Phase I study of the combination of oxaliplatin, irinotecan and continuous infusion 5-fluorouracil in digestive tumors

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Oxaliplatin (L-OHP), irinotecan (CPT-11) and 5-fluorouracil (5-FU) have shown their efficacy in metastatic colorectal cancer. The synergism of these drugs has been demonstrated *in vivo* and *in vitro*. The aim of this study was to determine the recommended dose of the triple combination of L-OHP, CPT-11 and CI 5-FU for a further phase II study. Eighteen patients received the study treatment in four dose levels. The male:female ratio was 15:3 and the median age was 51.6 years (range 30–71). The type of tumor was colon in eight patients, rectum in four and other locations in six patients. The treatment was repeated every 2 weeks, at the fixed dose of L-OHP, 85 mg/m^2, and escalated doses of CPT-11 and 48-h infusion 5-FU of 100/2000, 100/2250, 125/2250 and 150/2250 mg/m^2. Only one previous treatment for the advanced disease was permitted. Patients received a median of 8 cycles (range 1–26) and a total of 152 cycles were administered. Dose intensity administered at dose level L-OHP 85 mg/m^2, CPT-11 150 mg/m^2 and 5-FU 2250 mg/m^2 was 95, 92 and 95% for L-OHP, CPT-11 and 5-FU, respectively. One patient in level 2 and one patient in level 4 presented dose-limiting toxicity that was not confirmed in the three required additional patients by level. The anti-tumor activity was assessed in nine patients: seven partial responses, one stable disease and one progressive disease. The maximum-tolerated dose was not reached, and thus the recommended dose for this combination schedule is L-OHP, 85 mg/m^2, CPT-11, 150 mg/m^2 and 5-FU, 2250 mg/m^2 48-h continuous infusion, the same doses that were recommended for the drugs when administered in combination therapy of L-OHP + 5-FU or CPT-11 + 5-FU. A phase II study in first-line treatment of patients with metastatic colorectal cancer with this dose regimen is ongoing. *Anti-Cancer Drugs* 15:469–471

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Introduction

Two phase III trials have compared the combination of oxaliplatin (L-OHP) with 5-fluorouracil (5-FU)/leucovorin (LV) in first-line treatment [1,2]. The combination regimen significantly improved the overall response rate (ORR) and median time of progression (TTP), achieving 50% ORR and 9 months TTP.

The value of irinotecan (CPT-11) has been established in two randomized phase III trials [3,4]. The addition of CPT-11 to 5-FU/LV also significantly improved the ORR to 50%, TTP to 7 months and median survival to 17 months.

Despite the improvement of the treatment, a number of patients are non-responders to a double combination and also some of them cannot receive second-line treatment after progression to first-line chemotherapy. Triplet combination could increase the ORR, adding some of these patients to a responders group and also increasing the number of patients receiving all of the treatment possibilities. This strategy would be of great interest for patients with potentially resectable liver metastases. The combination of three drugs was assayed in phase II trials using folínic acid-modulated 5-FU schedules [5,6]. These trials demonstrated high anti-tumor activity for the triplet combination, achieving 58–71% ORR. The toxicity was high, although manageable—mainly neutropenia grade 3–4 in 45–55% of patients with 6–14% febrile neutropenia.

On the basis of these considerations, in this phase I trial we attempted to develop a new, less-toxic triplet combination by using a non-modulated a 5-FU biweekly treatment schedule.

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Patients and methods

Patients with evaluable non-resectable metastatic disease were eligible for inclusion in this phase I study. Written informed consent was obtained for all patients

Eligibility

The main eligibility criteria was patients with histologically proved evaluable metastatic disease, aged 18–75 years, WHO performance status score ≤ 2, creatinine clearance < 50 ml/min, total bilirrubin or AST and ALT < 2.5 times the upper limit of the normal, absolute neutrophil count $< 1.5 \times 10^9$/l or platelet count $> 100\,000 \times 10^9$/l. Previous chemotherapy for advanced disease (first-line treatment) was allowed. Intestinal occlusion, inflammatory enteropathy history, peripheral neuropathy or symptomatic brain/leptomeningeal metastasis were exclusion criteria.

Drug administration and toxicity assessment

The patients received the study treatment in four dose levels: level 1 (L-OHP 85 mg/m^2, CPT-11 100 mg/m^2, 5-FU 2000 mg/m^2), level 2 (L-OHP 85 mg/m^2, CPT-11 100 mg/m^2, 5-FU 2250 mg/m^2), level 3 (L-OHP 85 mg/m^2, CPT-11 125 mg/m^2, 5-FU 2250 mg/m^2) and level 4 (L-OHP 85 mg/m^2, CPT-11 150 mg/m^2, 5-FU 2250 mg/m^2). 5-FU doses were based on our experience using the combination of two drugs where we found that either with L-OHP or CPT-11, high-dose 5-FU had to be reduced due to unacceptable toxicity [7,8]. Drugs were delivered as follows: day 1, 2-h infusion of L-OHP followed by 30-min infusion of CPT-11 and 48-h infusion of 5-FU. All patients received prophylactic anti-emetic therapy with 5-HT$_3$ inhibitors plus dexamethasone. Subcutaneous atropine (0.25 mg) was allowed to prevent the acute cholinergic syndrome. If dose-limiting toxicity (DLT) was not observed, the increase to a superior dose level was allowed. The definition of DLT was as follows: grade 4 neutropenia lasting at least 5 days or grade 4 thrombocytopenia lasting at least 5 days or febrile neutropenia or any grade 3–4 non-hematologic toxicity except anemia and alopecia. The DLT was evaluated in the first 3 cycles of treatment. The maximum-tolerated dose (MTD) was defined as the dose at which two patients experienced DLT. The cycles were repeated every 2 weeks until disease progression or unacceptable toxicity occurred. Toxicities were graded according to the Common Toxicity Criteria version 2.0 of the National Cancer Institute (NCI-CTC).

