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Preoperative chemoradiation with capecitabine in locally advanced rectal cancer

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ABSTRACT

Background: Preoperative radiation therapy in combination with 5-fluoracil (5-FU) improves local tumour control in locally advanced rectal cancer. The aim of our study was to evaluate the toxicity and efficacy of preoperative chemoradiation using the oral 5-FU prodrug capecitabine in locally advanced rectal cancer.

Methods: Sixty patients with locally advanced rectal cancer were treated with preoperative chemoradiation. Radiotherapy consisted of a total dose of 50 Gy delivered in 25 fractions to the pelvis. Chemotherapy was concurrently administered and consisted of oral capecitabine only on radiotherapy days. Surgery was performed six to ten weeks after completion of chemoradiation.

Results: The patient population consisted of 19 females and 41 males, with a median age of 61 years. All but two patients received the full dose of chemoradiation. No grade 3 or 4 haematological toxicities developed. Two patients (3%) developed grade 3 radiation dermatitis and one a grade 3 diarrhoea.

All patients underwent definitive surgery; 19 patients underwent an abdominal perineal resection (APR), 25 a low anterior resection (LAR) and 16 patients a Hartmann's procedure. One patient with a low anterior resection developed an anastomotic leakage (4%). Final pathology demonstrated eight patients (13%) with a complete pathological response. Primary tumour and nodal downstaging occurred in 67 and 84% of the patients, respectively. Two patients (3%) had an R1 resection, one after an APR and one after an LAR.

Conclusion: Preoperative chemoradiation with oral capecitabine is safe and well tolerated in locally advanced rectal cancer patients. This preoperative treatment has a considerable downstaging effect on the tumour and lymph nodes.

KEYWORDS

Capecitabine, chemoradiation, rectal cancer

INTRODUCTION

Preoperative radiotherapy with concurrent 5-fluorouracil (5-FU) based chemotherapy has received increased interest over the last decade in the treatment of locally advanced colorectal cancer. The addition of chemotherapy to radiation therapy has been demonstrated to be feasible, with an increase in pathological complete response rate and possibility of sphincter preservation. Preoperative chemoradiation therapy with 5-FU confers a significant benefit with respect to local control.[1,2] Continuous 5-FU infusion has been proven superior to bolus administration in terms of tumour response and is associated with a lower incidence of haematological and nonhaematological toxicity.[3,4] Disadvantages of continuous infusion are requirement of hospitalisation and potential complications resulting from central venous access.[5]

Capecitabine is a fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumour cells as the concentration of the key enzyme thymidine phosphorylase is higher in tumour cells compared with normal tissue. After irradiation thymidine phosphorylase is upregulated in tumour tissue resulting in a supra-additive affect of capecitabine on radiotherapy.[6-8] Capecitabine is administered daily to mimic continuous infusion of 5-FU. A phase I study of preoperative radiotherapy with 50.4 Gy given in 28 fractions in five weeks combined with escalating doses of capecitabine was reported by Ngan *et al.*[9] For phase II studies, they recommended a capecitabine dose of 1800 mg/m^2/day. This overall dose is similar to that used when capecitabine is given as a single agent for metastatic disease either in the 42-day continuous regimen (825 mg/m^2 twice daily) or in the intermittent schedule (1250 mg/m^2 twice daily for two weeks, one every three weeks).[10,11] Dunst *et al.* also conducted a phase I study and recommended 825 mg/m^2 capecitabine twice a day for phase II evaluation.[12] Three phase II studies have been initiated to evaluate the tolerance and efficacy of chemoradiation with capecitabine. In these studies different regimes of capecitabine were used and in some studies leucovorin was added.[13-16]

We initiated a phase II study to evaluate the efficacy and toxicity of preoperative chemoradiation with capecitabine in large T3/T4 rectal tumours or in tumours with local lymph node metastasis. In this study capecitabine was only administered on radiotherapy days.

