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Combined radiotherapy, 5-fluorouracil continuous infusion and weekly oxaliplatin in advanced rectal cancer: A phase I study

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Abstract

The aim of this study was to determine the maximum-tolerated dose (MTD) of weekly oxaliplatin combined with 5-fluorouracil (5FU) continuous infusion administered concomitantly with fractionated radiotherapy in patients presenting advanced rectal cancer. Forty-three patients with rectal cancer (stage T3/T4 ($n = 24$), metastatic ($n = 17$) and 2 with local recurrence), were included. The radiotherapy dose delivered was 45 Gy over 5 weeks (1.8 Gy/fraction/day, 5 days per week). The initial weekly oxaliplatin dosage was 30 mg/m^2 and the 5FU dosage 150 mg/m^2/d. The oxaliplatin and 5FU doses were escalated. Eight dose levels were tested. At dose level 8 (oxaliplatin 80 mg/m^2, 5FU 225 mg/m^2/d), 2 patients out of 4 presented dose-limiting toxicity (severe diarrhoea with dehydration and fatal shock, rectovesical fistula). At dose level 7, 2 further patients presented with grade 3 diarrhoea. The main toxicity of the combination was diarrhoea. The hematological and neurological toxicities were not severe and were not dose-limiting. Out of the 30 patients undergoing surgery, 4 (13.3%) presented with pathological complete response and 4 (13.3%) only presented with microscopic residual disease. The results from this study enabled determination of the recommended weekly oxaliplatin dose (60 mg/m^2) combined with 5FU continuous infusion (225 mg/m^2) and fractionated radiotherapy (45 Gy) in the pre-operative treatment of advanced rectal cancer. The good safety profile of the regimen, associated with promising results in terms of histological response, suggest that the regimen could be developed in future phase II/III studies.

Keywords: Rectal cancer; Radiotherapy; Oxaliplatin; 5-Fluorouracil; Combined treatment; Phase I study

1. Introduction

Pre-operative radiotherapy was the standard treatment for rectal cancer [1–3]. Several controlled studies have shown that pre-operative radiotherapy decreases the local recurrence rate [1–3] and may even enhance overall survival [1]. The decrease in recurrence was

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obtained by combining pre-operative radiotherapy and total mesorectal excision [3]. The current data show that fractionated radiotherapy followed by delayed surgery can marginally increase the percentage of conservative procedures [4]. Among the various methods used to attempt to improve the results obtained, the combination of radio- and chemotherapy has been widely studied. Five-fluorouracil (5FU), due to its synergistic action with radiotherapy, has been preferentially used in various published studies. 5FU has been administered by bolus injection [5] or by protracted infusion [5,6]. Post-operatively, continuous infusion of 5FU is superior to bolus injection, due to the lower hematological toxicity, and superior recurrence-free and overall survival associated with the former [7]. However, a recent comparison of several modulated 5FU regimens in combination with postoperative radiotherapy did not show any significant difference between the various regimens investigated [8]. Recent results from randomised trials for rectal cancer showed that pre-operative chemoradiation is superior to postoperative chemoradiation in term of toxicity, probably due to a smaller volume of irradiated small bowel, and local control [9]. Moreover pre-operative chemoradiation showed a decrease of local recurrence compared to radiotherapy alone [10,11] and an increase in sphincter saving surgery [11]. At the present time, chemoradiation could be considered as the standard pre-operative treatment for T3–T4 resectable cancers. However, until now adjuvant chemotherapy did not show a statistically significant advantage for the patients having received a pre-operative radiotherapy. The European and French studies [10,11] employed 5FU bolus injection modulated with leucovorin. This method of administration is not optimal since 5FU administered by infusion is more effective and less toxic than 5FU by bolus injection [7,12]. In parallel, the results of palliative chemotherapy in colorectal cancer have been substantially improved by the combination of 5FU with oxaliplatin or irinotecan [13–17]. The poly-chemotherapeutic regimens induce not only an improvement in response rate and progression-free survival, but also an improvement in overall survival [13,14,17]. Both *in vivo* and *in vitro*, oxaliplatin has been shown to have an additive action with radiotherapy in the management of digestive tract tumours [18–20]. Incorporation of those drugs in combined treatment strategies could substantially improve the results obtained with 5FU alone. The authors have thus developed a dosage regimen combining the classic administration of 5FU by continuous infusion with weekly oxaliplatin. The preclinical data seem to show optimal synergy between 5FU and oxaliplatin when the latter is preceded and followed by 5FU administration [18]. Moreover, that regimen facilitates dosage adjustment during treatment. This combination warrants additional investigation in patients with rectal cancer.