Dose intensity

The dose intensity of L-OHP, CPT-11 and 5-FU (mean, mg/m^2/week) was calculated over the entire treatment period.

Statistical methods

All data was analyzed by SAS software, version 8.2 for Windows 95.

Table 1 Patient characteristics

Total no.	18
Median age [years (range)]	51 (30–71)
Gender (M/F)	15/3
ECOG	
0	5
1	10
2	3
Median CEA [ng/ml (range)]	78 (0.3–283)
Previous therapy [*n* (%)]	
no	13 (72)
yes	5 (28)
Tumor site	
colon	8
rectum	4
other	6
Site of metastasis [*n* (%)]	
liver	12 (75)
lung	5 (31)
nodes	7 (43)
abdomen	3 (19)
other (pelvis, peritoneum)	9 (50)

Results

Patient characteristics

Eighteen consecutive eligible patients were included in the study. The male:female ratio was 15:3 and the median age was 51.6 years (range 30–71). Five patients (27.8%) had a WHO performance status of 0, 10 (55.5%) had a WHO performance status of 1 and only three patients had a WHO performance status of 2. The type of tumor was colon in eight patients, rectum in four and other locations in six patients. Table 1 summarizes patient characteristics.

Dose intensity

The patients enrolled onto the study received a median of 8 cycles (range 1–26) and a total of 152 treatment cycles were provided; 37 at dose level 1, 52 at dose level 2, 23 at dose level 3 and 40 at dose level 4. Dose intensity administered at dose level L-OHP 85 mg/m^2, CPT-11 150 mg/m^2 and 5-FU 2250 mg/m^2 was 95, 92 and 95% for L-OHP, CPT-11 and 5-FU, respectively.

Toxicity

The DLT by level evaluated in the first 3 cycles is shown in Table 2. One patient at level 2 had grade 4 vomiting and grade 3 diarrhea. DLT was not observed in the required three additional patients. Another patient at level 4 had diarrhea grade 3 and no DLT was observed in the additional patients. The MTD was not achieved.

The overall toxicity during all cycles was as follows: three patients showed grade 3–4 anemia and four patients suffered grade 3–4 leukopenia at dose level 2. Grade 3–4 neutropenia was experienced by eight patients, six at dose level 2 and two at dose level 3. Two patients showed grade 3–4 thrombocytopenia at dose level 2. Three patients suffered from grade 3–4 AST/ALT at dose level 3. Grade 3–4 diarrhea was experienced by four

Table 2 DLT by level

Dose level	L-OHP	CPT-11	5-FU	Patients	DLT
1	85	100	2000	3	–
2	85	100	2250	3 + 3	1 patient: vomiting G4, diarrhea G3
3	85	125	2250	3	–
4	85	150	2250	3 + 3	1 patient: diarrhea G3

Table 3 Number of patient with grade 3–4 toxicity during all cycles

Level	Diarrhea	Neutropenia	Thrombopenia	Neurotoxicity
1	0	0	0	0
2	2	6	2	2
3	0	2	0	0
4	2	0	0	0

patients, two at dose level 2 and two at dose level 4. One patient presented grade 3–4 fever without infection and another showed grade 3–4 infection at dose level 2. Two patients presented peripheral neuropathy grade 3 at dose level 2. Finally, grade 3–4 anorexia and asthenia was present in one patient at dose level 2 and one patient at dose level 3, respectively (Table 3).

Anti-tumor activity

The tumor response was assessed in nine patients. There were seven partial responses with a median duration of 6.4 months, one stable disease and one progressive disease.

Discussion

The emergence of new active drugs in colorectal cancer has given very satisfactory results in metastatic and locally advanced disease treatment, achieving response rates up to 50% [1–3]. One of the most important consequences has been the possibility of resection of initially unresectable liver metastases after preoperative chemotherapy treatment. The results of this treatment strategy show a resection rate of 100, 59 and 13% in three French trials [9–11]. However, it is necessary to point out that in the biggest series, with 701 patients, resection was limited to only 13% of cases [11]. Therefore, evaluation of combinations that can clearly improve this resection rate is very interesting. Two trials assaying the triplet combination have been published. Souglakos *et al.* [5] included 31 patients to receive CPT-11 150 mg/m^2 day 1 plus low-dose L-OHP 65 mg/m^2 day 2 plus 5-FU/LV (de Gramont schedule) days 2 and 3 every 2 weeks. The ORR was 58% and the TTP was 13 months. No data concerning liver metastasis resection was shown. The grade 3–4 toxicity was high, mainly 45% neutropenia and 35% diarrhea. The second study from Falcone *et al.* [6] treated 42 patients with CPT-11 175 mg/m^2 plus L-OHP 100 mg/m^2 and 5-FU 3800 mg/m^2 with LV 200 mg/m^2 day 1 every 2 weeks. They achieved 71% ORR with 10.4 months TTP, but the toxicity was also high, showing 55% grade 4 neutropenia with 14% febrile neutropenia. Grade 3–4 diarrhea was 21%. Surgical radical resection of residual disease was performed in 26% of patients. Results of the present phase I study show a broad safety range for the combination. The toxicity is low with only 11% grade 3–4 neutropenia and diarrhea. The combination of these three drugs at the same doses as when they are used combining two of them, but without folinic acid biochemical modulation, permits safe treatment with good dose intensity. A phase II study to check if a triplet combination can clearly improve the resection rate for potentially respectable liver metastases has been started with the recommended dose of L-OHP 85 mg/m^2, CPT-11 150 mg/m^2 and 48-h continuous infusion CI of 5-FU 2250 mg/m^2.

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