

An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors

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Background: The aim of this study was to determine the maximum-tolerated dose (MTD) and the recommended dose of irinotecan and oxaliplatin with a fixed 5-fluorouracil (5-FU)/leucovorin (LV) regimen in patients with metastatic solid tumors.

Patients and methods: The trial was designed to evaluate escalating doses of oxaliplatin and irinotecan, starting at 60 mg/m² and 90 mg/m², respectively, given at day 1 with the full-dose LV5FU2 regimen, given on days 1 and 2 as follows: folinic acid 200 mg/m² followed by 5-FU 400 mg/m² bolus and 600 mg/m² 22 h continuous infusion, every 2 weeks. The second cohort of patients was treated at the recommended dose for oxaliplatin and irinotecan with the simplified LV5FU regimen: on day 1, a 2-h infusion of folinic acid (400 mg/m²), followed by a 10-min intravenous bolus of 5-FU (400 mg/m²), followed by a continuous infusion of 5-FU (2400 mg/m²) over 46 h.

Results: Thirty-four patients were treated at the following dose levels (oxaliplatin/irinotecan mg/m²): 60/90, 60/120, 85/120, 85/150, 85/180, 85/200 and 85/220 and seven patients were treated at the recommended dose with the simplified LV5FU scheme. The MTD was reached at dose level 85/220 mg/m² but the recommended dose chosen for the second step was 85/180 mg/m² to keep a better compliance with the biweekly schedule. Main grade 3/4 toxicities per patient included the following: neutropenia in 78% (febrile episodes in 12%), diarrhea in 27%, nausea/vomiting in 24% and peripheral neuropathy in 37% (Lévi's scale). Antitumor activity was observed at almost all dose levels. Most objective responses were observed in digestive malignancies, since 10 out of 11 were obtained in five colorectal cancers, two pancreatic cancers, two cholangiocarcinoma and one gastric cancer.

Conclusion: The recommended dose for the triple association is 85/180 mg/m² of oxaliplatin and irinotecan, respectively, with LV5FU2 or simplified LV5FU. The antitumor activity in gastrointestinal malignancies should be evaluated in phase II studies in different tumor types.

Key words: colorectal cancer, irinotecan, oxaliplatin, phase I trial, triple combination

Introduction

For several decades, the standard treatment for metastatic colorectal cancer (MCRC) has been 5-fluorouracil (5-FU)-based chemotherapy. Optimization of 5-FU-based therapies with different schedules and biomodulation, especially with folinic acid [leucovorin (LV)], has led to improvement in terms of both efficacy and toxicity profile [1]. Among these chemotherapy schemes, the 'LV5FU2' regimen, consisting of high-dose LV administered bimonthly in combination with high-dose 5-FU given as a single bolus together with a continuous infusion, was associated with an improved response rate and progression-free

survival compared with a low-dose LV/5-FU monthly regimen [2, 3].

In recent years, antitumor activity of two novel antineoplastic agents, irinotecan and oxaliplatin, has been shown in several solid tumors and especially in gastrointestinal cell lines, including colorectal cancer. Now, the emergence of these two new drugs allows the consideration of new therapeutic options in the clinical treatment of MCRC.

Irinotecan (Campto[®]) is a semi-synthetic derivative of camptothecin, with evidence of a cytotoxic action via a potent and specific inhibition of the eukaryotic enzyme DNA topoisomerase I [4]. The cytotoxic effect of this agent and of its main active metabolite, SN-38, is specific to the S-phase of the cell cycle. Clinical efficacy of irinotecan monotherapy has been proven in published phase II and III trials, both in chemotherapy-naïve patients and in patients in whom prior 5-FU-based chemotherapy

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failed [5–11]. The different mechanisms of action of both irinotecan and 5-FU and their non-overlapping toxicities, except for neutropenia, led to the evaluation of the combination of these two drugs in MCRC. The biweekly irinotecan/LV5FU2 combination was first evaluated in a phase I trial [12]. The association has been shown to be feasible and safe with an encouraging response rate, reaching 22% in pretreated MCRC patients. The recommended dose was 180 mg/m² for irinotecan with the LV5FU2 regimen, although the maximal tolerated dose (MTD) was reached at the 300 mg/m² dose level for irinotecan [12]. More recently, large European and American phase III trials confirmed the clinical benefit provided by the association of irinotecan with 5-FU and folinic acid. This included higher response rate (confirmed objective responses of 39–41%), longer time to progression and increased survival compared with the 5-FU and folinic acid regimen, widely used in patients receiving first-line therapy for MCRC [13, 14]. These trials led to registration of this combination in this indication in both Europe and the USA.