2. Patients and methods

2.1. Objectives

The primary objective was to conduct a phase I study to determine the maximum-tolerated dose (MTD) and to determine the recommended dose of 5FU continuous infusion and weekly oxaliplatin, combined with fractionated radiotherapy, in advanced rectal cancer. The secondary objective was to analyse the radiological response rate in evaluable patients and the percentage of sterilisation in case of surgery.

2.2. Inclusion criteria

All the patients included in the study presented with rectal adenocarcinoma that had been histologically documented. The tumours were either locally advanced (clinical stage T3–T4 and with radiological (ultrasound or CT) evidence of perirectal fat infiltration) and/or metastatic tumours of the rectum requiring local treatment, or tumour recurrence; no magnetic resonance imaging was used during this study. The tumours were located below the peritoneal reflection in all cases. The other inclusion criteria were performance status (Eastern Cooperative Oncology Group) 0–2, age >18 years, satisfactory hematological, liver function and other laboratory parameters (neutrophils $\geqslant 2 \times 10^9$/L, platelets 130×10^9/L, hemoglobin >100 g/L, creatinine <130 μmol/L, bilirubin <1.5 times the upper limit of the normal range (ULN), transaminases, alkaline phosphatase <2 ULN). Women of child-bearing potential were to have a negative pregnancy test. Patients were required to use effective contraception throughout the duration of treatment. Patients having received chemotherapy and/or pelvic radiotherapy were also excluded. Patients presenting with acute occlusion without colostomy and those presenting with rectovesical fistula, inflammatory disease of the bowel, a contra-indication to 5FU (uncontrolled ischemic heart disease or cardiac toxicities experienced while on 5FU therapy) and/or to oxaliplatin (known peripheral neuropathy), an uncontrolled serious systemic disease, or psychiatric or psychological disorders interfering with reliable follow-up could not be included in the study. All the patients signed an informed consent form prior to inclusion. The primary objective of the study was to determine the MTD and the protocol was approved by an institutional review board in compliance with French regulations and the principles of the Declaration of Helsinki. The inclusions in the phase I study took place between June 2000 and December 2002.

2.3. Diagnostic workup

Two weeks prior to treatment initiation, all the patients were assessed by patient interview and a full

physical examination, digital rectal examination, colonoscopy, abdominal and pelvic CT-scan and chest X-ray. Whenever possible, endorectal ultrasound was conducted. A baseline laboratory workup was run on all patients and consisted in complete blood count, and serum electrolytes, creatinine, total protein and liver function tests. Restaging was performed 4–6 weeks after the end of the treatment.

3. Treatment

3.1. Radiotherapy

All patients received radiation delivered by a linear accelerator of at least 10 MV. A multiple-field method was used (3 or 4 fields). The patients were treated in prone position with a full bladder. The clinical target volume included the primary rectal tumour, the perirectal nodes, the mesorectum up to the level of the first sacral vertebra, and the lymph nodes along the internal iliac vessels. Fields measured an average 14×12 cm; lateral fields involved the sacrum's posterior surface and they measured an average 14 cm high and 10–12 cm anteroposteriorly. Treatment planning and field positioning were performed with orthogonal film simulation and contrast barium in the rectum. Computerised dosimetry was routinely performed. Irradiation was delivered 5 days per week at a dose of 1.8 Gy/d to a total of 45 Gy as defined by the International Commission on Radiation Units and Measurements 50.