MATERIALS AND METHODS

All patients treated in this study were evaluated including a complete history and physical examination, colonoscopy, tumour biopsy, abdominal ultrasound, computed tomography (CT) scan of the abdomen and pelvis and magnetic resonance imaging (MRI) of the pelvis, a chest X-ray and/or chest CT scan. All CT and MRI images of the patients were discussed in our multidisciplinary meeting which includes a colorectal surgeon, gynaecologist, urologist, radiotherapist, radiologist and medical oncologist. Complete laboratory tests included a full blood count with differential, serum chemistries including electrolytes, liver function tests, creatinine, and carcinoembryonic antigen.

Inclusion criteria

All patients had a histologically proven adenocarcinoma of the rectum. This was defined as any tumour within 15 cm of the anal verge or a tumour located distal from the line between the promontory and symphysis on sagittal MRI. The location of the tumour was measured from the anal verge using colonoscopy.

Patients with large T3 or T4, Nx or any T3, N1-2 rectal adenocarcinoma were eligible for the study. Large T3 tumours were defined on pelvic MRI as tumours with narrow margins (<2 mm) to the circumferential rectal fascia. Mesorectal and obturator lymph nodes were considered positive on pelvic MRI if a node was larger than 8 mm or multiple nodes larger than 3 mm. All patients needed to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and be aged between 18 and 80 years. Patients also had to have adequate liver, renal and bone marrow function as follows: bilirubin <30 μmol/l, aspartate aminotransferase and alanine aminotransferase less than five times the upper level of normal (ULN), creatinine <1.5 x ULN, leucocytes >3.5 x 10^9/l, and platelets 100 x 10^9/l. Patients of child-bearing age were required to practice approved methods of birth control.

Exclusion criteria

Patients with severe comorbidity such as cardiomyopathy or other cardiovascular disease were excluded. Patients with known risk of adverse reaction to fluoropyrimidines were excluded, as well as patients who were participating in other trials or receiving any investigational drugs.

TRIAL DESIGN AND ENDPOINTS

This was a single-armed, multicentre phase II study of preoperative radiotherapy with concurrent capecitabine for locally advanced rectal cancer. Primary endpoints were toxicity, grade of tumour downstaging and pathological complete response. Secondary endpoints were rate of sphincter preservation and postoperative complications. Primary endpoints were haematological and nonhaematological toxicity. Toxicity was scored with Radiation Therapy Oncology Group criteria and the National Cancer Institute Common Toxicity Criteria version 3.0. Secondary endpoints were complete pathological response, pathological downstaging and sphincter preservation. Our definition of downstaging and complete response was based on the comparison of the clinical tumour node metastasis (TNM) and the pathological TNM stage. Pathological complete response was defined as no tumour cells in the pathological specimen, but only a fibrotic mass.

Chemotherapy

Capecitabine was administered orally at a dose of 825 mg/m^2 twice a day only on radiotherapy days. The first daily dose was given two hours before radiotherapy and the second dose twelve hours later. Dose modifications were applied if the patient experienced any grade 3 or 4 haematological toxicity or any grade 3 nonhaematological toxicity, such as hand-foot syndrome, except for alopecia. Chemotherapy was restarted at a 75% dose if toxicity levels resolved to grade 1 or less. If toxicity was clearly related to radiotherapy, for example radiation dermatitis, local therapy was administered and capecitabine was not stopped.

Radiotherapy

All patients were treated with preoperative radiotherapy and received a dose of 50 Gy delivered in 25 fractions of 2.0 Gy. Radiotherapy was administered by a three-field technique, using one posterior and two lateral portals, a four-field box or with five fields using intensity modulated radiotherapy. The lateral pelvic borders were defined as 1.5 cm lateral of the bony pelvis, the cranial border was the promontory, and the caudal border was below the foramina obturatoria to 2 cm under the anus, depending on tumour position. Patients were evaluated four times during the course of chemoradiation to assess acute toxicity and compliance with the oral capecitabine. Blood tests were taken each time and consisted of full blood count, platelets, leucocytes and neutrophils.

Surgery

Surgery was performed six to ten weeks after completing chemoradiation. Patients were reassessed for resectability by pelvis CT scanning or MRI of the pelvis. Total mesorectal excision technique was performed in all patients, and extended multivisceral resections were performed in clinically T4 patients. Intraoperative

radiotherapy was administered in those patients in whom the circumferential margins were considered at risk.

