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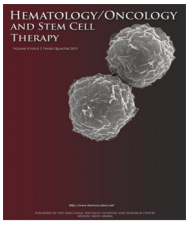

ORIGINAL RESEARCH REPORT

Pre-operative chemoradiotherapy using capecitabine and cetuximab followed by definitive surgery in patients with operable rectal cancer

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Abstract
Background: Achieving a high rate of complete pathological response with pre-operative chemoradiotherapy in rectal cancer is an unmet need. We evaluated the efficacy and toxicity of the combination of cetuximab, capecitabine and radiation therapy in the pre-operative setting of localized rectal cancer.
Patients and methods: Patients with clinically staged T3, T4 or nodepositive rectal cancer were treated with concurrent capecitabine and radiotherapy with weekly cetuximab starting one week before the start of radiation. This was followed by total mesorectal excision within 6-8 weeks. All patients achieving R0 resection received adjuvant capecitabine for 6 cycles.
Results: Fifteen patients were treated and all underwent surgery. Sphincter preservation was achieved in 11 patients (73.3%) and pathological complete response in two. With a median

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follow up of 48 months (range 8.4-57.5), 12 patients were relapse-free and 14 were alive with 4-year relapse free survival of 80%. Overall survival was 93%. Significant grade 3 and 4 toxicity was mainly cetuximab-induced skin reactions (33%), radiation-induced skin toxicity (13%) and diarrhea (20%).

Conclusions: Adding cetuximab to pre-operative concurrent capecitabine and radiotherapy provides modest efficacy with manageable toxicity.

Introduction

Colorectal cancer is one of the most common solid tumors worldwide with an estimated 1.4 million new cases and 693,900 deaths occurring in 2012 [1]. In Saudi Arabia, colorectal cancer is the most common solid tumor in men, and the third most common in women [2]. A high risk of loco-regional relapse of rectal cancer can cause significant morbidity and treatment failure. Locally advanced rectal cancer represents tumors with extension beyond the muscularis propria ($\geqslant$T3) and/or those with clinical or pathological evidence for lymph node metastasis (N+). In such cases, multimodal management approaches are recommended. Preoperative chemoradiotherapy followed by total mesorectal excision is considered a standard treatment for Stage II and III rectal cancer with potential benefits of decreasing the local relapse rate and improving the clinical outcome; nevertheless, approximately 8% of these patients develop local relapse [3—5]. Fluoropyrimidines, including 5-fluorouracil and the oral agent, capecitabine, are the most commonly used chemotherapeutic agents for preoperative chemoradiotherapy, with capecitabine often preferred for its convenience and safety profile [6,7].

Cetuximab (Erbitux, Merck, Darmstadt, Germany) is a chimeric immunoglobulin G1 monoclonal antibody directed against the epidermal growth factor receptor, a member of the HER tyrosine kinase growth factor receptor family that signals cellular differentiation, proliferation, and survival. Clinical trials have demonstrated significant clinical activity with cetuximab in patients with metastatic colorectal cancer [8—10], and this agent demonstrates synergistic antitumor activity with conventional chemotherapeutic drugs and irradiation both in vitro and in vivo [11]. This pilot study was carried out to assess the feasibility of adding cetuximab to the preoperative regimen of capecitabine and radiotherapy in locally advanced rectal cancer.

We have previously evaluated the addition of capecitabine to preoperative radiation therapy in locally advanced rectal cancer in a Phase II trial that included 31 patients, with a pathological complete response (pCR) achieved in 6.5% [12]. We hypothesized that the addition of cetuximab to preoperative chemoradiotherapy using capecitabine could improve the suboptimal results achieved with preoperative chemoradiotherapy alone. Here, we report the results of a pilot study evaluating this regimen in patients with operable rectal cancer.

Patients and methods

Eligibility

Eligible patients had histologically confirmed resectable rectal carcinoma, defined as a tumor within 15 cm from the anal verge as judged by rigid proctosigmoidoscopy and which can be encompassed by the radiation fields, T3—T4 and/or nodal involvement by rectal ultrasound, and/or magnetic resonance imaging (MRI). The colorectal surgical team at our institution was required to agree unanimously that a T4 tumor was resectable for the patient to be included in the study. In addition, eligible patients were aged $\geqslant$18 years, and were required to have no distant metastasis, no prior epidermal growth factor receptor-based therapy, Eastern Cooperative Oncology Group performance status of $\leqslant$2, and adequate bone marrow reserve, renal function, and hepatic function.

Patients were excluded from the study if they had evidence of metastasis, prior chemotherapy or radiotherapy, other serious medical conditions, prior diagnosis of cancer, and known or suspected dihydropyrimidine deficiency, or if the patient was pregnant.

