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ORIGINAL ARTICLE

Phase I study of postoperative radiotherapy with concomitant weekly irinotecan, 5-fluorouracil and folinic acid in locally advanced rectal cancer.

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Summary

Purpose: *5- fluorouracil (5-FU)-based chemotherapy with concomitant pelvic radiotherapy represents the gold standard of the adjuvant treatment of high-risk rectal cancer. This study aimed to determine the maximum tolerated dose (MTD) of weekly irinotecan (CPT-11) when combined with fixed 5FU/FA doses and pelvic irradiation.*

Patients and methods: *Twenty- four patients with stage II or III rectal cancer were accrued. All had undergone curative surgery before entering the study. Standard pelvic radiotherapy was delivered (50.4 Gy, 1.8 Gy/ fraction in 5.5 weeks). The 5-FU/FA doses were 350/250 (mg/m^2) in the first 6 patients and 250/100 in the remaining patients. Weekly doses of CPT-11 started at 30 mg/m^2 with escalation steps of 10 mg/m^2. CPT-11 was escalated when 3 patients had been monitored for 8 weeks, without a dose limiting toxicity (DLT).*

Results: *Twenty-three out of 24 patients completed the chemoradiation course. Only 1 patient discontinued the treatment due to persistent grade 3 diarrhea. Of the 144 planned weekly chemotherapy cycles, only 7 were omitted as a result of persisting grade 2-3 gastrointestinal toxicity in 3 patients and grade 3 neutropenia in 1 patient. Grade 3 gastrointestinal DLTs were observed at doses at the level of 30/250/100 in 1 patient and 70/250/100 in 2 patients. Late DLTs were severe radiation dermatitis and colitis at 40/ 350/250 (1 patient) and 70/250/100 (2 patients), respectively. With a follow-up of 18 months 20 (83.3%) patients remain disease- free.*

Conclusions: *The administration of weekly CPT-11/ 5FU/FA with concomitant pelvic radiotherapy is feasible and effective. This treatment schedule is associated with mild myelosuppression and mild to moderate gastrointestinal toxicity. Caution should be paid on late radiotherapy-induced toxicities. The MTD of weekly CPT-11 is 30 mg/m^2 when combined with 5FU/FA doses (mg/m^2) of 350/250 and reaches 60 mg/m^2 with lower doses of 5FU/FA (250/100).*

Key words: adjuvant treatment, 5-fluorouracil, irinotecan, radiotherapy, rectal cancer

Introduction

Colorectal cancer accounts for an estimated 10-15% of newly diagnosed cancer cases [1]. High-risk rectal cancer, staged as B2 and C according to Astler-Coller classification, is common and accounts for an important rate of failures despite radical resection with curative intent.

Postoperative pelvic irradiation plus 5-FU-based chemotherapy represents the gold standard adjuvant treatment of rectal cancer, as supported by many clinical trials and a recent meta-analysis [2-3]. Furthermore, when adjuvant chemotherapy is concerned, 5-FU plus FA is a standard regimen to which other chemotherapy combinations are compared [4].

New chemotherapeutic agents are currently being evaluated in order to determine a more effective adjuvant treatment for high-risk colorectal cases [5]. Among them oxaliplatin has shown favorable results

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when combined with 5-FU and postoperative irradiation in rectal cancer [6]. CPT-11 (irinotecan) has also been proved to be an effective agent in the treatment of metastatic colorectal cancer [7,8]. A recently published greek phase I trial evaluated the toxicity profile of irinotecan plus bolus 5-FU and FA with concomitant pelvic radiotherapy in resected stage B and C rectal cancer [9]. The study showed that the combination of the 3 drugs with concurrent conventional radiotherapy is a reasonable treatment option with acceptable toxicity, as long as the patients are followed carefully for acute and late sequelae [9].

Optimum doses for this promising schedule in the adjuvant setting remain unknown. The present phase I trial aimed to evaluate the MTD of CPT-11, when administered in combination with fixed doses of 5-FU/FA and concurrently to conventional radiotherapy.

Patients and methods

Patients

Twenty-four patients were recruited in this study in a 17 month period from March 2002 to December 2003. All patients had histologically confirmed rectal adenocarcinoma staged as B2, C1 and C2 according to the Astler-Coller classification or II (T3-4, N0, M0) and III (any T, N1-2, M0) according to the TNM staging system. The patient characteristics are shown in Table 1. Eight of the patients had stage II and the remaining 16 had stage III disease. Nine of the patients were female and 15 were male. The median age was 66 years (range 48-74 years).