RESULTS

A total of 60 patients were included between July 2005 and November 2006. The median age was 61 years (range 32 to 82 years) and the majority of patients had T3N1-N2 (48%) stage of disease. Other patient characteristics are shown in *table 1*. Median distance to the anal verge was 5 cm (range 0 to 20 cm). Most of the tumours were located in the lower parts of the rectum, with only a minority (13%) above 10 cm (*table 2*). In one patient the tumour was measured at 20 cm from the anal verge, but after discussing this case in our multidisciplinary team, we considered the bulk of the tumour to be in the upper part of the rectum, in close relation to the bladder. In this case downsizing of the tumour was aimed for and chemoradiation was proposed. All patients underwent surgery and were evaluated for pathological response and downstaging.

Toxicity

Toxicity was moderate and is summarised in *table 3*. Hand-foot syndrome did not occur in any of the patients.

Table 1. *Baseline patient characteristics*

Category	Number (%)
Gender:	
• Male	41 (68)
• Female	19 (32)
Performance status (ECOG):	
• 0	40 (67)
• 1	20 (33)
Histological differentiation:	
• Moderate	44 (73)
• Poor	3 (5)
• Unknown	13 (22)
Clinical tumour stage:	
• T3NO	3 (5)
• T3N+	29 (48)
• T4NO	12 (20)
• T4N+	16 (27)

ECOG = Eastern cooperative oncology group.

Table 2. *Tumour location and surgical treatment*

Tumour location	Number	APR (%)	LAR (%)	Hartmann (%)
>10 cm	8	1 (12)	4 (50)	3 (38)
5-10 cm	20	2 (10)	13 (65)	5 (25)
<5 cm	32	16 (50)	8 (25)	8 (25)
All tumours	60	19 (32)	25 (42)	16 (27)

APR = abdominal perineal resection; LAR = low anterior resection.

No haematological grade 3 or 4 toxicities occurred. Haematological toxicity was mild with grade 2 anaemia, leucocytopenia and neutropenia in 7, 12 and 3% of the patients, respectively. The only grade 3 nonhaematological toxicity was radiation dermatitis (3%) and diarrhoea (2%). Chemoradiation was not stopped in two patients who developed grade 3 radiation dermatitis. This occurred at the end of therapy and was managed by applying local therapy. All but two patients received the full dose of chemoradiation. A 56-year-old male reported severe chest pain while taking capecitabine, which was absent in the weekend. There was no history of cardiac disease. Capecitabine was stopped and radiation continued. A second patient was a 49-year-old female who experienced grade 3 diarrhoea which required intravenous fluid replacement. Capecitabine was stopped and not restarted at patient's request; radiotherapy was continued.

Response

Surgery was performed in ten different hospitals and all patients underwent definitive surgery. In 19 patients an abdominal perineal resection (APR) was performed, in 16 a Hartmann's resection and in 25 a low anterior resection (LAR). Of the patients with T4 tumours, 18 underwent a multivisceral resection: five posterior exenterations, three total exenterations, three vagina resections, two partial bladder resections, three seminal vesicle resections and two partial prostate resections.

A complete pathological response was achieved in eight patients (13%) (*table 4*). Overall tumour and nodal downstaging occurred in 51 patients (85%). Tumour downstaging was seen in 40 patients (67%) and overall nodal downstaging in 38 patients (84%). Tumour progression during chemoradiation was not observed. Final pathology demonstrated To in eight patients (13%), T1 in six patients (10%), T2 in 14 patients (23%), T3 in 27 patients (45%) and T4 in five patients (8%).

Table 3. *Haematological and nonhaematological toxicity*

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Haemoglobin	-	4 (7)	-	-
Platelets	15 (25)	-	-	-
Leucocytes (total WBC)	22 (37)	7 (12)	-	-
Neutrophils	-	2 (3)	-	-
Hand-foot skin reaction	1 (2)	-	-	-
Radiation dermatitis	14 (23)	11 (18)	2 (3)	-
Nausea	9 (15)	1 (2)	-	-
Vomiting	-	-	-	-
Lower gastrointestinal (diarrhoea)	11 (18)	1 (2)	1 (2)	-
Genito-urinary	13 (2%)	-	-	-

WBC = white blood count.