3.2. Chemotherapy

Chemotherapy consisted of 5FU delivered by protracted venous continuous infusion (7 days/week) for 5 weeks, concomitantly with radiotherapy. The initial 5FU dosage was relatively low (150 mg/m^2/d) to avoid an unexpected initial toxicity. 5FU doses were planned at 150, 175, 200 and 225 mg/m^2/d (Table 1). Oxaliplatin was administered by infusion over 2 h once per week, from the first day of radiotherapy, and for duration of 5 weeks. Oxaliplatin doses were planned at 30, 40, 50, 60, 70 and 80 mg/m^2/week (Table 1). The starting dose of oxaliplatin was chosen because this dose intensity was just below that used in chemotherapy of metastatic disease [15]. For the first dose level, 5FU was administered at a dosage of 150 mg/m^2/d and oxaliplatin at a dosage of 30 mg/m^2/week (Table 1). Eight dose level combinations were planned (Table 1). For each level, only one of the two drugs was escalated (either 5FU or oxaliplatin). However, given the preliminary results of a phase I study with a similar dosage regimen [21] and in the absence of significant toxicity, it was decided to increase both the oxaliplatin and 5FU doses at dose level 4. Each dose level was administered to at least 3 patients. If a dose-limiting toxicity (DLT) was observed in more than 1 patient, a total of 6 patients had to be treated at that dose level. After treatment of the 3 patients and in the absence of dose-limiting toxicities (DLT), the next dose level was administered. It was however possible to include more than 3 patients in a dose level, in the absence of dose-limiting toxicity, prior to initiating the following dose level. We defined the maximum-tolerated dose (MTD) as the level at which at least two patients experienced DLTs. The recommended dose was the level below. In all, 8 doses levels were tested (Table 1). In the event of emergence of dose-limiting toxicity or toxicity considered as severe, after the therapeutic measures necessary to manage the adverse reaction, chemotherapy was resumed or continued at a lower dose level.

Table 1
Chemotherapeutic dose levels

Level	No. patients	5FU dose (mg/m^2)	Oxaliplatin dose (mg/m^2)
1	3	150	30
2	3	175	30
3	8	175	40
4	5	200	50
5	4	225	50
6	8	225	60
7	8	225	70
8	4	225	80

4. Monitoring and management during treatment

Each week, a physical examination was conducted, in particular to investigate for adverse reactions. On the visit day, a complete blood count, electrolytes, creatinine and total protein were determined. The systematic use of growth factors (erythropoietin, granulocyte-macrophage or granulocyte stimulating-factor) was not authorised during treatment. Conventional supportive treatment was authorised. The use of setron anti-emetics was encouraged. The objective of the study was to define a feasible weekly oxaliplatin dosage associated with continuous 5FU infusion in the context of pre-operative radiochemotherapy by defining the MTD. Adverse events were classified according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 2.0. except for peripheral neuropathy. For the latter we used Levi's specific scale [22].

DLT was defined as hematological toxicity (leukopenia, neutropenia, thrombocytopenia) of grade 4, febrile neutropenia (38.5 °C or more over more than 24 h associated with a neutrophil count $<0.5 \times 10^9$/L), severe infection (requiring hospitalisation and antibiotic therapy), grade 4 anaemia, grade 3 diarrhoea of duration greater than 3 days or emergence of grade 4 diarrhoea,

grade 3 or 4 vomiting despite satisfactory prophylactic and curative treatment, mucositis of grade 3 or 4, or grade 3 sensory neuropathy (Levi's specific scale) [22], any life-threatening event and/or any event resulting in hospitalisation not scheduled in the context of treatment. In the event of emergence of 2 or more dose-limiting toxicities for a given dose level, dose escalation was to be discontinued and the dose level considered as the MTD. The following recommendations for dose reductions were applied: if a patient experienced a grade 3 or 4 toxicity that was considered possibly related to chemotherapy it was stopped but the radiotherapy schedule was not modified. When grade 3–4 toxicity was no longer present chemotherapy was decreased to the lower dose level. If a grade 3 or 4 toxicity was considered possibly related to chemotherapy or to radiotherapy the chemoradiation was interrupted until the toxicity had resolved to grade 2 and chemotherapy was decrease to the lower dose level and the radiotherapy was resumed.