Eligibility criteria

All accrued patients had undergone a curative surgical procedure, either an abdominoperineal or a low anterior resection, with no evidence of residual microscopic or macroscopic disease. The patients should enter the study within 45 days after surgery. An informed consent was obtained from all participating patients before the protocol enrollment (Table 1).

Eligible patients should be older than 18 years of age with a WHO performance status of 0-1 and should also fulfill the following criteria: no prior chemotherapy or irradiation; no history of other malignancies except for non-melanoma skin cancer or in situ carcinoma of the uterine cervix, either successfully treated; and absence of any serious condition that would affect the treatment compliance or tolerance to therapy, such as psychiatric disorders, chronic renal, liver and cardiac failure, ischemic heart disease, malabsorbtion syndrome, and inflammatory bowel disease. Pregnant or lactating women were excluded.

Laboratory criteria included: polymorphonuclear count >1500/m^3, hemoglobin (Hb) >11g/dl, platelets >100.000 m^3, serum creatinine < 1.5 mg/dl, total serum bilirubin <1.5 mg/dl, and alkaline phosphatase < 3×normal value.

Clinical assessment and follow- up

Before the initiation of adjuvant treatment, all patients provided a detailed medical history and underwent a complete physical examination, which included a digital rectal examination, evaluation of body weight and height and a pelvic examination for women or a digital examination of the prostate for men. Imaging included a chest x-ray and a computed tomography (CT) scan of the upper and lower abdomen. Cardiac function was assessed by cardiac ultrasound and electrocardiogram (ECG). Laboratory tests included complete blood cell count, biochemistry profile and serum tumour markers (CEA and CA 19-9). During treatment, blood cell counts were assessed every week and biochemistry tests every second week, until the end of treatment, and every month thereafter. A physical examination with special attention to possible sequelae of therapy (dermatological

Table 1. Patient characteristics

Characteristic		*No. of patients*		*%*	
Gender					
male		15		62.5	
female		9		37.5	
Age (years)					
median		66			
range		48-74			
Stage					
Astler-Coller	TNM				
B2	II	8	8	33.3	33.3
C1/C2	III	3/13	16	12.5/54	66.7
Performance status (WHO)					
0		20		83.3	
1		4		16.7	
Surgery					
abdominoperineal resection		10		41.7	
low anterior resection		14		58.3	
Interval between surgery and study entry (days)					
median		42			
range		36-45			

or mucosal complications) was undertaken once a week during treatment and every month thereafter. CT scans and chest x-rays were performed at the completion of treatment and every 6 months thereafter. Colonoscopy was performed 3 months after the completion of treatment and annually thereafter.

Treatment schedule

Patients were treated with conventional pelvic radiotherapy and concomitant chemotherapy. Chemotherapy was administered once a day every week, concomitantly with the delivery of radiotherapy for a total of 6 cycles, until the completion of radiotherapy. Each cycle of chemotherapy consisted of CPT-11: 30-70 mg/m^2 in 250 ml normal saline in 90-min i.v. infusion, followed by FA: 100 or 250 mg/m^2 in 500 ml normal saline in 120-minute i.v. infusion, followed by 5-FU: 250 or 350 mg/m^2 i.v. bolus.

Concomitant to chemotherapy, standard pelvic radiotherapy was delivered: 50.4 Gy, in daily fractions of 1.8 Gy, 5 fractions per week in 5.5 weeks. Radiotherapy was delivered with linear accelerator (energy range: 6 to 18 MeV). The whole pelvis was treated in prone position with a distended bladder. Pb blocks and wedges were used to account for in homogeneities and to spare normal tissues. A 3-field technique was used. The clinical target volume (CTV) included the primary tumour bed, as assessed by the preoperative CT scan with a 2 cm margin, as well as the surgical anastomosis and the surgical scar, indicated by radiosensitive means. The presacral and internal iliac lymph nodes were included in the posterior-anterior, as well as in the oblique fields. Patients received a minimum dose of 45 Gy to the whole pelvis and a 5-10 Gy boost to the CTV.