Of the 32 patients with initial tumour location less then 5 cm from the anal verge, 16 underwent an abdominal perineal resection and eight (25%) sphincter preservation by performing a low anterior resection. The majority of patients with the initial tumour location more than 5 cm from the anal verge underwent an LAR; only three patients underwent an APR, and eight a Hartmann's resection. In two patients (3%) an R1 resection was performed; one male patient with a tumour located at 3 cm from the anal verge underwent an APR and another male patient with a tumour located at 8 cm from the anal verge underwent a low anterior resection. No R2 resections were performed. Anastomotic leakage in the low anterior group occurred in one patient (4%).

DISCUSSION

Patients with locally advanced rectum carcinoma should preferably receive some form of neoadjuvant treatment to downstage the tumour and enable a potentially curative resection. 5-FU-based chemoradiation is currently a well-accepted approach in the management of locally advanced rectum carcinoma. We conducted the present study to evaluate toxicity and efficacy of preoperative chemoradiation using oral 5-FU (capecitabine) in locally advanced rectal cancer. This should potentially lead to improved local tumour control and improved chance of sphincter preservation. We demonstrated that preoperative chemoradiation therapy with capecitabine is feasible with acceptable overall grade 3 toxicity of 5% and a 13% complete response rate.

All patients treated in this study completed radiotherapy and all but two completed chemotherapy. The incidence of acute toxicity in the present study was slightly lower than other phase II trials using capecitabine.[13-15] *Table 5* demonstrates the results from the present study and three previously published studies. These differences can possibly be explained by the regime of capecitabine that was administered. Considering the radiation sensitising dose and effect of capecitabine in this set-up,[17] we designed the study to give capecitabine only on radiotherapy days. Because of the two-day resting period every five days, toxicity might therefore be lower than in the other series where capecitabine was administered twice daily, seven days a week. Kim *et al.* used a regime consisting of two cycles of 14 days followed by a resting period of seven days and also added leucovorin to their regime. It is noteworthy that one of the patients in the present study had severe chest pain with no history of any myocardial disease. Cardiotoxicity is a well-known but rare adverse effect of capecitabine and has been reported in several case reports.[18-20]

In a previous study of locally advanced rectal carcinoma in our centre, radiotherapy was used at a similar dose (25 x 2 Gy), but without capecitabine demonstrating a complete pathological response rate of only 2%.[21] In the present study a large group of patients (47%) who had a clinical T4 tumour were treated and despite this a complete pathological response of 13% and a total tumour downstaging of 67% were observed. Complete pathological response rates were slightly higher in the other reported phase II trials, but these differences can be explained by the fact that other phase II studies had considerably less patients with clinical T4 tumours. In the subgroup of patients with T4 staged tumours, one patient (4%) had a complete response and 24 of 28 patients (84%) had a total tumour downstaging. Of the 45 patients with clinical positive nodal status only eight (18%) had pathological nodal involvement. Unfortunately, there is a potential bias in all studies that report on rectal cancer downstaging. The real downstaging effect of the chemoradiation treatment can not be accurately measured, since clinical nodal staging is based on diagnostic imaging and is not pathologically proven. However, we used strict criteria for node positivity on pelvic MRI and all patients were discussed in a multidisciplinary team.

All patients in our study had definitive surgery after preoperative therapy. Multivisceral resection, which was previously proven to enable good local control and acceptable survival, was performed in 18 patients.[22] The considerable downstaging effect of the addition of capecitabine to a long series of radiation may increase the chance of sphincter preservation and decrease the need for multivisceral resection. Bujko *et al.* demonstrated no significant increase in sphincter preservation after 5-FU based chemoradiation therapy, despite an increased clinical response rate.[23] Other studies demonstrated a significant correlation between

Table 4. *Distribution of clinical tumour stage compared with pathological tumour stage*