Oxaliplatin, a diaminocyclohexane platinum compound, acts, like cisplatin, through the formation of DNA adducts, but is bulkier and more hydrophobic than cisplatin adducts with activity markedly different from other platinum complexes [15]. Oxaliplatin, especially, has shown consistent clinical antitumoral activity in MCRC treatment. Efficacy of monotherapy was demonstrated in phase II trials, in both 5-FU previously untreated and treated patients, with an overall response rate ranging between 10 and 24% [16–18]. Evidence of oxaliplatin and 5-FU synergism *in vitro* [19] led to numerous clinical trials to assess oxaliplatin in combination with 5-FU/folinic acid. Those trials reported increased response rates reaching 18–51% [20–22], with improvement in time-to-progression but no statistical benefit in overall survival compared with 5-FU/folinic acid chemotherapy alone [22]. The combination has been approved in Europe for first-line treatment of MCRC. In this latter combination, oxaliplatin is administered at a dose of 85 mg/m² every 2 weeks, in combination with 5-FU/folinic acid, according to the LV5FU2 regimen described by De Gramont [21, 22].

In vitro synergism of oxaliplatin and SN-38 was also demonstrated when administered in combination in the human colon cancer cell line HT29 [23]. More cytotoxicity was consistently found *in vitro* when oxaliplatin was given before or concurrently with the camptothecin derivative [23]. Results obtained in a number of clinical trials with the combination of irinotecan and oxaliplatin showed promising efficacy in gastrointestinal malignancies, especially in MCRCs resistant to 5-FU-based therapies (objective responses of 23–64%) [24–28]. The toxicity profile of this combination remained manageable. The recommended dose was 175 mg/m² for irinotecan and 85 mg/m² for oxaliplatin, given every 2 weeks, for patients with performance status (PS) zero or one, and 150/85 for patients with a PS of two [26].

Overall, combining irinotecan or oxaliplatin with 5-FU/LV or the two new drugs together, has provided, in the last few years, new therapeutic approaches for treatment of MCRC patients with proven efficacy.

The different mechanisms of action of 5-FU, irinotecan and oxaliplatin and their relatively non-overlapping toxicities sup-

ported a rationale for evaluating the feasibility of combining the three drugs together.

In the present study, we assessed for the first time the triple combination, given every 2 weeks, with a fixed LV5FU2 regimen and a planned dose escalation for the new drugs, irinotecan and oxaliplatin.

Patients and methods

Patients

Patients were eligible if they had histologically proven non-resectable metastatic solid tumors, or advanced or metastatic disease refractory to conventional therapy and for which no effective therapy was available. Eligibility criteria also included: age between 18 and 75 years; a WHO PS of two or less; adequate hematological, hepatic and renal functions defined by hemoglobin ≥ 10 g/dl, absolute neutrophil count $\geq 2 \times 10^9$ /l, platelets count $\geq 100 \times 10^9$ /l, total bilirubin $\leq 1.25 \times$ the upper normal limit (UNL) of the institution, serum transaminases (aspartate aminotransferase, alanine aminotransferase) and alkaline phosphatase $\leq 3 \times$ UNL (or in cases of liver metastasis, bilirubin $\leq 1.5 \times$ UNL and serum transaminases $\leq 5 \times$ UNL) and serum creatinine level ≤ 125 μ mol/l. Patients must have discontinued previous antitumor treatment for at least 4 weeks (6 weeks in the case of aplasing chemotherapy such as nitrosourea, mitomycin C and carboplatin). Exclusion criteria included: prior chemotherapy regimens with irinotecan or oxaliplatin; symptomatic brain metastasis or carcinomatous leptomeningitis; prior abdomino-pelvic radiation therapy; prior history of severe toxicity with 5-FU; unresolved bowel obstruction or partial bowel obstruction; current uncontrolled infection or serious illness or medical condition (including contraindication to 5-FU); prior history of peripheral neuropathy; concomitant treatment with another anticancer therapy or with another experimental drug; pregnancy or patients with reproductive potential without contraception. All patients had signed a written informed consent before study entry.

Treatment administration

Treatment was given every 2 weeks. Oxaliplatin was diluted in 5% dextrose and administered as a 120-min intravenous (i.v.) infusion at day 1. Irinotecan, diluted in 5% dextrose, was administered as a 90-min i.v. infusion, 1 h after the end of the oxaliplatin infusion. 5-FU and folinic acid were used in commercially available formulations. The LV5FU2 regimen was administered at a fixed dose after the end of irinotecan infusion as follows: on day 1 and day 2 of the 14-day cycle, folinic acid (400 mg/m², DL form) was administered in a 2-h i.v. infusion, followed by 5-FU (400 mg/m²) in a 10-min i.v. bolus, followed by 5-FU (600 mg/m²) in a continuous 22-h infusion.