Pretreatment evaluation

Pretreatment evaluation included complete medical history and physical examination. Surgical evaluation prior to enrolment included location of the tumor from the anal verge, fixation of the tumor, lumen status of the rectum at the tumor site, laterality and position of tumor, as well as prostate, bladder, or vaginal involvement. Evaluation also included the intended surgical procedure; abdominoperineal resection versus anterior resection. In addition, complete blood count, renal and hepatic profile, carcinoembryonic antigen (CEA), chest X-ray, colonoscopy, computed tomography (CT)/MRI, and abdominal/pelvic and endoscopic rectal ultrasound were performed.

Treatment

Chemoradiotherapy

The treatment schema is shown in Fig. 1. An initial cetuximab dose of 400 mg/m [2] was administered 1 week before the 1st day of radiotherapy, and continued as weekly cetuximab 250 mg/m [2] for a total of 7 weeks. Patients received concurrent chemotherapy with capecitabine 1,650 mg/m [2] (in two divided doses, 12 hours apart) daily throughout

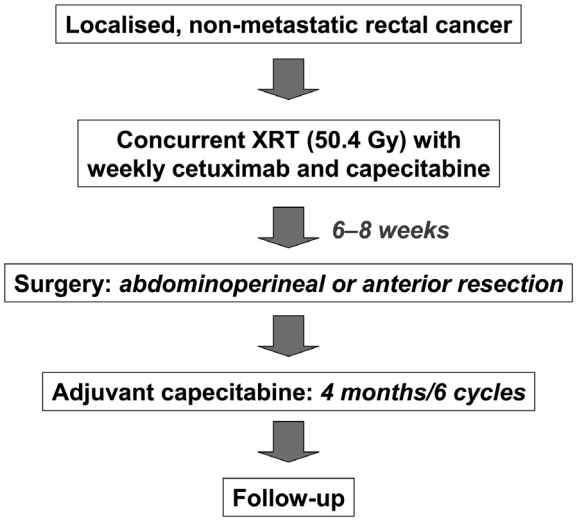

Fig. 1 Treatment schema. *Note*. XRT = external beam radiation therapy.

the 6-week course of preoperative irradiation, starting with the 1st day of radiation and ending with the last day of radiation.

Preoperative radiotherapy was delivered concurrently to the whole pelvis at a dose of 45 Gy in 25 fractions, followed by 5.4 Gy in a three-fraction boost to the primary tumor. All patients underwent a planning CT scan in the prone position with a full urinary bladder. Rectal contrast (30—50 mL of gastrografin mixture [two parts gastrografin to one part water]) was used for all patients. Initially, a four-field box technique (postero-anterior, antero-posterior, and two open lateral fields) was used, encompassing the primary tumor with a margin, and presacral and internal iliac lymph nodes. This was followed by a boost of 5.4 Gy in three fractions over 3 days to the gross tumor volume plus a 2-cm margin using a three-field technique. The tumor dose was prescribed at the isocenter according to the International Commission on Radiation Units and Measurements [13].

Surgery

Surgery was planned 4—6 weeks after completion of radiotherapy. The type of surgical approach was left to the discretion of the operating surgeon: anterior resection if feasible, otherwise abdominoperineal resection. Total mesorectal excision was performed on all patients according to the principles pioneered by Heald and Ryall [14] using open technique. Details of the surgical intervention have been previously described [8].

Adjuvant chemotherapy

The initial protocol for administration of adjuvant chemotherapy specified four cycles of 5-fluorouracil and leucovorin (Mayo Clinic regimen). However, on November 28, 2008, the protocol was amended to change adjuvant chemotherapy to capecitabine at a dose of 2,500 mg/m [2] daily (in two divided doses) on Days 1—14 every 21 days for six cycles, starting 4—6 weeks postsurgery. Patients with a body surface area value >2 m were rounded to 2 m [2].

Dose modification

Toxicity grading and dose modification were conducted according to the National Cancer Institute Common Terminology Criteria Version 3 [15]. Dose modifications were made according to the most severe toxicity observed during the previous week. For hand-foot syndrome, only the capecitabine dose was modified. For an acne-like rash, only the cetuximab dose was modified.

Capecitabine was withheld for neutropenia until the neutrophil count was $\geqslant 1.0 \times 10^9$/L and for thrombocytopenia until the platelet count was $\geqslant 75 \times 10^9$/L. For nonhematological toxicity, treatment was interrupted until resolution to Grade 1 or less.

Follow-up evaluation

All patients had CT scans of the abdomen and pelvis 8 weeks after last cycle of adjuvant chemotherapy and then annually for 5 years. Clinical evaluation and CEA measurement was performed every 4 months for the 1st 2 years, and then every 6 months up to the 5th year, for a total planned follow-up of 5 years. Colonoscopy was performed 1 year after surgery, then every 3 years.

