The Journal of International Medical Research
2010; 38: 645 – 654

Phase II Study of Pre-operative Radiotherapy with Capecitabine and Oxaliplatin for Rectal Cancer and Carcinoembryonic Antigen as a Predictor of Pathological Tumour Response

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This study investigated the efficacy and tolerability of pre-operative radiotherapy with concurrent capecitabine and oxaliplatin in patients with rectal cancer. Forty-seven patients with rectal adenocarcinoma (stages T3 – T4; node-positive) were enrolled and received radiotherapy (46 Gy in 23 fractions) in combination with capecitabine (1000 mg/m^2 twice daily on days 1 – 14 and 22 – 35) and oxaliplatin (130 mg/m^2 on days 1 and 22) (XELOX regimen). The main endpoints were safety and efficacy, as assessed by pathological complete response (pCR). All patients received pre-operative chemoradiotherapy (CRT) as planned. The most common severe toxicity was diarrhoea (12.8%); post-operative complications were rare (9.8%). The pCR rate was 20.9% in all patients and 34.8% in patients with normal pre-CRT serum carcinoembryonic antigen (CEA ≤ 5 ng/ml) level, compared with 5.0% in the patients with elevated CEA (> 5 ng/ml). In conclusion, pre-operative radiotherapy with concurrent XELOX regimen in rectal cancer patients is feasible and effective. Serum CEA may be a suitable predictor of pCR.

KEY WORDS: Rectal cancer; Capecitabine; Oxaliplatin; Carcinoembryonic antigen; Chemoradiotherapy

Introduction

For many years, rectal adenocarcinoma was thought to be a radiotherapy (RT)-resistant tumour. This opinion has changed over the last 20 years as considerable progress has been made in pre-operative chemoradiotherapy (CRT) of rectal cancer. Compared with post-operative CRT or surgery alone, pre-operative CRT leads to tumour regression, improves local control and has acceptable toxicity.[1] Although the use of pre-operative RT with or without chemotherapy remains a controversial issue, two recent phase III trials have confirmed

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the advantages of pre-operative CRT over RT alone in terms of achieving better local control.[2,3] To date, however, clinical trials have not shown any improvement in the survival rates of patients who received pre-operative CRT compared with the survival rates of those who received RT alone.[4] Since fluorouracil (FU) and leucovorin are used regularly in pre-operative CRT, integration of a more effective chemotherapy into the multimodality schedule may provide better results.

Capecitabine is an effective oral fluoropyrimidine that exploits the high intratumoural activity of thymidine phosphorylase (TP) to generate an active metabolite preferentially within tumour tissue.[5] Radiation up-regulates TP in tumour cells, but not in normal tissues, thereby improving the efficacy of capecitabine.[6] Oxaliplatin is another ideal candidate for chemotherapy: it acts in synergy with fluoropyrimidines and has potent radiosensitizing ability.[7] The combination of capecitabine (1000 mg/m^2 twice daily on days 1 – 14) and oxaliplatin (130 mg/m^2 intravenously on day 1) every 3 weeks (standard XELOX regimen) has been proven to be safe, convenient and non-inferior to oxaliplatin plus 5-fluorouracil (5-FU) and folinic acid (FOLFOX-4) as first-line treatment for metastatic colorectal cancer.[8] Thus, the combination of capecitabine, oxaliplatin and concomitant pre-operative RT would be expected to result in a favourable outcome.

The present study was conducted to explore further the efficacy and tolerability of pre-operative RT with a XELOX regimen in patients with locally advanced rectal cancer. The prediction of tumour response to pre-operative CRT will help in identifying patients who are most likely to benefit from the treatment and to prevent overtreatment. Since carcinoembryonic antigen (CEA) plays a significant role in the diagnosis, prognosis and monitoring of relapse in colorectal cancer, it was of clinical significance also to determine whether CEA can be used as a predictor of tumour response to neoadjuvant CRT in rectal cancer.

Patients and methods

PATIENTS

This prospective, single-arm study included patients with histologically proven rectal adenocarcinomas who were attending the Cancer Centre, Sun Yat-sen University, Guangzhou, China, and patients were sequentially enrolled between March 2007 and June 2008.