When the recommended dose had been determined, published data about the 'simplified LV5FU regimen' were available [29–31] and led us to treat a second cohort of patients treated at the recommended dose for oxaliplatin and irinotecan in conjunction with this simplified LV5FU regimen administered as follows: on day 1, a 2-h i.v. infusion of folinic acid (400 mg/m², DL form), followed by a 10-min i.v. bolus of 5-FU (400 mg/m²), followed by a continuous infusion of 5-FU (2400 mg/m²) over 46 h.

For all patients, systematic prophylactic treatment was not recommended at the first cycle except for anti-emetic prophylaxis, which was allowed and left to the investigator's discretion. However, in the case of severe cholinergic syndrome during one cycle, preventive treatment with atropine (0.25 mg subcutaneously) was to be given at subsequent cycles. If patients experienced delayed diarrhea, early prescription of high-dose loperamide was done according to specific guidelines for symptomatic treatment and, if diarrhea persisted >48 h, prophylactic oral fluoroquinolones were given. In the case of

severe neutropenia, defined as grade 4 for ≥ 7 days and/or no recovery to grade ≤ 1 at day 15, further cycles were administered with G-CSF (granulocyte colony-stimulating factor) at a dose of 263 $\mu\text{g/day}$ from day 7 to day 12.

Treatment was continued for up to 12 cycles unless stopped before because of disease progression, unacceptable toxicity or patient's refusal. After the end of treatment, patients were followed up every 3 months until death or cut-off date.

Dose-escalation schedule

Eight dose levels of oxaliplatin/irinotecan were planned for dose escalation: 60/90, 60/120, 85/120, 85/150, 85/180, 85/200, 85/220 and 85/240 mg/m^2 with a fixed dose of the LV5FU2 regimen. In the absence of any dose-limiting toxicity (DLT) observed at the first cycle, a minimum of three patients had to be treated at each dose level. Before escalating to the next dose level, patients at the dose level below had to be observed for acute toxicity during a minimum of 2 weeks (one cycle). When at least one DLT was observed at a dose level, the recommended dose level for all subsequent patients was evaluated by the continual reassessment method (CRM) [32], which provides a method for estimating the dose level nearest to the MTD. The MTD was defined as the dose level for which at least one DLT occurred for 50% of patients during the first cycle.

When the MTD was reached, a minimum of six patients had to be treated at the recommended dose level and a second cohort of patients was also treated at the recommended dose for oxaliplatin and irinotecan with the simplified LV5FU regimen.

DLT was defined as follows: grade 4 neutropenia (absolute neutrophil count $< 0.5 \times 10^9/\text{l}$) for ≥ 7 days; febrile neutropenia or neutropenia grade 3/4 concomitant with infection, any grade 3/4 diarrhea or grade ≥ 2 concomitant with grade 4 neutropenia; symptomatic thrombocytopenia; either grade 4 peripheral sensitive neuropathy or grade 3 necessitating treatment reduction at the 60 mg/m^2 dose level for oxaliplatin—grading according to Lévi's scale [33]; any grade 4 toxicity related to study treatment (except vomiting in the absence of appropriate medication) or any toxicity which necessitated a cycle delay of > 15 days.

Study assessment

Before inclusion, patients were subjected to a pre-trial evaluation including physical examination, assessment of medical history, hematological and biochemical tests and tumor assessment by computed tomography scan. During therapy, a complete blood cell and platelet count was performed weekly. Clinical examination and biochemical tests were required before each cycle. All adverse events experienced during the study were recorded and graded according to the National Cancer Institute common toxicity criteria, or, if not applicable, as mild, moderate, severe or life-threatening. Oxaliplatin neurosensory toxicity was described according to the specific grading proposed by Lévi et al. [33]. Presence of measurable lesions was not required in this study but, in the case of measurable or assessable disease, tumor assessments were performed every four cycles. Responses, as determined by investigators, were recorded according to WHO response criteria.

Statistical analysis

Descriptive statistics (median and range) were provided according to the initial planned dose and for all assessable patients for safety. Percent toxicities are presented per patient and per cycle. Confidence intervals (CIs) for proportions were calculated from the binomial distribution. Response duration was calculated from either inclusion to progression for patients with either partial response or stable disease or from complete response to progression for patients in complete response. Median survival was obtained

from the 50th percentile of the estimated Kaplan–Meier survival rates and presented with the 95% CI.