Levels of dose escalation

The 5-FU/FA doses (mg/m^2) were 350/250 in the first 6 patients and 250/100 in the remaining. The weekly doses of CPT-11 started at the level of 30 mg/m^2 with planned escalation steps of 10 mg/m^2. In every level 3 patients were included. The dose of CPT-11 could be escalated when all 3 patients (enrolled at any level) had been monitored for at least 8 weeks after the chemoradiation course, without the presence of a DLT. In the occurrence of a DLT, 3 further patients were accrued and if DLT was restricted to only 1 of the 6 patients, escalation could proceed. Intrapatient escalation was not allowed. The trial included the following dose levels of CPT-11/5-FU/FA (mg/m^2): 30/350/250 (n=3), 40/350/250 (n=3), 30/250/100 (n=6), 40/250/100 (n=3), 50/250/100 (n=3), 60/250/100 (n=3) and 70/250/100 (n=3).

Definition of MTD and DLT

The toxicity of the above treatment program was to be evaluated during the chemoradiation course and during an 8-week period after the completion of the combined therapy. Toxicity was graded using the Common Toxicity Criteria [10]. The MTD was defined as the dose level at which more than 1 of the 3-6 patients had experienced DLTs. The following adverse events were determined as DLTs: grade 4 neutropenia or thrombocytopenia lasting $\geq$3 days; grade 3 febrile neutropenia; any grade 3-4 non hematological toxicity, except alopecia and nausea/ vomiting, neither resolving to grade $\leq$2 within one week of starting appropriate symptomatic therapy; and persisting grade $\geq$2 toxicity requiring more than 50% dose reduction of 5-FU/FA or leading to the omission of $\geq$2 successive weekly chemotherapy cycles.

Toxicity management and dose modification

In the absence of any grade >1 toxicity, the weekly chemotherapy courses were administered as planned. Prophylactic use of haemopoietic growth factors was not allowed. No prophylactic treatment was also permitted for other possible toxicities, including diarrhea. Antiemetic drugs were independently provided. In patients who experienced grade 2-3 hematological or grade 2 non-hematological toxicity, chemotherapy was delayed until recovery to grade $\leq$1, and in the subsequent chemotherapy cycles the 5-FU/FA doses were reduced to 75% of the starting dose at the first appearance and to 50% at the second occurrence. If DLTs occurred, treatment was discontinued and the patients could restart radiotherapy alone when the toxicity resolved to grade $\leq$2.

Diarrhea was initially treated with loperamide and the patient was hospitalized if necessary. In case of angina or myocardial infarction the treatment was discontinued. Dermatological complications as well as mucositis were carefully monitored and if graded >2, treatment delay and dose modification were performed as described above. Antiemetic drugs were independently provided. No prophylactic treatment was permitted for any of the possible toxicities, including diarrhea. Chemotherapy was continued concomitant to irradiation until the completion of therapy, or when consent was withdrawn or DLTs occurred.

Results

The median length of follow-up was 18 months (range 6- 27). Table 2 shows the treatment characteristics. Overall, 23 out of the 24 patients completed the scheduled treatment program. Only 1 patient discontinued the chemoradiation course because of persistent grade 3 diarrhea. Of the 144 planned weekly chemotherapy cycles, only 7 were omitted due to toxicity. Thus, a total of 137 chemotherapy cycles were administered during the study (median number of cycles per patient: 6, range: 2-6). The 7 chemotherapy cycles omitted in 4 patients were due to persisting grade 2-3 gastrointestinal toxicity in 3 patients and grade 3 afebrile neutropenia in 1 patient. However, chemoradiation was not permanently discontinued in 3 out of those 4 patients. A total of 125 chemotherapy cycles were given at full doses and dose reduction was required in only 12 of the 137 administered weekly cycles. Radiation was delivered as planned in all but 1 of the enrolled patients. No hospitalization during the chemoradiation course was required. Nevertheless, 2 patients required admission for surgical management of late radiation-induced complications.

Acute toxicities

The toxicities observed during the chemoradiation course are presented in Table 3. The most common grade 1 acute toxicities were: neutropenia (8 patients, 33.3%); nausea/vomiting (8 patients, 33.3%); enteritis/colitis (7 patients, 29.1%); diarrhea (6 patients, 25%); dermatitis/proctitis (5 patients, 20.8%); anaemia (4 patients, 16.6%); thrombocytopenia (3 patients, 12.5%); mucositis (3 patients, 12.5%); constipation (2 patients, 8.3%); and alopecia (2 patients, 8.3%). Grade 2 acute toxicities included: neutropenia (7 patients, 29.1%); diarrhea (3 patients, 12.5%); enteritis/colitis (3 patients, 12.5%); nausea/vomiting (2 patients, 8.3%); dermatitis/proctitis (1 patient, 4.1%); anemia (1 patient, 4.1%); and constipation (1 patient, 4.1%). One patient experienced grade 3 emesis, which was, however, sufficiently managed with antiemetic drugs and did not lead to any treatment discontinuation. Grade 3 gastrointestinal DLTs (diarrhea and enteritis/colitis) were observed at the dose levels of 30/250/100 in 1 patient and 70/250/100 in 2 patients (Tables 3, 4). Unscheduled admissions to the hospital for management of acute reactions to treatment were not necessary for any of the treated patients.