The inclusion criteria were: age > 18 years; Eastern Cooperative Oncology Group (ECOG) performance status[9] ≤ 2; tumour stage T3 – T4 and/or nodal stage N1 – N2 confirmed by transrectal ultrasound, computerized tomography (CT), and/or magnetic resonance imaging (MRI); tumour location within 10 cm above the anal verge; adequate haematological, liver and renal function (granulocyte count > 1.5 × 10^9/l; platelet count > 100 × 10^9/l; aspartate aminotransferase/alanine aminotransferase level ≤ 2.5 × upper limit of normal [ULN]; bilirubin level ≤ 1 × ULN; and creatinine clearance ≥ 50 ml/min); and no evidence of metastasis based on abdominal/pelvic CT and chest radiography.

The exclusion criteria were: prior chemotherapy and/or pelvic irradiation; active malignancy during the previous 5 years (with the exception of non-melanomatous skin cancer); inflammatory bowel disease or an uncontrolled severe disease; and pregnancy or sexually active patients unwilling to practice effective contraception.

All patients provided written informed

consent. The study protocol was approved by the Ethics Committee of the Sun Yat-sen University Cancer Centre.

PRE-TREATMENT EVALUATION

The pre-treatment examination included a review of each patient's history, and clinical and laboratory examinations including a digital rectal examination, colonoscopy and biopsy, transrectal ultrasound, abdominal and pelvic CT, chest radiography, electrocardiography and complete laboratory tests (complete blood count and tests for levels of blood electrolytes, creatinine, urea nitrogen, liver transaminases, bilirubin, alkaline phosphatase and serum CEA). Serum levels of CEA ≤ 5 ng/ml were defined as being normal and levels > 5 ng/ml were defined as being elevated. A pelvic MRI scan was optional.

RADIOTHERAPY

A linear accelerator with a minimal energy of 6 MeV through a three-field box technique was used. The clinical target volume (CTV) included the primary tumour, entire mesorectum, pararectal lymph nodes, together with internal iliac, promontory and pre-sacral lymph nodes up to the level of the fifth lumbar vertebra. The anal sphincter complex was included only for low-lying tumours (< 6 cm above the anal verge). All patients received a total dose of 46 Gy, with daily fractions of 2.0 Gy on five consecutive days per week.

CHEMOTHERAPY

Capecitabine (1000 mg/m^2) was administered orally, twice daily (30 min after breakfast and dinner) on days 1 – 14 and 22 – 35, and oxaliplatin (130 mg/m^2) was administered intravenously over 2 h on days 1 and 22 (XELOX regimen). Review of the patient's history, clinical examination and laboratory tests was performed every week during CRT. The CRT treatment was halted if toxicity of grade 3 or 4 was encountered (with the exception of anaemia). The chemotherapy dose was reduced according to standard guidelines in the event of adverse events.[10]

SURGERY AND FOLLOW-UP

Experienced surgeons performed resection of rectal tumours within 4 – 8 weeks after completion of RT. Total mesorectal excision was performed whenever possible. After surgery, adjuvant chemotherapy according to the XELOX regimen (4 – 6 cycles) was recommended for all patients. These patients were followed up regularly every 3 months.

EVALUATION OF SAFETY AND EFFICACY

The extent of residual tumour in the resected specimen was classified according to the tumour–node–metastasis (TNM) staging system of the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC).[11] A semi-quantitative evaluation of histological regression was performed according to a five-point tumour regression grading (TRG) system established by Dworak *et al.*:[12] TRG 0, no regression; TRG 1, dominant tumour mass with obvious fibrosis and/or vasculopathy; TRG 2, predominantly fibrotic changes with few tumour cells or groups (easy to find); TRG 3, very few (difficult to find, microscopically) tumour cells in fibrotic tissue with or without mucous substance; and TRG 4, no tumour cell, only fibrotic mass, total regression or response. A pathological complete response (pCR, TRG4) was defined as the absence of viable tumour cells in a primary tumour and in lymph nodes. The primary endpoint of this phase II study was the pCR rate after pre-

operative CRT. Other endpoints included R0 resection rate in patients with T4 tumours, rate of sphincter-sparing surgery in low-lying tumours, pathological downstaging, and a decline in the serum CEA level.

