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Oxaliplatin combined with irinotecan and 5-fluorouracil/leucovorin (OCFL) in metastatic colorectal cancer: a phase I–II study

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Background: A phase I–II multicenter trial was conducted to define the maximal tolerated dose and describe the activity of an OCFL combination using oxaliplatin (OHP), irinotecan (CPT-11) and 5-fluorouracil (FU)/leucovorin (LV) in metastatic colorectal cancer (CRC).

Patients and methods: CRC patients not pretreated with palliative chemotherapy, with performance status ≤1 and adequate haematological, kidney and liver function, were eligible. Treatment consisted in weekly 24-h infusion 5-FU (2300 mg/m^2)/LV (30 mg) and alternating OHP (70–85 mg/m^2, days 1 and 15) and CPT-11 (80–140 mg/m^2, days 8 and 22) repeated every 5 weeks. OHP and CPT-11 were escalated in cohorts of three to six patients.

Results: Thirty patients received a median of five cycles. Dose-limiting toxicity occurred at dose level 3, and the recommended dose was OHP 70 mg/m^2, CPT-11 100 mg/m^2, LV 30 mg and 5-FU 2300 mg/m^2/24 h. Grade ≥3 toxicities were diarrhea 23%, neutropenia 20%, fatigue 7%, and neurologic 7%. Two febrile neutropenia episodes (one fatal) were recorded. Among 28 patients with measurable disease (90%), we observed two complete and 20 partial responses; overall RR was 78% (95% CI, 59% to 92%). Median time to progression and overall survival were 9.5 and 25.4 months, respectively. Seven patients underwent liver metastases resection.

Conclusion: OCFL is an overall well tolerated regimen with very high efficacy, which makes it most suitable for tumour control before surgery of metastatic disease.

Key words: colorectal cancer, irinotecan, oxaliplatin, triplet regimen

Introduction

Colorectal cancer (CRC) is the second cause of cancer death in Western countries. About 50% of all patients with CRC develop distant metastatic disease and will be candidates for palliative chemotherapy. Up to the mid-1990s, systemic therapy of CRC was essentially based on 5-fluorouracil (FU) with response rates of 15%–25% and overall median survival times rarely exceeding 10–13 months in metastatic disease [1, 2]. The development of CPT-11, a topoisomerase I inhibitor, and of oxaliplatin (OHP), a new platin derivative, has dramatically changed the prospect of systemic therapy in this disease. The combination of 5-FU with either CPT-11 or oxaliplatin has allowed an increase in response rates to over 50% in first-line therapy, and 20% when used as second-line chemotherapy [3–9]. In addition, the consecutive prescription of CPT-11 and OHP-containing regimens to metastatic CRC patients has also increased life expectancy of patients with metastatic colorectal cancer to over 20 months from only 9–12 months previously [10].

In patients with liver metastases only, these high response rates have allowed for resection of initially inoperable disease [11]. In order to increase the response rate further and to consider subsequent curative intent resection of liver metastases, we aimed to develop a five-drug combination regimen using all known active agents concomitantly and alternately. In a disease-specific phase I/II trial design we administered weekly infusional 5-FU/leucovorin (LV) in combination with either CPT-11 or oxaliplatin.

Patients and methods

Patient selection

Patients with measurable or evaluable (e.g. increased carcinoembryonic antigen) disease from histologically proven colorectal adenocarcinoma

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were eligible. No previous chemotherapy for metastatic disease was allowed. Patients who had received prior adjuvant 5-FU/ LV chemotherapy after resection of the primary tumour were eligible, provided the adjuvant chemotherapy was completed more than 6 months before relapse. Other inclusion criteria were a World Health Organisation (WHO) performance status of 0–1, age between 18 and 70 years, adequate blood counts (leucocytes $\geq 4 \times 10^9$/l and platelets $\leq 100 \times 10^9$/l), adequate renal and liver functions creatinin 1.25 upper normal limit (UNL), bilirubin $1.25 \times$ UNL, AST and ALT $\leq 3 \times$ UNL (in cases of liver metastasis bilirubin 1.5 UNL, AST and ALT $\leq 5 \times$ UNL). Patients suffering from chronic grade ≥ 2 diarrhoea, other serious illness and past or concurrent history of cancer, except non-melanoma skin cancer, and *in situ* cervical cancer were excluded.

