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ORIGINAL ARTICLE

The RACOX phase I study: radiation (RA), capecitabine (C) and oxaliplatin (OX) as adjuvant treatment of stage II and III rectal cancer

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Summary

Purpose: *The aim of this phase I trial was to determine the maximum tolerated dose (MTD) of adjuvant chemotherapy (CT) with oxaliplatin in combination with capecitabine during concomitant pelvic radiotherapy (RT) in patients with rectal cancer.*

Patients and methods: *Eligible patients had pathological stage II (T3-4N0M0) or III (any T N1-2M0) rectal adenocarcinoma, and no prior treatment other than curative resection. Fixed capecitabine dose (825 mg/m^2 bid on days 1-14 and 22-35) was given and external beam RT was delivered to the pelvis (50.4 Gy in 27 fractions in 5.5 weeks, with field reduction after 45 Gy in linear accelerator, 18Mev). Oxaliplatin was tested at 4 dose levels: 100, 110, 120 and 130 mg/m^2. The dose of oxaliplatin was escalated when all 3 entered patients at each level had been monitored for at least 8 weeks after the CT/RT course without dose limiting toxicities (DLTs). In the presence of a DLT at any dose level, a further 3 patients were enrolled. If only 1 of the 6 patients experienced a DLT, escalation could proceed. The MTD was defined as the level at which ≥ 2 of 3 to 6 patients experienced DLTs. Fifteen patients (10 males and 5 females, median age 62 years) were enrolled at oxaliplatin dose levels of 100 (n=3), 110 (n=3), 120 (n=3) and 130 mg/m^2 (n=6).*

Results: *All patients completed the planned CT/RT course. Dose reduction or delay of the 2nd CT cycle was not required. No DLTs were observed at all dose levels. Overall, gastrointestinal and neurological toxicities were mild and transient. Toxicities included non-dose-limiting nausea / vomiting, diarrhea, dysesthesias in 2 level III and in 1 level IV patients. Grade II myelotoxicity, mainly neutropenia, was seen in 6 patients. With a median follow-up of 4 months (range 2-12) after the completion of CT/RT, late toxicities were restricted to grade II radiation colitis and dermatitis in 2 and 2 patients, respectively.*

Conclusion: *The combination of pelvic RT, capecitabine and 3-weekly oxaliplatin is feasible and well tolerated. The MTD was not reached up to the dose of 130 mg/m^2 of oxaliplatin, which is the recommended dose.*

Key words: adjuvant setting, capecitabine, chemotherapy, oxaliplatin, radiotherapy, rectal cancer

Introduction

Curative surgical resection of primary rectal cancer is usually associated with a high rate of relapse, with up to 30% of patients developing recurrent disease. However, local tumor control and overall survival in patients with stage II and III rectal cancer is improved by the administration, before or after surgery, of RT in combination with CT [1,2]. Adjuvant CT and RT have been generally accepted in the USA and Canada as standard therapy for patients who have had surgical resection for adenocarcinoma of the rectum with tumor extending through the muscularis propria (T3 or T4) or with nodal metastases [3]. This adjuvant therapy has generally been given as initial 5-fluorouracil (5-FU)-based chemotherapy followed by concurrent chemoradiation and further additional CT.

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Patients with stage II or III rectal cancer are at high risk for local relapse and systemic metastases. Adjuvant therapy should address both problems. Most trials of preoperative or postoperative RT alone have shown a decrease in the local recurrence rate but no definite positive effect on survival [4-5], although a Swedish trial has shown a survival advantage of preoperative RT compared to surgery alone [6]. Two trials have confirmed that 5-FU plus RT is effective and may be considered standard treatment. In these trials, combined modality adjuvant treatment with RT and CT following surgery also resulted in local failure rates lower than with either treatment modality [7,8]. An analysis of patients treated with postoperative CT and RT suggests that these patients may have more chronic bowel dysfunction compared to those who undergo surgical resection alone [9].