Safety was assessed by documenting adverse events and performing clinical laboratory tests. Adverse events were graded using the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0.[13]

STATISTICAL ANALYSIS

This study was designed as a one-stage phase II trial using the pCR rate as the primary endpoint. Current standard pre-operative CRT with 5-FU yields pCR rates in the range of 5 – 10%;[1] thus, a pCR rate of ≤ 7% was considered to be ineffective and a rate of ≥ 20% was considered as effective. With a type I error of 0.05, a type II error of 0.10 and a dropout rate of ≤ 15%, the planned sample size was 47 patients. The data were analysed using the SPSS® statistical package, version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Crosstabs were used to identify different pCR rates among patients with different CEA levels. The difference in pCR achieved by patients with normal pre-treatment serum CEA levels (≤ 5 ng/ml) versus those with elevated serum CEA levels (> 5 ng/ml) was compared using Fisher's exact test. A *P*-value < 0.05 was considered to be statistically significant.

Results

PATIENT DISPOSITION AND CHARACTERISTICS

A total of 47 patients with histologically proven rectal adenocarcinomas were sequentially enrolled into this study between March 2007 and June 2008. Patient demographics and baseline disease characteristics are shown in Table 1. All 47 patients received pre-operative CRT as planned and were then evaluated for toxicity. Six patients did not undergo surgery. Tumours in two of these patients were assessed as unresectable after pre-operative CRT and these patients subsequently received palliative chemotherapy. Another three patients refused to undergo an operation after a good clinical response to CRT and one patient did not undergo surgery for an unknown reason; these four patients were excluded from the efficacy analyses. In total, 43 patients were evaluated for efficacy; the 41 patients who underwent surgery after a median of 43 days (range 5 – 8 weeks) following the completion of radiation therapy and the two patients in whom the tumours were assessed as unresectable.

TABLE 1:
Demographic and disease characteristics at baseline for all the patients with histologically proven rectal adenocarcinoma who were entered into the study and received pre-operative chemotherapy (*n* = 47)

Age (years), median (range)	54 (26 – 75)
Gender, *n* (%)	
Male	30 (63.8)
Female	17 (36.2)
Lower tumour margin to anal verge, *n* (%)	
< 6 cm	30 (63.8)
6 – 10 cm	17 (36.2)
Primary tumour size (cm), median (range)	4.5 (2.0 – 8.0)
Tumour, node pre-treatment clinical stage, *n* (%)	
T3N0	11 (23.4)
T3N+	16 (34.0)
T4N0	3 (6.4)
T4N+	17 (36.2)

SURGICAL PARAMETERS AND EFFICACY

The surgical parameters and efficacy of

treatment, as measured by the TRG are shown in Table 2. R0 resection was achieved in 38 of 43 patients (88.4%) and in 15 of 18 patients (83.3%) with T4 tumours. For resectable low-lying tumours (< 6 cm from the anal verge), the sphincter preservation rate was 28.6% (eight of 28 patients). A temporary stoma was created in only one of the 21 patients (4.76%) undergoing sphincter-sparing surgery. At 1 month, post-operative complications of various grades were present in four of 41 patients (9.8%); these included wound-healing problems (4.9%), pelvic infection (2.4%) and vaginal fistula (2.4%). No patient required reoperation or died of complications.

A pCR was achieved in nine of 41 patients (22.0%) who underwent surgery; the pCR rate was 20.9% in all 43 of the patients who could be evaluated for efficacy. An additional 10 patients of the 41 patients (24.4%; 23.3% of 43 patients) showed good tumour regression (very few tumour cells in fibrotic tissue). Thus, 44.2% of all 43 of the patients who could be evaluated for efficacy responded well to pre-operative CRT. Moreover, serum CEA levels decreased by 31.5% after pre-operative CRT (mean baseline level of 23.56 ng/ml [range 0.54 – 219.80 ng/ml]).