Study design and treatment scheme

The treatment consisted of weekly administration of a 24-h infusion of 5-FU (2300 mg/m^2), LV 30 mg i.v. on days 1, 8, 15 and 22, escalating doses of OHP (70–85 mg/m^2) on day 1 and 15, and CPT (80–100 mg/m^2) on days 8 and 22, as shown in Figure 1. Treatment cycles were repeated every 5 weeks. Dose levels and escalation scheme are presented in Table 1. A minimum of three patients were to be treated at the same dose level. If no dose limiting toxicity (DLT)—defined as grade 4 haematological toxicity with fever (single oral temperature >38.5 °C, or three elevations to 38 °C during a 24-h period) and/or grade 3 toxicity of any other kind apart from alopecia—occurred during the first cycle of treatment, the next three patients were treated at the next higher dose level. If one DLT occurred in cycle 1, three additional patients had to be treated at the same dose level. If two or more DLTs occurred at a given dose level, this would define the maximally tolerated dose (MTD) and the dose just below would be considered the recommended dose for future phase II trials.

Another six patients were to be treated at the recommended dose, in order to ensure the safety of the regimen.

Administration of treatment

Patients were treated through an implantable central venous device in an outpatient setting. OHP was given as a 2-h i.v. infusion on days 1 and 15, and CPT-11 as a 30-min i.v. infusion on days 8 and 22, always followed by 5-FU as a continuous infusion over 24 h. Patients received standard antiemetic premedication, including 5-hydroxytryptamine 3 receptor antagonists and steroids. In order to prevent a cholinergic syndrome, on the days of CPT-11 administration, patients received atropin 0.25 mg s.c. Patients were instructed to manage late diarrhoea by loperamide and nausea and vomiting with metoclopramide. No granulocyte colony stimulating factors were to be used except for febrile neutropenia.

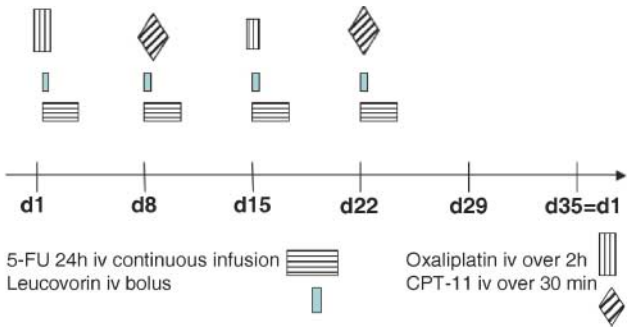

Figure 1. Treatment scheme

Table 1. Dose escalation scheme

Level	OXA (mg/m^2)	CPT-11 (mg/m^2)	LCV (mg)	5-FU (g/m^2)
1	70	80	30	2.3
2	70	100	30	2.3
3	85	100	30	2.3
4	85	120	30	2.3

Toxicity assessment, dose reductions and evaluation of response

Physical examination and blood cell counts were performed weekly and biochemistry at the beginning of each cycle. Adverse reactions were graded according to the WHO common toxicity criteria with specific scales to assess plantar–palmar syndrome and OHP-related neuropathy. In case of $\geq$grade 3 neutropenia or thrombocytopenia or for any grade 3–4 non-haematological toxicity, doses of all cytotoxic agents were reduced by 25% for the subsequent courses. OHP was to be discontinued if peripheral neuropathy grade 3 or other severe neurotoxicity were observed. A maximum of a 1-week delay (14 days between two treatments) was allowed for severe toxicity. Responses were assessed according to the WHO criteria at the end of every two cycles of treatment. The main goal of the trial was to determine the MTD of the regimen under investigation. Statistical analysis was descriptive and survival was calculated according to the Kaplan–Meier method.

The trial was approved by the ethics review boards of all participating institutions. All patients gave informed written consent.

Results

Patient characteristics

From December 1999 to June 2001, 31 patients were enrolled in the study. One patient presented cardiac arrhythmia just after inclusion and never started study treatment. He was therefore excluded from the analysis. All the remaining 30 patients received at least two cycles of treatment and were fully assessable. The baseline patients' characteristics are summarised in Table 2. There were 24 males and six females;

Table 2. Characteristics of patients

No. of patients	30
Age, years [median (range)]	58 (31–70)
Sex (male/female)	24/6
Performance status (0/1)	23/7
Bidimensionally measurable disease	28/30
Primary tumour:	
Colon	8
Sigmoid-rectum	5
Rectum	17
Metastasis sites:	
Liver	15
Lung	6
Lymph nodes	2
Liver and lung	4
Lymph nodes, liver and lung	1
Previous surgery of primary tumor	15/30
Prior adjuvant therapy by 5FU/LCV	6/30

the median age was 58 years. Fifteen patients had had their primary tumour resected and six patients had received prior 5-FU/LV adjuvant chemotherapy. Twenty-eight patients had bidimensionally measurable disease and two patients had evaluable disease only.