5. Results

Between June 2000 and December 2002, 43 patients were enrolled in the study (Table 2). Their median age was 59 years (range: 36–78 years) and there were 34 men and 9 women. The tumours were accessible to digital rectal examination in 41 out of 43 patients (95.3%). The tumours were located, on average, 4.9 ± 2.8 cm above the anal margin. Thirty-three patients had endorectal ultrasound examination (1 T2, 25 T3, 7 T4). Seventeen patients presented with metastatic and 26 with local tumours that were CT and clinically staged (21 T3, 3 T4 and 2 with a local recurrence).

Table 2
Patient characteristics ($n = 43$)

Characteristics	No.
Age (years)	
Median	59
Range	36–78
Gender	
Men/Women	34/9
Performance status	
0–1/2	42/1
Tumour stage	
Locally advanced	24
Metastatic	17
Local disease recurrence	2
Anal margin distance (cm)	
Median	5
Range	0–12
0–5 cm	24
>5 cm	16
Unknown	3

6. Toxicity

6.1. Dose-limiting toxicities

Table 3 shows the toxicities associated with each dose level. Before level 4, no dose-limiting toxicities was observed. At dose level 4 (oxaliplatin 50 mg/m^2, 5FU 200 mg/m^2/d), 1 patient presenting with multiple metastases experienced grade 4 diarrhoea necessitating hospitalisation and intravenous fluids. The patient also presented with grade 3 depression. After 3 treatment-free days, 5FU was resumed at a dose level of 175 mg/m^2/d and radiotherapy was pursued unchanged. No other patient presented with dose-limiting toxicity and,

Table 3
Toxicity in the study population ($n = 43$)

Toxicity grade (NCI CTC V2.0)	Level 3[a] $N = 8$		Level 4 $N = 5$		Level 5 $N = 4$		Level 6 $N = 8$		Level 7 $N = 8$		Level 8 $N = 4$	
	3	4	3	4	3	4	3	4	3	4	3	4
Hematological												
Leukopenia												
Neutropenia												
Thrombopenia											1	
Anaemia									1		1	
Gastrointestinal												
Diarrhoea	1			1			1		2			1
Abdominal pain							1		1			
Systemic												
Asthenia									1			1
Urinary tract												1
Others			1									1
Neurotoxicity (Levi's scale)									1			

[a] Levels 1 and 2 were not associated with any grade 3 or 4 adverse event.

in compliance with the protocol, the next dose level was initiated. At dose level 6, one patient presented with grade 3 diarrhoea and grade 3 anorexia requiring short-duration hospitalisation with intravenous fluids. At dose level 7 (oxaliplatin 70 mg/m^2, 5FU 225 mg/m^2/d), the first 3 patients did not present with grade 3 or 4 toxicity. However, 2 patients secondarily included in that dose level, after level 8 had been tested, presented with severe toxicity. One of the patients, aged 74 years, with a metastatic tumour, presented with diarrhoea grade 3 and abdominal pain graded 3. Another patient, aged 76 years, with hepatic and lymph node metastases, presented 3 grade 3 toxicities: diarrhoea, asthenia and anaemia. In addition, grade 3 dysesthesia (Levi's specific scale) [22] occurred. The neurotoxicity prevented subsequent administration of oxaliplatin. The neurological disorders completely resolved in a few weeks. The dose inducing dose-limiting toxicity was dose level 8 (oxaliplatin 80 mg/m^2, 5FU 225 mg/m^2/d). One patient presented with grade 3 diarrhoea and grade 4 asthenia during week 3 of treatment and required emergency hospitalisation. Despite intravenous fluids, the patient died suddenly in a context of dehydration and renal failure. Another patient whose tumour invaded the posterior surface of the bladder developed a rectovesical fistula requiring nephrostomy. Grade 3 thrombopenia was observed in a third patient. Hematological toxicity was never dose-limiting. With the exception of 2 cases of grade 3 anaemia at dose levels 7 and 8, no hematological toxicity of grade greater than 2 was observed. In particular, no grade 3 or 4 neutropenia or leukopenia was observed in the 43 patients.