Many CT regimens have been examined in the adjuvant therapy of rectal cancer, although virtually all of them have been based on 5-FU. Bolus 5-FU alone is now rarely used because data from patients with metastatic disease have suggested that other regimens are more effective [10-13]. Although attempts to improve the efficacy of 5-FU-based chemoradiation by incorporating semustine [14] or 5-FU modulation with the addition of leucovorin or levamisole have failed to demonstrate any significant benefit [15], continuous infusion of 5-FU during RT has been shown to be superior to bolus 5-FU in terms of disease-free and overall survival [16]. Capecitabine is an oral fluoropyrimidine that mimics the pharmacokinetics of continuous 5-FU infusion and is preferentially converted to the active FU metabolite within tumor cells by exploiting the higher activity of thymidine phosphorylase in tumor tissue compared with normal tissue [17]. This tumor-selective activation of capecitabine might be improved further when combined with RT, which upregulates thymidine phosphorylase in tumor cells but not in healthy tissue [18]. Two phase I studies have been conducted to determine the maximum tolerated dose (MTD) of capecitabine in combination with RT in patients with rectal cancer [19,20]. Capecitabine plus RT demonstrated promising activity in the first study, including one pathologic complete remission (pCR) and 9 partial responses in the 10 patients treated in the neoadjuvant setting [19]. Furthermore, no grade 3 or 4 toxicities occurred in patients treated at the recommended dose (continuous capecitabine, 825 mg/m^2 twice daily, in combination with RT). In a second study, the MTD of capecitabine was reached at a dose level of 1,000 mg/m^2 twice daily (Monday to Friday) throughout the course of preoperative RT for patients with locally advanced rectal cancer [20].

Oxaliplatin is a prime candidate for chemoradiotherapy in rectal cancer because its large and rapid cytoreductive effects in colorectal malignancies and its relative lack of acute dose-limiting side effects when added to 5-FU or capecitabine. It has also been shown to possess radiosensitizing properties *in vitro* and in preclinical models.

Two randomized phase III trials have demonstrated the superiority of combined oxaliplatin and 5-FU/leucovorin compared with 5-FU/leucovorin alone in metastatic colorectal cancer [21,22]. As a preoperative regimen for initially unresectable liver metastases, the combination of oxaliplatin and 5-FU/leucovorin resulted in tumor downsizing in 59% of patients and in a complete resection rate of 38% [23]. Moreover, recent *in vitro* and *in vivo* preclinical and clinical studies have demonstrated oxaliplatin to be a potent radiosensitizing agent [24]. Available data from phase I and II trials with capecitabine and oxaliplatin in metastatic colorectal cancer established a 21-day treatment cycle of oral capecitabine, 1,000 to 1,250 mg/m^2 bid on days 1 to 14, in combination with oxaliplatin, 130 mg/m^2 administered on day 1 [25,26].

The aim of our phase I study was to determine the MTD of oxaliplatin when administered with fixed capecitabine dose along with adjuvant postoperative RT.

Patients and methods

The study was conducted according to the principles of the Declaration of Helsinki as amended in Somerset West in 1996, and to good clinical practice guidelines. Approval was gained from the institutional review board, and each patient gave written informed consent before recruited into the trial.

Eligibility criteria

Eligible patients had to fulfil the following criteria:

1. Age 18 to 80 years;
2. Histologically confirmed rectal adenocarcinoma after potentially curative resection of the primary tumor and regional lymph nodes with neither gross nor microscopic residual disease;
3. Tumor with either extension through the bowel wall or positive lymph nodes without evidence of distant metastatic disease (T3-T4, or N1-N3 and M0). A tumor was considered to be rectal cancer if a portion of the tumor was located below the peritoneal reflection or if the lower margin of the tumor was within 12 cm of the anal verge on endoscopy;
4. Pathological stage II (T3-4N0M0) or III (anyTN1-2M0) rectal adenocarcinoma;

5. No prior treatment other than curative resection, and no history of inflammatory bowel disease, malabsorption syndrome and peripheral neuropathy;
6. ECOG performance status 0-2;
7. Estimated life expectancy more than 3 months;
8. Female patients were not pregnant or lactating;
9. Adequate hematologic, liver, and renal function (neutrophils $\geq 2.5 \times 10^9$/L, platelet count $\geq 125 \times 10^9$/L, creatinine clearance $\geq$ 50 mL/min, total serum bilirubin < 1.5 times the upper limit of normal, and serum transaminases or alkaline phosphatase concentrations < 2 times the upper limit of normal).