Dose escalation findings

The number of patients entered in each dose level and the type of DLTs encountered are summarised in Table 3.

Twelve patients were enrolled at dose level 1 (OHP 70 mg/m^2 and CPT-11 80 mg/m^2). Among the first six patients enrolled, we observed the occurrence of one episode of febrile neutropenia and grade 3 diarrhoea in the same patient during the first cycle of treatment (one DLT), necessitating an additional three patients to be treated at this dose level. Subsequently, another patient developed grade 4 neutropenia and an ileus due to peritoneal carcinomatosis during cycle 2. It was therefore decided to confirm the safety in another six patients before allowing dose escalation. No further DLT was observed.

At dose level 2 (OHP 70 mg/m^2 and CPT-11 100 mg/m^2), six patients were initially entered. One patient developed non-haematological DLT consisting of grade 3 nausea/vomiting and grade 3 fatigue. After determining this dose level as the recommended dose, an additional five patients were treated without severe toxicity.

At dose level 3 (OHP 85 mg and CPT-11 100 mg/m^2) two out of six patients developed grade 3 diarrhoea. Thus, this dose level was considered to be the MTD and dose level 2 the recommended phase II dose.

Because of delayed reporting of the second DLT in level 3, one patient started therapy at dose level 4 (OHP 85 mg/m^2 and CPT-11 120 mg/m^2). No significant toxicity was observed during four cycles at this dose level before undergoing curative resection of liver metastasis.

Toxicity assessment

The toxicity analysis is based on 30 patients and 135 cycles of treatment. Overall this regimen was well tolerated and a median of 4 cycles/patient was administered (range 2–9). Treatment delays were required in 12% of cycles (16 patients). Twelve patients completed 6 or more cycles of treatment, and five patients with responding tumours discontinued therapy early in order to undergo surgery and resection of their liver metastases. Reasons for treatment discontinuation were tumour progression in five patients (17%), toxicity also in five patients [grade 3 neurotoxicity after 4 cycles (one patient), grade 3 diarrhoea after 2 cycles (one patient), ileus or pulmonary embolism after cycle 2 (two patients), fatal fungal septicaemia at the end of the second cycle (one patient)], and personal treatment unrelated reasons in three patients.

Details on the treatment-related worst toxicity are reported in Tables 4 and 5. Grade 3/4 toxicity was infrequent, grade 3/4 diarrhoea occurred in seven patients (23%) and 8% of all treatment cycles. Grade 3/4 neutropenia was observed in 20% of patients and 6% of cycles, but only two febrile episodes, although one fatal fungal infection.

Treatment efficacy

Twenty-eight patients had bidimensionnally measurable disease (Table 6). Two complete (CR) and 20 partial responses (PR) were recorded, for a response rate of 78% (22/28 patients, 95% CI 59% to 92%). Five patients had stable disease during at least 4 cycles of treatment and one patient progressed after 2 cycles. The median time to progression was 9.5 months, and the median overall survival was 25.4 months

Table 3. Dose limiting toxicity according to dose level

Dose levels	No. of patients	DLTs	Cycle number (median)
1	12	Diarrhoea + febrile neutropenia grade 3 (×1)	5
2	6	Nausea-vomiting grade 3 + fatigue grade 3 (×1)	6
3	6	Diarrhoea grade 3 (×2)	4
4	1	None	NA

Table 4. Worst toxicity in percentage of patients (patient number = 30)

Toxicity grade	1	2	3	4
Nausea/vomiting (%)	43	43	3	0
Diarrhoea (%)	30	17	20	3
Mucositis (%)	13	3	0	0
Fatigue (%)	57	27	7	0
Neurological according to OHP scale (%)	60	7	7	NA
Plantar–palmar syndrome (%)	3	0	0	NA
Other neurological/dizziness (%)	13	0	0	0
Alopecia (%)	13	0	0	0
Neutropenia (%)	23	20	17	3
Febrile neutropenia (%)	NA	NA	3	3
Thrombopenia (%)	53	7	0	0

Table 5. Toxicity in percentage of cycles (number of cycles = 135)