6.2. Others toxicities

The first two dose levels were not associated with grade 3 or 4 toxicity. Other occasional toxicities were a short grade 3 (24 h) at level 3; and a transient marked elevation of γ-glutamyl transpeptidase (grade 4), at dose level 5. At level 6 one patient presented with grade 2 diarrhoea associated with grade 3 abdominal pain. Dose level 6, oxaliplatin 60 mg/m^2 and 5FU 225 mg/m^2/d, was deemed to be the recommended dose level. Of a total of 8 patients treated at the recommended dose level, grade 3 diarrhoea occured in one patient.

7. Objective responses

Tumour staging was not the primary objective of the study. However, post-treatment staging was conducted on 36 patients. By radiological criteria, an objective response was observed in 21 of these patients (58.3%) of which 2 were radiological complete responses and 19 partial responses. Thirty patients underwent surgery. For 4 patients (13.3%), the surgical specimen was disease-free and, for a further 4 patients (13.3%), the surgical specimen only showed rare residual microscopic disease. The post-radiotherapeutic staging yielded: 5 pT0, 2 pT1, 5 pT2, 16 pT3, 2 pT4. In addition, 19 patients (63%) showed no lymph node involvement on the surgical specimen, it should be noted that one patient with pT0 tumour had lymph node involvement.

8. Discussion

Pre-operative chemoradiation is a standard of care for locally advanced rectal cancer. Among the objectives for future pre-operative treatments, improving the tumour regression rate is one of the most important. Research to determine the most synergistic radiochemotherapeutic combinations are in line with that objective. In this study, the authors conducted a phase I study using 5FU continuous infusion in combination with weekly oxaliplatin. Weekly administration of oxaliplatin seems more suitable with continuous 5FU infusion. Moreover, as the present results show, the oxaliplatin dose intensity achieved is similar to that observed in metastatic disease chemotherapy [15,17]. The dose inducing dose-limiting toxicity was oxaliplatin 80 mg/m^2 weekly combined with 5FU 225 mg/m^2/d. At that dose level (level 8), 1 patient presented with severe diarrhoea associated with dehydration that was abruptly fatal, despite intensive care. Another patient with an invading tumour of the posterior wall of the bladder presented with rectovesical fistula. At the next lower dose level (level 7), among the patients included secondarily, 2 presented with severe diarrhoea (grade 3). In consequence, the level 7 dose was considered the maximum-tolerated dose. The recommended dose is thus 60 mg/m^2 of oxaliplatin weekly associated with 225 mg/m^2/d of 5FU and radiotherapy delivering 45 Gy. This dose recommendation is also that from the phase I/II study by Aschele [21]. It should be noted that the limiting toxicities of the combination were mainly gastrointestinal and, above all, diarrhoea. Other regimens combining 5FU and oxaliplatin have been developed [23,24]. For those regimens also, diarrhoea is the main toxicity but the administration of 5FU by bolus injection induces a higher frequency of gastrointestinal disorders. Freyer's phase I study [25] is noteworthy for the lower gastrointestinal toxicity observed. Only 1 patient presented with grade 4 diarrhoea, at the first dose level. It should be noted that the patient was aged 83 years and that 2 of the patients who presented with severe diarrhoea at level 7 in our study were aged 74 and 76 years. The administration of combined treatments including chemotherapeutic combinations to the elderly thus requires caution. Gastrointestinal disorders are regularly encountered with 5FU combined or not