Exclusion criteria included previous RT to the pelvis, or a planned course of RT with a total dose of less than 45 Gy or a high dose (more than 2 Gy) per fraction, previous CT or immunotherapy, other malignancy within the last 5 years, other serious medical illnesses that would limit the patient's ability to receive protocol therapy. Patients with known sensitivity to fluoropyrimidines and patients who participated in another clinical trial within 4 weeks from the start of treatment were ineligible. Patients began therapy between 3 and 10 weeks post-surgery.

Study design and treatment

The primary objective of the study was to determine the MTD of oral fixed-dose capecitabine administered concomitantly with oxaliplatin in combination with standard pelvic RT in patients with rectal cancer, using a standard escalation design. Secondary objectives included evaluation of the safety profile and preliminary assessment of the antitumor activity of the combined modality treatment.

Pretreatment evaluation

Pretreatment evaluation included a complete medical history and physical examination, biopsy, digital rectal examination, rigid rectoscopy, colonoscopy, transrectal ultrasound, pelvic and abdominal computed tomography (CT), and chest x-ray. Complete laboratory tests included full blood count, serum electrolytes, creatinine, urea, transaminases, alkaline phosphatase, and total bilirubin. Cardiac function was investigated both by electrocardiogram and echocardiogram.

Radiotherapy

RT was delivered with linear accelerator (6-10 MV photons) and a 3 or 4-field box technique with the patient in prone position. The planning target volume was designed to include all macroscopically identified disease and the internal iliac and presacral nodes up to the level of the 5th lumbar vertebra (superior border: L4/L5 junction). The distal border was 5 cm below the distal extent of the primary tumor or at the bottom of the obturator foramen. The anal canal was not irradiated unless the tumor extended close to the anus (i.e., the distal border of the tumor extended $\leq$ 2 cm from the dentate line). In these cases, the perineum surrounding the anus was included up to a total dose of 45 Gy. The dorsal border encompassed the entire sacrum, and the lateral borders extended 1-1.5 cm lateral to the bony margins of the true pelvic side walls. The field also extended to the posterior aspect of the symphysis pubis, with shielding of the anterior parts of the bladder and vagina. All patients received a total tumor dose of 50.4 Gy with daily fractions of 1.8 Gy on 5 consecutive days per week.

Chemotherapy

Capecitabine was given orally at a fixed dose of 825 mg/m^2 twice daily on days 1-14 and 22-35 of RT (Figure 1). The first daily dose was administered approximately 2h before RT, with the second dose given 12h later. Because the extent of radiation sensitization and the synergy with capecitabine in this multimodal treatment was unknown, the investigators' committee chose to start oxaliplatin at a dose level of 100 mg/m^2, which was administered as a 2h infusion on days 1 and 22, with planned increments of 10 mg/m^2 to a maximum dose of 130 mg/m^2.

Dose escalation and dose-limiting toxicities

While capecitabine was given orally at a fixed dose (825 mg/m^2 bid), 4 dose levels of oxaliplatin were planned to be administered to the patients (Table 1):

Level I: 100 mg/m^2
Level II: 110 mg/m^2
Level III: 120 mg/m^2
Level IV: 130 mg/m^2

Three patients were planned at each level. Adverse events were monitored weekly during treatment, for 2 weeks, 1 month, 2 months and 6 months after the end of RACOX therapy. The oxaliplatin dose was escalated when all 3 patients had completed the entire chemoradiation course and were monitored for at least 2 weeks after the end of treatment without occurrence of DLTs. If one of the first 3 patients experienced a DLT at any dose level, a further 3 patients were treated at that level. If only one in 6 patients at a given level experienced a DLT, escalation could proceed. The MTD was defined as the level at