On comparing the baseline tumour stage with the post-operative pathological stage, downstaging with respect to tumour stage was observed in 24 (58.5%) of 41 patients, while downstaging with respect to nodal stage was observed in 21 (75.0%) of 28 patients (Table 3). Metastasis was found in five (10.6%) of all 47 patients after pre-operative CRT.

TABLE 2:
Surgical parameters and treatment efficacy as measured by tumour regression grade after pre-operative chemoradiotherapy in patients with rectal adenocarcinoma

Parameter	Patients *n* (%)
Type of surgery (*n* = 43)	
Anterior resection	21 (48.8)
Abdominal perineal resection	17 (39.5)
Hartmann's operation	2 (4.7)
Resection of infiltrated organ	1 (2.3)
Unresectable	2 (4.7)
Resection status (*n* = 43)	
R0	38 (88.4)
R1	0
R2	3 (7.0)
Unresectable	2 (4.7)
Surgical complications (*n* = 41)	4 (9.8)
Wound healing	2 (4.9)
Pelvic infection	1 (2.4)
Fistula to vagina	1 (2.4)
Tumour regression grade (*n* = 41)	
Grade 0	3 (7.3)
Grade 1	9 (22.0)
Grade 2	10 (24.4)
Grade 3	10 (24.4)
Grade 4 (pCR)	9 (22.0)

pCR, pathological complete response.

TOXICITY

Table 4 lists the incidence of adverse events (acute toxicity) according to NCI CTC version 3.0 grading[13] during pre-operative CRT. The second cycle of chemotherapy was cancelled in two patients due to grade 4 diarrhoea and ongoing leucopenia, respectively. The dose of oxaliplatin was modified in one patient because of grade 3 diarrhoea. The other 44 patients received the full course of CRT. No-one died of toxicity. Diarrhoea was the most common severe adverse effect, with six patients (12.8%) experiencing grade 3 – 4 diarrhoea. Other grade 3 – 4 toxic reactions included anaemia (6.4%), neutropenia (4.3%), and nausea/vomiting (2.1%).

pCR IN PATIENTS WITH DIFFERENT PRE-TREATMENT SERUM CEA LEVELS

A total of 23 patients had a pre-treatment serum CEA of ≤ 5 ng/ml and, of these, eight patients (34.8%) achieved pCR compared

TABLE 3:
Numbers of patients at each post-operative pathological stage compared with their pre-treatment clinical stage in rectal adenocarcinoma patients who underwent surgery following pre-operative chemotherapy (n = 41)

Pre-treatment clinical stage[a]	Total	Post-operative pathological stage[a]							
		Tumour stage					Nodal stage		
		ypT0	ypT1	ypT2	ypT3	ypT4	ypN0	ypN1	ypN2
cT3	25	6	0	6	10	3			
cT4	16	3	1	1	7	4			
cN0	13						9	4	0
cN+	28						21	5	2
Total	41	9	1	7	17	7	30	9	2

[a]Patients could have more than one type of tumour at different pre-treatment clinical and post-treatment pathological stages.

with only one (5.0%) out of the other 20 patients who had serum CEA levels > 5 ng/ml. This difference was statistically significant (P = 0.024) according to Fisher's exact test.

Discussion

Although pCR is not the primary aim of pre-operative CRT for rectal cancer, several retrospective analyses suggest that the pathological stages of the disease after neoadjuvant treatment and tumour regression rate have a significant correlation with survival.[14,15] Patients who achieve a pCR seem to have a better prognosis. Thus, the pCR rate has become a common end-point for short-time evaluation of pre-operative CRT.