Statistical analysis

The study was planned to enroll 15 patients to assess the feasibility and toxicity of preoperative concurrent chemotherapy with capecitabine, weekly cetuximab, and external beam radiation in the treatment of localized resectable rectal cancer as a primary endpoint. Secondary endpoints were to evaluate efficacy, including pCR, sphincter preserving surgery rate, local recurrence rate, disease-free survival, and overall survival. Patient accrual was planned to be over a period of 12 months. Progression-free survival was defined as the time from registration to local recurrence, distant failure, or death, whichever occurred first. Overall survival was defined as the time from registration to death due to cancer or any other cause. Patients who were alive at the time of our analysis were censored for survival. Our analysis was done on an intention-to-treat basis. Kaplan—Meier actuarial survival curves were constructed using SPSS.

RAS analysis

KRAS and *NRAS* analysis was conducted retrospectively and on separate occasions in view of the recent extended *RAS* data. DNA was extracted manually from paraffin-embedded tissue samples. For *KRAS* testing, genetic examinations to evaluate the status of codons 12 and 13 were carried out using polymerase chain reaction with exon 1-specific primers for the *KRAS* gene [16]. The amplified sequences were then determined using the BigDye terminator sequencing kit and analyzed on an ABI 3730 XL automated sequencer for both strands. Mutation nomenclature was based on GeneBank accession number;NM_004985. *NRAS* testing was done by next generation sequencing performed by Clarient Diagnostic Services, Inc. (Aliso Viejo, CA, USA).

Ethics

All procedures were conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki and the trial protocol was approved by the Institutional Ethics Committee and Review Board. All patients provided signed informed consent before enrolment. The trial was registered at ClinicalTrials.gov with the trial number: NCT01310985.

Results

Patients

Fifteen patients were enrolled in this study between June 2008 and June 2009. The characteristics of patients are shown in Table 1. Most tumors were well or moderately differentiated, with elevated CEA. About half of the patients had N2 tumors. All but one patient had wild-type *KRAS*. *NRAS* was available in only six patients with one mutant and five wild types.

Efficacy

All 15 patients underwent surgery. Sphincter preservation was achieved in 11 patients (73.3%), and pCR occurred in two patients (13.3%). Tumor and nodal downstaging occurred in 60% and 53.3%, respectively. One patient was found to have peritoneal metastases at the time of surgery and no resection was performed. All 14 patients who underwent resection had negative proximal and distal margins; the radial margin was positive in one and negative in 13. Details of post-therapy pathological staging are shown in Table 2. Twelve patients were relapse-free and 14 patients were alive (Fig. 2), with a 4-year relapse free survival of 80% and overall survival of 93%, over a median follow-up of 48 months (range, 8.4—57.5 months).

Safety

The most common occurrences of Grade 3 and 4 toxicity (Table 3) were cetuximab-induced skin reactions (33%), radiation-induced skin toxicity (13%), diarrhea (20%), and

Table 1 Characteristics of the fifteen patients enrolled in the study

Parameter	Value
Median age, years (range)	52 (25—65)
Male gender, n (%)	10 (67)
Performance status, n (%)	
0	4 (27)
1	11 (73)
Histological grade, n (%)	
Well differentiated	3 (20)
Moderately differentiated	10 (66.7)
Poorly differentiated	1 (6.7)
Undifferentiated	1 (6.7)
Colostomy required, n (%)	
Yes	8 (53.3)
No	7 (46.7)
Carcinoembryonic antigen status, n (%)	
Normal	5 (33.3)
Elevated	10 (67.7)
Tumor distance from anal verge, n (%)	
$\leqslant$ 5 cm	8 (53.3)
> 5 cm	7 (46.7)
Patients with tumors arising below levator ani muscle, n (%)	4 (26.7)
Tumor stage by MRI, n (%)	
T2	3 (20)
T3	11 (73.3)
T4	1 (6.7)
N stage by MRI, n (%)	
N0	1
N1	6 (40)
N2	8 (53.3)
Patients with tumor within 1 mm from mesorectal fascia, n (%)	6 (40)
K-ras status, n (%)[a]	
Wild type	14 (93.3)
Mutant	1 (6.7)

Note. MRI = magnetic resonance imaging.
[a]Evaluated retrospectively.

Table 2 Pathological TNM staging.