Late toxicities

During the 8-week interval of monitoring after the completion of the chemoradiation course, late DLTs occurred in 3 patients. Two patients at the dose level of 40/350/250, who had developed grade 1 radiation dermatitis in the perianal area during treatment, deteriorated (grade 3 dermatitis) within 2 months after the completion of the chemoradiation course. Reconstructive and plastic surgery was required in 1 of those patients. At the dose level of 70/250/100, 1 patient experienced persistent grade 3 diarrhea, nutritional disorders, progressive weight loss and repeated episodes of ileus. This patient was admitted as an emergency and at laparotomy evidence of severe enterocolitis was

Table 2. Treatment characteristics

Characteristic	*N (%)*
Weekly chemotherapy cycles per patient	
median	6
range	2-6
Scheduled chemotherapy cycles	144
Administered chemotherapy cycles	137
Cycles omitted due to toxicity	7
Cycles administered at a full dose	125 (91.2)
Cycles requiring dose reduction	12 (8.8)
Patients that completed the chemoradiation course	23 (95.8)
Patients requiring hospitalization for acute toxicity	0 (0)
Patients requiring hospitalization for late toxicity	2 (8.3)

Table 3. Acute and late toxicities

Toxicities	*No. of patients (%)*			
	Grade 1	*Grade 2*	*Grade 3*	*Grade 4*
Acute				
anemia	4 (16.6)	1 (4.1)		
neutropenia	8 (33.3)	7 (29.1)	1 (4.1)	
thrombocytopenia	3 (12.5)			
nausea/vomiting	8 (33.3)	2 (8.3)	1 (4.1)	
diarrhea	6 (25)	3 (12.5)	3 (12.5)	
constipation	2 (8.3)	1 (4.1)		
enteritis/colitis	7 (29.1)	3 (12.5)		
mucositis	3 (12.5)			
dermatitis/proctitis	5 (20.8)	1 (4.1)		
alopecia	2 (8.3)			
Late				
enteritis/colitis	5 (20.8)	1 (4.1)	1 (4.1)	
dermatitis			2 (8.3)	

*No grade 4 toxicities were encountered

Table 4. Dose limiting toxicities (DLTs)

Grade 3 DLTs	*Dose levels of CPT-11/5-FU/FA mg/m²*		
	40/350/250 *No. of patients*	*30/250/100* *No. of patients*	*70/250/100* *No. of patients*
Acute			
diarrhea, enteritis/colitis		1	2
Late (radiation-induced)			
perianal dermatitis	2		
enteritis/colitis		1	

found and a radiation circumscribed postcecal abscess was revealed, which was successfully resected.

At a median follow-up of 18 months, the most common radiation-induced late toxicity, as assessed by colonoscopy, was enteritis-colitis graded as 1 in 5 (20.8%) patients and 2 in 1 (4.1%) patient.

Dose modification

The doses of 5-FU/FA had to be reduced according to the guidelines of the protocol in a total of 12 weekly chemotherapy cycles in 5 of the patients. The reasons for that were acute toxicities, namely grade 3 afebrile neutropenia (6 cycles in 2 patients) and grade 2 diarrhea (6 cycles in 3 patients).

MTD

The MTD of weekly CPT-11 was only 30 mg/m^2 when combined with 5FU/FA doses (mg/m^2) as high as 350/250 and reached 60 mg/m^2 with the lower doses of 250/100.

Efficacy

At a median follow-up of 18 months (range 6-27) relapses have been documented in 4 patients : liver metastases in 2 patients at 6 and 13 months, respectively, and local recurrence in 2 patients at 18 and 24 months, respectively. Two patients have died of metastatic disease. Twenty-two patients are still alive and 20 of them remain disease-free.

