.5 (1.5–9) cm
Pretreatment CEA Level (ng/mL)	1.4 (<1–14.8)

CEA: carcinoembryonic antigen

Table 3

Highest Grades of Acute And Post-operative Toxicity

	Number of Patients		
	Grade 2	Grade 3	Grade 4
<u>Acute Toxicity</u>			
Acneiform rash	7	0	0
Pain	5	0	0
Radiation dermatitis	4	0	0
Diarrhea	3	0	0
Nausea/vomiting	3	0	0
Fatigue	3	0	0
Stomatitis	2	0	0
Hand foot syndrome	1	0	0
Cystitis	1	0	0
Hyperbilirubinemia	1	0	0
Hypertension	0	1	0
<u>Post-operative Toxicity</u>			
Pelvic abscess	2	1	0
Small bowel obstruction	0	1	0
Ileus	0	1	0
Cellulitis	0	1	0
Anal fissure	1	0	0

Table 4

Pathologic Response

Characteristic	Number of Patients (%)
Complete Response (ypT0N0)	8 (44%)
Complete Response with Positive Nodes (ypT0N+)	1 (6%)
10% viable tumor	8 (44%)
20–25% viable tumor	1 (6%)