A meta-analysis showed that a chemotherapy regimen consisting of continuous infusion of 5-FU or capecitabine, two antineoplastic drugs and a dose of RT ≥ 45 Gy was significantly associated with a higher rate of pCR.[16] Theoretically, to maximize tumour shrinkage before surgery and to improve systemic control, chemotherapy schedules should be as intense as possible. Since the combination of capecitabine and oxaliplatin has been proven to be safe and effective in palliative chemotherapy and to have potent radiosensitizing effects, several phase II trials have been performed to investigate their safety and efficacy with concomitant pre-operative radiation therapy (Table 5)[17 – 23] and have endeavoured to identify the optimal chemoradiation regimens. In these studies, the radiation doses were all similar, ranging from 45 to 50.4 Gy. Capecitabine was mostly administered at 825 mg/m^2 twice daily on days 1 – 14 and 22 – 35 or for 5 days a week, while oxaliplatin was usually administered at 50 mg/m^2 on days 1, 8, 22 and 29, or once weekly for 5 weeks. The dosage regimen used in the study performed by Hospers *et al.*[17] differed from other studies and comprised capecitabine at 1000 mg/m^2 twice daily on days 1 – 14 and 25 – 38, and a relatively low level of oxaliplatin at 85 mg/m^2 on days 1 and 29 only. A pCR rate ranging from 9.5% to 20.9% was achieved in these studies. Toxicity levels were acceptable; the most frequent severe adverse event was grade 3 – 4 diarrhoea, which occurred in 2.2 – 20% of patients in the majority of studies, although Machiels *et al.*[18] reported 30% of

TABLE 4:
Treatment-related adverse events (acute toxicity according to National Cancer Institute Common Toxicity Criteria [NCI CTC] version 3.0 grade[13]) during pre-operative chemoradiotherapy in all rectal adenocarcinoma patients included in the study (*n* = 47)

	NCI CTC version 3.0 grade[13]		
Adverse event	**Grade 1 – 2** ***n* (%)**	**Grade 3** ***n* (%)**	**Grade 4** ***n* (%)**
Blood/bone marrow			
Leucopenia	33 (70.2)	0	0
Neutropenia	18 (38.3)	2 (4.3)	0
Thrombocytopenia	5 (10.6)	0	0
Anaemia	30 (63.8)	2 (4.3)	1 (2.1)
Gastrointestinal			
Diarrhoea	23 (48.9)	5 (10.6)	1 (2.1)
Nausea/vomiting	28 (59.6)	1 (2.1)	0
Anorexia	35 (74.5)	0	0
Obstipation	2 (4.3)	0	0
Stomatitis	2 (4.3)	0	0
Dermatology/skin			
Hand-foot syndrome	6 (12.8)	0	0
Radiation dermatitis	40 (85.1)	0	0
Rash	0	0	0
Renal/genitourinary			
Dysuria	0	0	0
Urinary frequency	1 (2.1)	0	0
Creatinine/urea nitrogen	1 (2.1)	0	0
Liver function			
Transaminases (ALT, AST)	5 (10.6)	0	0
Hyperbilirubinaemia	2 (4.3)	0	0
Neurotoxicity	18 (38.3)	0	0
Fatigue	9 (19.1)	0	0
Infection/fever	2 (4.3)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

patients with grade 3 – 4 diarrhoea.

The XELOX regimen has been proven to be convenient, safe and non-inferior to FOLFOX-4 as first-line treatment for metastatic colorectal cancer,[8] and has also become a popular choice in palliative chemotherapy and adjuvant chemotherapy. The efficacy and tolerability of pre-operative RT combined with a concomitant standard XELOX regimen was further assessed in the present study. Capecitabine was administered at 1000 mg/m^2 twice daily on days 1 – 14 and 22 – 35, and oxaliplatin was given at a dose of 130 mg/m^2 on days 1 and 22. This multimodality schedule was well tolerated. As observed in other studies, the most frequent severe adverse effect was diarrhoea; a total of six patients (12.8%) had grade 3 – 4 diarrhoea. The pCR rate was 20.9% in all patients who could be evaluated for efficacy, which was the same as the highest pCR rate reported in the studies listed in Table 5. Downstaging and R0 resection were achieved in most patients and post-operative complications were rare. In conclusion, the present study demonstrated

TABLE 5:
Published phase II studies that have used capecitabine and oxaliplatin with concomitant pre-operative radiotherapy for the treatment of rectal cancer