Toxicity grade	1	2	3	4
Nausea/vomiting (%)	32	13	1	0
Diarrhea (%)	26	7	7	1
Mucositis (%)	4	1	0	0
Fatigue (%)	36	11	1	0
Neurological according to OHP scale (%)	39	4	1	NA
Plantar–palmar syndrome (%)	1	0	0	NA
Other neurological/dizziness (%)	4	0	0	0
Neutropenia (%)	18	7	5	1
Febrile neutropenia (%)	NA	NA	1	1
Thrombopenia (%)	41	1	0	0

Table 6. Response rate

Response	No. of patients	%
Measurable disease	28	
CR	2	7
PR	20	71
SD	5	18
PD	1	4
Not assessable	2	–

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

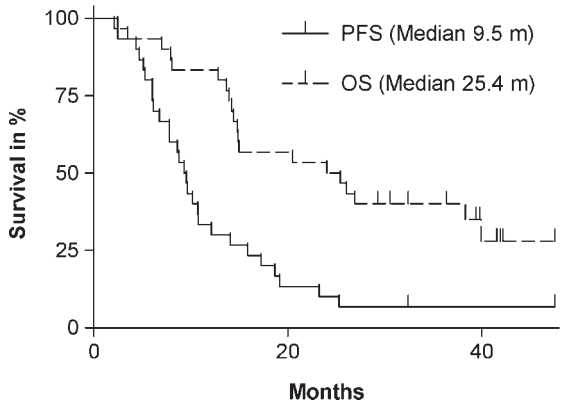

Figure 2. Progression free and overal survivals

(Figure 2). At the time of the present analysis, 19 patients have died.

Discussion

This study shows that oxaliplatin, irinotecan and 5-FU/LV (OCFL) can be safely combined in a single regimen. Alternating oxaliplatin and irinotecan within the same treatment regimen allows the use of non-cross-resistant chemotherapy agents while avoiding overlapping toxicity and potential, at the time of study conception, unknown pharmacological interactions [12]. Compared with other triplet regimens, where all the drugs are administered on the same day, alternating OCFL is less haematoxic. Grade 3/4 neutropenia in 20% patients with 7% febrile neutropenia, as reported in our study, compares favourably with the 38% and 86% reported by others [12, 13] with 14% febrile neutropenia. Diarrhoea was our main non-haematological toxicity with 23% of the patients experiencing grade 3/4 diarrhoea during the course of their treatment. Five of these patients resumed therapy after a 25% dose reduction of the 5-FU dose and no further severe diarrhoea occurred. Recent publications suggest the use of 5-FU at a slightly lower dose, i.e. 2 g/m^2/24 h weekly in association with LV and irinotecan [14, 15]. Similarly, our experience with this regimen after closure of this trial suggests a significant reduction in severe diarrhoea with the lower dose of 5-FU. Recently, Cals et al. [16] reported on their experience of escalating doses of a similar regimen of weekly 5-FU and alternating CPT11 and oxaliplatin. Their regimen did not contain LV and the recommended phase II doses are slightly higher than in our OCFL regimen.

Our trial only included patients who had not received prior chemotherapy for metastatic disease. This allowed us to assess the activity of this regimen. The observed response rate of 78% is amongst the highest response rates ever reported for metastatic colorectal cancer [12, 13, 17, 18] and almost identical to the reported 71% by Falcone et al. [12] with the concomitant biweekly association of 5-FU/LV, CPT11 and oxaliplatin. Similarly, the time to progression and overall survival are also comparable between the two studies (9.5 and 25.4 months, respectively, in our study compared with 10.5 and 26.5 months).

High response rates and a short time to response make these triplet regimens especially suited for patients planning surgical resection of metastases, in particular liver metastases initially considered unresectable. In our trial, seven patients (23%) with a diagnosis of unresectable liver metastases underwent curative-intent resection of the residual disease after an initial response to chemotherapy. Similarly, in the trial reported by Falcone, 25% of patients underwent subsequent surgery.

The occurrence of severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy has recently been reported in patients with metastatic colorectal cancer [19]. Liver surgery is more difficult and prone to complications in this situation. The dose of oxaliplatin per cycle (140 mg/m^2) in our OCFL regimen is lower than in other triplet regimens and thus less likely to induce such liver lesions.

In conclusion, OCFL is an efficient and, overall, usually well-tolerated outpatient regimen. It is associated with high response rates and most suitable for tumour control before surgical treatment of metastatic disease.

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