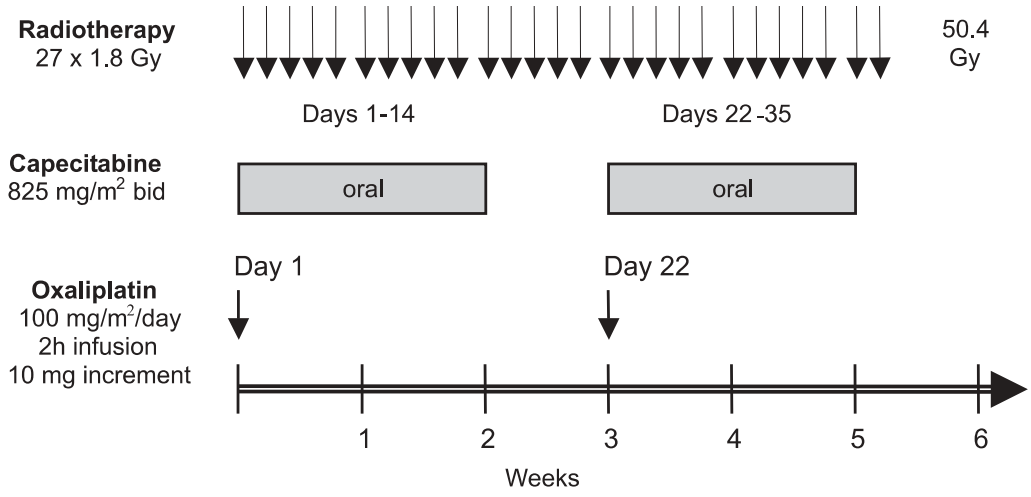

Figure 1. Postoperative concomitant chemoradiotherapy with capecitabine and oxaliplatin in patients with colorectal cancer.

which 2 or more of 3 to 6 patients experienced DLTs. The recommended dose of oxaliplatin for the subsequent phase II study was defined as the preceding dose level before the MTD was attained. DLTs were defined as the occurrence of one or more of the following: grade 4 neutropenia, grade 4 hyperbilirubinemia, grade 4 nausea/vomiting, grade 3 neutropenic fever, grade 3 thrombocytopenia, haemorrhage, anaemia, severe infection requiring hospitalization, grade 3 shift in liver transaminases, grade 3 stomatitis, grade 3 diarrhea or grade 3 hand-foot syndrome (neither resolving to grade ≤ 2 within 1 week of starting symptomatic treatment), and other grade 3 gastrointestinal toxicities including severe proctitis or colitis. Adverse events requiring interruption, dose reduction, or omission of capecitabine or oxaliplatin were not considered as limiting toxicities unless more than 50% of the scheduled dose could not be administered.

The following recommendations for CT dose reductions were applied: In patients who experienced grade 3 toxicity, according to National Cancer Institute common toxicity criteria [27], capecitabine and oxaliplatin were interrupted, and appropriate symptomatic and prophylactic treatment was administered. When the toxicity resolved to grade 0 or 1, treatment was continued at 75% of the original dose at the first appearance of the respective toxicity and at 50% of the starting dose at the second appearance. In patients who experienced grade 2 hand-foot syndrome, capecitabine was reduced to 50% of the original dose, and it was stopped in patients with grade 3 toxicity until this side effect resolved to grade ≤ 2. Capecitabine was then restarted at 50% of the original dose. In patients who developed grade 2 and 3 sensory neuropathy, oxaliplatin was withheld until recovery to grade ≤1 and then restarted at 75% of the original dose (after grade 2) and 50% of the dose (after grade 3). If the total WBC count was ≤ 3.0 X 10^9/L, ≤ 2.5 X 10^9/L, or ≤ 2.0 X 10^9/L at the beginning of the second chemotherapy cycle, oxaliplatin and capecitabine doses were reduced to 75%, 50%, and 0%, respectively, of the starting doses.

Statistical considerations

An escalation design with 3 to 6 (subsequently expanded to 12) patients was chosen on empiric grounds,

Table 1. Dose levels of the RACOX study

Dose level	*RT (Gy)*	*Oxaliplatin mg/m² q3w*	*Capecitabine (mg/m² twice daily, day 1-14 q3w)*
1	50.4	100	825
2	50.4	110	825
3	50.4	120	825
4	50.4	130	825

according to current standards in phase I cancer trials [28]. The chance of not detecting a toxicity that occurs in fact in every second patient is only 1.6% in a cohort of 6 patients and less than 0.1% in a cohort of 12.