Study	No. of patients	Treatment schedule	pCR (%)	Severe toxicity (grade 3 – 4)
Rödel *et al.*, 2003[19]	26	Radiotherapy 50.4 Gy; capecitabine 825 mg/m^2 twice daily on days 1 – 14 and 22 – 35; oxaliplatin 50 mg/m^2 on days 1, 8, 22 and 29	19	Diarrhoea 8%, skin toxicity 8%
Machiels *et al.*, 2005[18]	40	Radiotherapy 45 Gy; capecitabine 825 mg/m^2 twice daily, 5 days/week; oxaliplatin 50 mg/m^2 once weekly for 5 weeks	14	Diarrhoea 30%
Rutten *et al.*, 2006[20]	85	Radiotherapy 45 Gy; capecitabine 825 mg/m^2 twice daily, 5 days/week; oxaliplatin 50 mg/m^2 once weekly for 5 weeks	13	Diarrhoea 16%
Hospers *et al.*, 2007[17]	21	Radiotherapy 50.4 Gy; capecitabine 1000 mg/m^2 twice daily on days 1 – 14 and 25 – 38; oxaliplatin 85 mg/m^2 on days 1 and 29	9.5	Diarrhoea 18%
Rödel *et al.*, 2007[21]	104	Radiotherapy 50.4 Gy; capecitabine 825 mg/m^2 twice daily on days 1 – 14 and 22 – 35; oxaliplatin 50 mg/m^2 on days 1, 8, 22 and 29	16	Diarrhoea 12%, infection 5.8%
Koeberle *et al.*, 2008[22]	60	Capecitabine 1000 mg/m^2 twice daily on days 1 – 14; oxaliplatin 130 mg/m^2 on day 1; radiotherapy (45 Gy) plus capecitabine 825 mg/m^2 twice daily on days 22 – 35 and 43 – 56; oxaliplatin 50 mg/m^2 on days 22, 29, 43 and 50	11.7	Lymphocytopenia 43%, diarrhoea 20%
Carlomagno *et al.*, 2009[23]	46	Radiotherapy 45 Gy; capecitabine 825 mg/m^2 twice daily on days 1 – 14 and 22 – 35; oxaliplatin 50 mg/m^2 on days 1, 8, 22 and 29	20.9	Diarrhoea 2.2%
Present study	47	Radiotherapy 46 Gy; capecitabine 1000 mg/m^2 twice daily on days 1 – 14 and 22 – 35; oxaliplatin 130 mg/m^2 on days 1 and 22	20.9	Diarrhoea 12.8%, Anaemia 6.4%, Neutropenia 4.3% Nausea/vomiting 2.1%

pCR, pathological complete response.

that two cycles of XELOX with concomitant irradiation with 46 Gy was feasible and effective. Additional studies need to be carried out in order to confirm this result.

Previous studies have shown that patients seem to have different tumour responses to pre-operative CRT. The identification of predictive molecular markers of tumour response would provide an additional tool for selecting patients who are most likely to benefit from the treatment. CEA, an important biomarker in the diagnosis and monitoring of relapse in colorectal cancer, is considered to be a suitable predictor of tumour regression. A study by Yoon *et al.*,[24] to identify pre-treatment clinical parameters that could predict the pathological tumour response to pre-operative CRT for rectal cancer, involved 351 patients and showed that the pre-treatment CEA level was the most important clinical predictor. The data from Park *et al.*[25] also suggested that elevated pre-CRT serum CEA levels were associated with poor tumour response. Similar results were observed in the present study: 34.8% of patients with normal pre-CRT serum CEA levels (≤ 5 ng/ml) achieved pCR, as compared with only 5% of patients with elevated pre-CRT serum CEA (> 5 ng/ml), which suggested that serum CEA level may be a suitable biomarker for predicting tumour response to pre-operative CRT for rectal cancer.

Acknowledgements

We thank Qing Liu for statistical assistance and Justin Wang for linguistic revision. We also thank the participating surgeons at the Cancer Centre, Sun Yat-sen University, Guangzhou, China: You-Qing Zhan, Zhi-Wei Zhou, Wei Li, Ying-Bo Chen and Ling-Heng Kong.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

• Received for publication 9 October 2009 • Accepted subject to revision 14 October 2009
• Revised accepted 29 January 2010

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