Stage	Tumor, *n* (%)	Nodes, *n* (%)	Metastasis, *n* (%)
0	2 (13.3)	8 (53.3)	14 (93.3)
1	2 (13.3)	6 (40.0)	1 (6.7)
2	5 (33.3)	0 (0)	
3	5 (33.3)		
4	0 (0)		
x	1 (6.7)	1 (6.7)	–

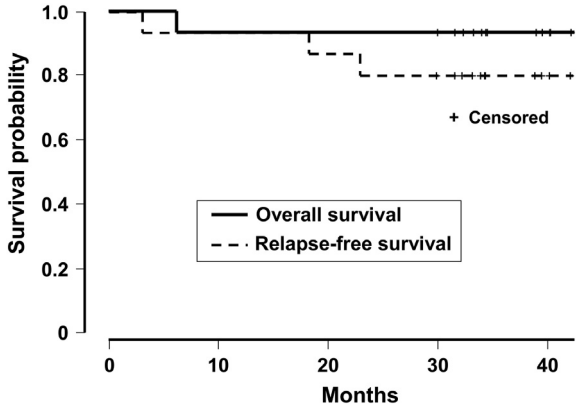

Fig. 2 Relapse-free and overall survival (product-limit survival estimates).

gastro-intestinal upset (13%). Mucositis, fatigue, and febrile neutropenia each occurred in a single patient.

Dose interruptions and modifications

A total of six patients had their capecitabine dose interrupted and four patients had their dose reduced. The actual median dose intensity for capecitabine was 10,614 mg/m^2 per week. The relative median dose intensity was 1.05 (range, 0.73—1.15) mg/m^2 per week. Seven patients received less than seven doses of cetuximab, mostly related to toxicity or patient refusal.

Eleven patients received the planned dose of radiation over 5.5 weeks combined with cetuximab and capecitabine. Five patients had their radiation interrupted, although the majority (11 patients) received their complete dose of radiation (5,040 cGy).

Thirteen patients received all six cycles of adjuvant capecitabine, as specified in the amended study protocol. One patient had only five cycles and one had metastatic disease on exploration. Six patients had their adjuvant chemotherapy started more than 60 days postsurgery.

Discussion

The addition of cetuximab to preoperative chemoradiotherapy with capecitabine for patients with localized rectal cancer was feasible, and associated with encouraging efficacy and manageable toxicity. We have previously published the results of our Phase II trial of concurrent capecitabine and external beam irradiation in localized rectal cancer, with a pCR rate of 6.5%, tumor and nodal downstaging in 53.9% and 50% of patients, respectively, and a 3-year disease-free and overall survival of 59.8% and 76.6%, respectively [12]. The current study demonstrated a higher pCR (13%), with similar tumor and nodal downstaging and an apparent improvement in disease-free and overall survival.

Previous studies that evaluated the addition of cetuximab to a single-agent fluoropyrimidine (four with capecita-

Table 3 Toxicity According to National Cancer Institute Common Toxicity Criteria.

Toxicity	Number with toxicity (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	4 (26.7)	1 (6.7)	0	0
Neutropenia	0	2 (13.3)	1 (6.7)	1 (6.7)
Thrombocytopenia	1 (6.7)	0	0	0
Febrile neutropenia	0	0	1 (6.7)	0
PPE*	5 (33.3)	0	0	0
Nausea/vomiting	6 (40)	3 (20)	1 (6.7)	1 (6.7)
Fatigue	0	7 (46.7)	1 (6.7)	0
Mucositis	0	1 (6.7)	1 (6.7)	0
Diarrhea	1 (6.7)	10 (66.7)	2 (13.3)	1 (6.7)
Skin toxicity	3 (20)	7 (46.7)	5 (33.3)	0
Radiation skin reaction	5 (33.3)	5 (33.3)	2 (13.3)	0
Cystitis	9 (60)	4 (26.7)	0	0

*Palmar-Plantar Erythrodysesthesia.

bine and two with 5-fluorouracil) reported pCR values ranging from 0% to 13% [17—22]. These response rates were low compared with the range of reported pCRs (8—17%) with the use of preoperative single agent fluoropyrimidines with radiation therapy in large randomized trials [23—28]. Several trials reported the combination of concurrent chemoradiotherapy using capecitabine, cetuximab, and either oxaliplatin or irinotecan. In these trials, pCRs were 8—18% for oxaliplatin and 8—25% for irinotecan [29—33] The lack of significant improvement in efficacy with the addition of cetuximab to preoperative capecitabine and radiotherapy may be related to the potential negative interaction between capecitabine and cetuximab as has been suggested in metastatic disease [34].

In our trial, we retrospectively evaluated *KRAS* and *NRAS* status. Surprisingly 14/15 patients had wild type *KRAS*, which is higher than the 44% reported previously in our local population with metastatic colorectal cancer [35]. This difference likely arose due to the small number of patients enrolled and represents a limitation of the study. No conclusion could be drawn from the *NRAS* result in view of the limited samples tested.

Conclusion

Our pilot study, conducted on a limited number of patients and retrospective limited *RAS* genotyping, confirms that the addition of cetuximab to concurrent preoperative capecitabine and radiotherapy in operable rectal cancer is feasible, with a modest pCR and manageable toxicity.

Conflicts of interest

None declared.

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