Results

Between March 2003 and April 2004 a total of 17 patients were enrolled into the study. The patient characteristics are listed in Table 2. All patients had newly diagnosed rectal cancer and were primarily treated with surgery. No patient had any prior adjuvant CT or RT.

All 17 patients completed the scheduled chemoradiation course. The oxaliplatin dose was escalated when all 3 patients had completed the entire chemoradiation course and were monitored for at least 2 weeks after the end of treatment without occurrence of DLTs. Dose reduction or delay of the 2nd CT cycle was not required. No DLTs were observed at all 4 dose levels (100-130 mg/m^2).

Table 2. Patient and tumor characteristics (all dose levels)

Characteristic	*No. of patients (n=17)*	*%*
Sex		
male	14	82
female	3	18
Age, years		
median	62	
range	48-68	
ECOG performance status		
0	17	100
TNM clinical staging		
T1/2	1	6
T3	14	82
T4	2	12
N0	14	82
N1	3	18

Nonhematologic toxicity

Overall, gastrointestinal and neurological toxicities were mild and transient. Non-dose-limiting nausea and vomiting were recorded in 2 level III and in one level IV patients. Mild diarrhea (with only one level IV patient experiencing grade III diarrhea, which resolved within 3 days after adequate hydration and loperamide) was recorded during treatment.

Two level IV patients experienced grade I cystitis with no further complications, although adequate hydration was ensured. Despite the neurotoxic potential of oxaliplatin, only one patient presented grade II dysesthesia occurring after the 2nd cycle of CT, which resolved spontaneously after the completion of the CT course. Neurologic toxicities consisted primarily of perianal pain (30% of patients) and only one patient experienced short-lasting insomnia and fatigue.

Only one patient (level III) suffered grade I hand-foot syndrome, occurring after 28 days of treatment and no dose modifications were done. One patient experienced mild tachycardia after the administration of the 2nd cycle of capecitabine (30th day) with no further complications. Three patients suffered perianal and local skin reactions after the completion of treatment while no allergic reactions were recorded. Grade I mucositis, mainly stomatitis and proctitis, were observed in 2 patients during the trial. Mild elevation in transaminases and bilirubin levels was recorded in one patient after the first course of CT, which resolved spontaneously before the start of the 2nd cycle (19th day).

Myelotoxicity

The distribution characteristics of baseline WBC and platelet counts during treatment and during the first month after treatment are listed in Table 3. WBC suppression was the most common toxicity encountered during the trial. RBCs and platelets were only slightly affected. Neutropenia was limited to grade II in 6 patients while no febrile neutropenia was recorded.

With a median follow-up of 4 months (range 2-

Table 3. Baseline WBC and platelet counts during and after treatment (all dose levels)

		WBC (10^3/nL)		*Platelets (10^3/nL)*	
	No. of patients	*Median*	*Range*	*Median*	*Range*
Baseline	17	6.1	4.8-10.6	295	216-422
Day 15	17	5.4	3.6-9.1	250	186-325
Day 22	17	4.5	4.5-5.7	232	150-206
Day 36	17	4.3	3.8-6.3	198	138-298
Day 45	17	3.7	3.6-15.3	200	188-229

12) after the completion of chemoradiation, late toxicities were restricted to grade II radiation colitis and dermatitis in 3 and 2 patients, respectively. Incidence and maximum severity of toxicities at all dose levels are listed in Table 4. Increased levels of bilirubin without clinical relevance, observed in other capecitabine trials, were recorded in 2 patients.

Discussion

The aim of postoperative adjuvant chemoradiation is to improve local and systemic disease control. Chemotherapy schedules should be as dense as possible in order to maximize local effectiveness by radiation sensitization, and as intense as possible to eradicate microscopic distant disease.