Clinical: tumour and node	pT0N0	pT1N0	pT2N0	pT2N1	pT3N0	pT3N1	pT3N2	pT4N0	pT4N2	Total (%)
cT3N0	1	1	1	-	-	-	-	-	-	3 (5)
cT3N1	3	-	4	-	8	3	-	-	-	18 (30)
cT3N2	3	3	1	-	2	-	2	-	-	11 (18)
cT4N0	1	2	3	1	2	-	-	3	-	12 (20)
cT4N1	-	-	4	-	9	-	-	1	-	14 (23)
cT4N2	-	-	-	-	-	-	1	-	1	2 (3)
Total (%)	*8 (13)*	*6 (10)*	*13 (22)*	*1 (2)*	*21 (35)*	*3 (5)*	*3 (5)*	*4 (7)*	*1 (2)*	*60*

Table 5. *Comparison of trials of preoperative chemoradiation therapy in locally advanced rectal cancer*

Study	Patients (n)	Treatment	Down-staging rate (%)	Response (%)	Ro/R1 resec-tions	Toxicity	T3/T4	Sphincter preserva-tion
De Paoli[15]	53	Pelvic RT (45 Gy in 25 fractions, 5 days/week)+ boost to tumour (5.4 Gy in 3 fractions) +c (825 mg/m² bid) 7-days/week	57%	pCR 24%,	48/3	Grade 3 6 patients (11%) = leucopenia 4% + hand-foot syndrome 4%	46/7	59%
Kim[16]	38	Pelvic RT (45 Gy in 25 fractions, 5 days/week)+ boost to tumour (5.4 Gy in 3 fractions) + c (825 mg/m² bid) + LV (20 mg/m²/day) days 1-14 week, 2 cycles of 14 days	63%	pCR 31%,	NR	Grade 3 hand-foot syndrome (7%), fatigue (4%), diarrhoea (4%) and radiation dermatitis(2%)	33/4	72%
Krish-nan[13]	54	Pelvic RT (45 Gy in 25 fractions, 5 days/week)+ concomitant boost to tumour (7.5 Gy in 5 fractions) + c (825 mg/m² bid) continuous 35 days.	51%	pCR 18%	51/0	Grade 4 diarrhoea 2%, Grade 3 lymphopenia 70%, anaemia and neutropenia 2%, radiation dermatitis 9%, proctitis 4%, fatigue 2%, diarrhoea 2%	52/2	67%
Present	60	Pelvic RT (50 Gy in 25 fractions, 5 days/week) + c (825 mg/m² 5 days/week)	67%	pCR 13%	58/2	Grade 3 2% diarrhoea, 3% radiation dermatitis	32/28	50%

RT = radiotherapy; pCR = pathological complete response; LV = leucovorin; bid = twice daily.

chemoradiation and sphincter preservation.[24] In the present study only eight patients (25%) with a low-lying tumour (≤5 cm from anal verge) underwent sphincter preserving surgery. Therefore, conclusions regarding the benefit of chemoradiation on sphincter saving surgery can not be made based on the experience in this study.

The incidence of circumferential margin involvement in patients with locally advanced rectal cancer is higher compared with rectal cancers were the tumour is confined to the mesorectum. Especially in APR patients circumferential resection margins are more often involved compared with patients who undergo an LAR.[25] In the present study, two patients (3%) had an R1 resection; one after an APR and one after an LAR. The downstaging effect of chemoradiation might decrease the risk of circumferential involvement, but surgical technique is also important. For instance, in patients who underwent an APR resection, wide perineal resection seems to decrease the risk of involved margins and improve outcome.[26] Further improvement of outcome can be expected using new neoadjuvant chemoradiation protocols including chemotherapeutic drugs such as oxaliplatin or irinotecan.[27,28] Willet *et al.* have reported promising results using a vascular endothelial growth factor (VEGF) specific antibody (Bevacizumab) in combination with 5-FU-based radiotherapy.[29] This has lead to the conduction of a multicentre feasibility trial (RAX) in the Netherlands for which patients are currently being included.

CONCLUSION

Preoperative chemoradiation with oral capecitabine is safe and well tolerated in locally advanced rectal cancer patients. In addition, this preoperative treatment has a considerable downstaging effect on the tumour and lymph nodes resulting in few R1/R2 resections in large T3 and T4 rectal carcinoma. Capecitabine is used as a radiation sensitiser and there seems to be no need to administer it on nonradiotherapy days. By doing so it might minimise toxicity without influencing response.

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