Discussion

This phase I study was designed to assess the toxicity profile and MTD of CPT-11 given postoperatively in combination with weekly fixed doses of 5-FU/FA and concomitant conventional pelvic radiotherapy in patients with high-risk rectal cancer. The results of the present trial showed that this combined treatment modality is feasible and effective. The MTD for weekly CPT-11 was only 30 mg/m^2 when combined with 5-FU/FA doses (mg/m^2) as high as 350/250 and reached 60 mg/m^2 with lower doses of 5-FU/FA such as 250/100.

The optimal adjuvant treatment of rectal cancer is currently under extensive research. A standard regimen consisting of 5-FU and FA concomitantly to radiotherapy remains the most widely accepted standard of care, at least for stage III patients [11]. For stage II patients, the adjuvant therapy is controversial, but still there is a trend in incorporating such patients in clinical trials containing the 5-FU/FA regimen [12,13].

Among the new agents being tested, CPT-11 and oxaliplatin , after having proved to be beneficial for metastatic colorectal cancer, are gaining attention in the adjuvant setting [14]. A phase I trial showed that CPT-11 might be a reasonable approach to adjuvant treatment with tolerable toxicities [9]. However, the optimal dosage of this agent remains unknown, especially when combined with 5-FU/FA and radiotherapy.

CPT-11 is an inhibitor of the enzyme topoisomerase I, which is crucial for DNA synthesis. This inhibition results in “single-strand breaks” in DNA, so that its replication and subsequent RNA synthesis are inhibited and cell division is ceased [15]. CPT-11 acts mainly during the S-phase of the cell cycle. It has a potent action on colorectal cancer cells and acts in a different way to 5-FU, as indicated by its action as second or third-line treatment in 5-FU-refractory colorectal cancer [16]. CPT-11 is now considered standard therapy for patients with stage IV disease who do not respond or progress on 5-FU [17]. Common toxicities involving CPT-11 are diarrhea, nausea, vomiting and neutropenia [18].

Overall, the toxicities presented in this trial were mild to moderate and rather well manageable. Nausea and vomiting were mild and only in 1 patient were

graded as 3. All cases were easily managed with common antiemetic drugs. Only 5 patients developed grade 2 diarrhea or grade 3 afebrile neutropenia, which led to a dose reduction of 5FU and FA, but not to a permanent discontinuation of the treatment. Only 7 out of the 144 planned weekly chemotherapy cycles were omitted due to persisting grade 2-3 gastrointestinal toxicity or grade 3 afebrile neutropenia. Grade 3 gastrointestinal DLTs were observed at the dose levels of 30/250/100 (1 patient and 70/250/100 (2 patients). Late DLTs included severe radiation dermatitis (2 patients) and enteritis/colitis (1 patient) at the levels of 40/350/250 and 70/250/100, respectively. No hospitalization was required during the chemoradiation course, but 2 patients were admitted for surgical management of late radiation-induced complications after the completion of treatment.

As no treatment-related death occurred in this study and severe toxicities were rather uncommon , this combination seems to be a reasonable adjuvant treatment option in patients with high-risk rectal cancer. There is also an indication that attention should be paid on possible late radiation-induced toxicities. As the present study monitored the toxicity profile in an 8-week period after the completion of the chemoradiation course, intermediate to late toxicities could be evaluated and integrated in the MTD assessment. These toxicities were mainly gastrointestinal ones and should be attributed to radiotherapy rather than to chemotherapy. However, late and acute toxicities were rather low in this trial compared to other studies employing 5-FU and FA plus radiotherapy [19,20]. The combination of bolus 5-FU plus FA may be the cause of severe bowel complications, particularly in patients with neutropenia, as well as fistulas in 2% of patients [21,22]. In the treatment schedule we studied, acute complications were mild to moderate, but late toxicities proved severe and dose limiting in 3 of the patients.

In conclusion, the administration of weekly CPT-11/5-FU/FA with concomitant pelvic radiotherapy is feasible in the adjuvant setting of high-risk rectal cancer. The chemoradiation course is associated with mild myelosuppression and mild to moderate gastrointestinal toxicity. However, caution should be paid on late radiation-induced toxicities. Overall, low doses of CPT-11 can be safely administered and dose escalation depends on 5-FU/FA dosage. This treatment program seems to be effective, as at a median follow-up of 18 months 20 out of the 24 accrued patients (83.3%) were alive and free of relapse. In a further phase I/II study, we currently evaluate the tolerability and efficacy of 12 additional weekly chemotherapy cycles after the completion of the chemoradiation course.

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