Freyer et al. [29] published results from a phase I study of RT plus oxaliplatin and 5-FU/leucovorin, demonstrating the feasibility of such an intensified CT regimen when given concomitantly with RT. In that trial, CT was administered only in the 1st and 5th week of RT, using escalating doses of oxaliplatin (80, 100, or 130 mg/m^2 on days 1 and 29), 5-FU (350 mg/m^2 on days 1-5 and 29-33), and leucovorin (100 mg/m^2 on days 1-5 and 29-33) and the MTD was not reached. Dunst et al. [19] in a phase I trial have demonstrated the feasibility and good tolerability of continuous capecitabine administration during a conventional RT period of approximately 6 weeks. The only DLT in that study was grade

Table 4. Incidence and maximum severity of toxicities (all dose levels)

	*NCIC-CTC**							
	Grade 1		*Grade 2*		*Grade 3*		*Total*	
	No. of patients	*%*	*No. of patients*	*%*	*No. of patients*	*%*	*No. of patients*	*%*
Haematologic								
anemia	1	6	0	0	0	0	1	6
leucopenia	1	6	6	35	0	0	7	41
thrombocytopenia	1	6	0	0	0	0	1	6
infection (febrile neutropenia)	0	0	0	0	0	0		0
Gastrointestinal								
nausea/ vomiting	2	12	1	6	0		3	18
diarrhoea	2	12	2	12	1	6	5	30
stomatitis	2	12	0	0	0	0	2	12
proctitis	2	12	0	0	0	0	2	12
colitis	1	6	2	12	0	0	3	18
Hepatic								
hyperbilirubinemia	2	12	0	0	0	0	1	12
AST/ALT elevation	1	6	0	0	0	0	1	6
Genitourinary								
proteinuria	1	6	0	0	0	0	1	6
haematuria	2	12	0	0	0	0	2	12
cystitis	2	12	0	0	0	0	2	12
alopecia	1	6	0	0	0	0	1	6
cardiovascular	1	6	0	0	0	0	1	6
hand-foot syndrome	1	6	1	6	0	0	2	12
Neurologic								
paresthesia/dysesthesia	2	12	1	6	0	0	3	18
fatigue/asthenia	1	6	0	0	0	0	1	6
pain (perianal)	4	24	1	6	0	0	5	30
insomnia	1	6	0	0	0	0	1	6
Skin								
rash/itch	1	6	0	0	0	0	1	6
skin, local toxicity (perianal)	1	6	2	12	0	0	3	18
allergy	0	0	0	0	0	0	0	0
flu-like symptoms	1	6	0	0	0	0	1	6

No grade 4 adverse events were observed; *NCI-CTC: National Cancer Institute Common Toxicity Criteria

3 hand-foot syndrome at a capecitabine dose of 1,000 mg/m^2 bid; consequently, the recommended dose of capecitabine in this setting was 825 mg/m^2 bid.

Apart from their well established role in colorectal cancer when used as single agents, capecitabine and oxaliplatin can also be combined. Rodel et al. [30] first reported a feasible and well tolerated combination of capecitabine and oxaliplatin given concomitantly with preoperative RT. Good tolerance and acceptable results in terms of response in patients with metastatic colorectal cancer were also reported in phase I and II studies by Diaz-Rubio et al. [25] and Borner et al. [26], respectively.

The objective of our phase I study was to determine the DLTs of escalated oxaliplatin doses when combined with fixed doses of capecitabine and postoperative RT. The recommended dose of capecitabine when combined with RT is 825 mg/m^2 bid. The addition of oxaliplatin to chemoradiation in the adjuvant setting, in our study, is reasonable due to both synergistic antitumor activity with fluoropyrimidines and radiosensitizing properties. According to criteria of our study, the combination of pelvic RT, capecitabine, and 3-weekly oxaliplatin is feasible and well tolerated. The MTD was not reached up to the dose of 130 mg/m^2 of oxaliplatin, the maximum dose used in combination with 5-FU when CT is given alone. Thus, the recommended dose of oxaliplatin is 130 mg/m^2.

In an already ongoing phase II trial, we study the RACOX treatment program followed by 4 more cycles of the same CT after the completion of the chemoradiation course.

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