combined with leucovorin [26,27]. The oxaliplatin-5FU combination does not markedly increase the toxicities observed, compared to those observed with 5FU alone. A phase II study [28] was conducted using the regimen described by Freyer [25]. The grade 3/4 diarrhoea rate was 7.5%, comparable to the published data on 5FU alone. It is likely that the volume irradiated plays a decisive role in the emergence of toxicity, particularly gastrointestinal toxicity. A large irradiated volume of the small bowel is associated with increased toxicity. There was no specific quality assurance for the radiotherapy for this study but for future phase II/III studies, a quality assurance system should be include to avoid a lower quality of treatment delivery and protocol deviation. For example the quality assurance in radiotherapy for EORTC clinical trials showed a considerable variation in the individual case review in the 22921 EORTC study [29]. It is also possible that the use of oral derivatives of 5FU such as capecitabine affords an improved risk/benefit ratio through an increase in intratumourous thymidine phosphorylase levels [30]. However, this requires confirmation since, in the phase I study by Rödel [31], the recommended oxaliplatin dosage was 50 mg/m^2/week. Given the treatment regimen, Rödel's dosage was equivalent to a cumulative dose of 200 mg/m^2, markedly inferior to the 300 mg/m^2 used in the present study or the 360 mg/m^2 used in Aschele's study [21]. Moreover, the preliminary results of a phase II study reported by Honhon [32], who used a regimen similar to Rödel's, showed noteworthy gastrointestinal toxicity, since 20% of the patients presented with grade 3 or 4 diarrhoea. Continuous infusion of 5FU, while more cumbersome than oral derivative administration, probably enables a more precise adjustment of the chemotherapeutic doses.

In the present study, peripheral neuropathy was rare and never induced persisting functional disorders. Only 1 case presented with grade 3 neuropathy (Levi's specific scale) over a short period. All the signs resolved in less than 3 weeks. In contrast, 25 out of 43 patients (58%) presented with grade 1/2 neurological toxicity (Levi's scale). Aschele reported a similar percentage (64%) of neurotoxicity. These figures are probably overestimated since the specific scale was developed in the context of 3-weekly oxaliplatin administration. Grade 2 toxicity, equivalent to persistence of dysesthesia more than 2 weeks, is probably more frequently observed with weekly administration, but does not have the same alert significance. No patient presented with residual neuropathy even as early as the surgical period. This is related to the short duration of oxaliplatin administration, although the dose intensities of the last dose levels were greater than the doses used in the FOLFOX4 chemotherapeutic protocol, the reference standard for metastatic colonic cancer [17]. The neurotoxicity of oxaliplatin is mainly related to the cumulative dose received and may become severe beyond a cumulative dose of 750–1000 g/m^2. At the recommended dose level (60 mg/m^2 weekly), the cumulative oxaliplatin dose was 300 mg/m^2, markedly below the zone in which severe toxicity emerges. The value of administering the protocol pre-operatively resides in the fact that it enables the incipient signs of neurotoxicity to regress during the weeks of the surgical phase and should thus enable full doses of oxaliplatin to be administered post-operatively, if necessary. The administration of high doses of oxaliplatin over a short period, followed by a drug-free interval, is reported to improve neurological tolerability, while enabling subsequent reintroduction of the drug [33].

While determining the objective response rate or frequency of disease-free surgical specimens was not the objective of the present safety study, the results obtained in the population of patients presenting with advanced disease are very encouraging. Four patients out of 30 obtained complete histological remission and 4 only presented with microscopic residual disease. The major tumour regression rate was thus 26.6%. Out of 30 patients undergoing surgery, 19 (63.3%) were free from lymph node involvement. Efficacy similar to that observed in this study has also been reported in the phase I or II studies by Aschele [21], Sebag-Montefiore [24] and Gérard [28], with very different 5FU and oxaliplatin regimens. Achieving an objective response seems more related to the cumulative oxaliplatin dose than to the scheme of chemotherapy. However, caution is required in the analysis, since the present phase I study and the similar studies were mainly designed to determine the maximum-tolerated dose. However, given that the patient population presented with advanced disease, it is interesting to note such a high tumour regression rate, particularly the complete histological remission frequency and the frequency of residual microscopic disease. As the primary objective of this study was to determine the maximum-tolerated dose and patients presenting metastatic disease were included, the study population was heterogeneous and follow-up of patients with such different prognoses does not enable analysis of survival or recurrence mode. In conclusion, the use of weekly oxaliplatin associated with 5FU continuous infusion and pre-operative radiotherapy is feasible and the toxicity is relatively limited. The results of this study and the published data demonstrate a high complete remission rate. This type of combination could be compared with pre-operative radiotherapy in future phase III studies.

Conflict of interest statement

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