Results

Patient characteristics

Between April 1998 and January 2000, 42 patients were included in three centers. One patient was not assessable for tolerance because he never received any treatment because of consent withdrawal before the first cycle. A summary of patient characteristics at baseline is presented on the overall population (Table 1). Among the treated population, the median age was 56 years (range 32–73) and most patients had a PS of zero or one (80%). The most common tumors were gastrointestinal tumors (68%) including colorectal, pancreatic, gastric and esophageal cancers and cholangiocarcinoma. More than 60% of patients had at least two organs involved and 69% of patients had visceral involvement with 61% including liver. Seventy-eight percent of patients had received prior chemotherapy.

Study treatment exposure and determination of MTD

A total of 277 treatment cycles were administered with a median number of cycles per patient of six (range 1–12) (Table 2). Eleven patients (27%) received 12 cycles, the maximum number of cycles planned per protocol, and seven patients (17%) received between eight and 11 cycles.

Most patients (78%) had at least one cycle delay ≥ 3 days related to study treatment (35% of cycles). The main reason for delayed administrations was hematological toxicity (56%) but the frequency of cycle delays was not clearly dose-dependent (Table 2), even if all patients who had received more than one cycle at dose levels 85/200 and 85/220 mg/m^2 experienced at least one delay. Only patients treated at the first dose level (60/90 mg/m^2) and in the second cohort (dose level 85/180 with the simplified LV5FU regimen) could have nearly 90% of cycles administered every 2 weeks according to protocol.

To maintain this biweekly schedule, overall, 51% of patients required therapeutic G-CSF during 38% of cycles. However, it is noteworthy that 56% of patients required G-CSF in the first cohort (in 42% of cycles) compared with only 29% of patients in the second cohort (in 18% of cycles). Altogether, dose reductions occurred in 21 patients (51%) and in 13% of cycles and especially at dose levels $\geq 85/150$ mg/m^2 . Irinotecan was reduced in 15 patients (37%) and in 7% of cycles, mainly for hematological toxicity (more than 70% of irinotecan dose reductions). Nine patients (22%) underwent an oxaliplatin dose reduction in 6% of cycles, primarily (88%) because of peripheral neuropathy experienced at previous cycles. Overall, the median cumulative dose for oxaliplatin was 359 mg/m^2 (range 82–1020). Its administration had to be stopped in three patients after nine, 10 and 11 cycles. Only two patients (5%; three cycles) had a 5-FU dose reduction, both for stomatitis.

The dose level escalation was carried out according to the CRM method based on the observation on DLTs at cycle 1 (Table 3). The DLTs were mainly severe neutropenia. Since two out of four

Table 1. Patient characteristics at study entry

Characteristic	No. of patients	Percent
No. included	42	–
No. treated	41	–
Sex, male/female	24/17	59/41
Age, median (range)	56 (32–73)	–
WHO performance status		
0	12	29
1	21	51
2	8	20
Prior treatment		
Surgery	31	76
Chemotherapy	32	78
Median no. of lines (range)	1 (0–6)	–
Radiotherapy	13	32
Site of primary tumor		
Colorectal	11	27
Pancreas	6	15
Gastric	5	12
Esophagus	3	7
Cholangiocarcinoma	3	7
Kidney	3	7
Breast	2	5
Lung	2	5
Unknown primary site	2	5
Others ^a	4	10
No. of organs involved ^b		
0	1	2
1	14	34
2	13	32
≥3	13	32

^aOne pleural mesothelioma, one thyroid cancer, one carcinoid tumor of bowel and one retroperitoneal sarcoma.

^bOne patient had no metastatic disease at study entry (error of diagnosis).

evaluable patients at dose level 85/220 mg/m² presented a DLT, this dose level was considered as the MTD. Therefore according to the protocol, the recommended dose level should have been the dose level just below, in this case 85/200 mg/m². However, at this dose level, all patients who received more than one cycle had at least a one-cycle delay related to study treatment and three patients out of five had at least one dose reduction of irinotecan. Consequently, the decision was taken to complete the lower dose levels 85/150 and 85/180 mg/m² with the inclusion of three extra patients by dose level. Since no major difference was observed between those two dose levels in terms of drug delivery (dose reductions or cycle delays), the recommended dose chosen for the second step of the study was oxaliplatin 85 mg/m² and irinotecan 180 mg/m².

Table 2. Drug delivery

Dose level, oxaliplatin/irinotecan (mg/m ²)	Total no. of patients/cycles	Median no. of cycles per patient (range)	Dose reductions, no. of patients (percent of cycles)		Delayed cycles (≥3 days) related to study treatment, no. of patients (percent of cycles)	G-CSF support, no. of patients (percent of cycles)
			Oxaliplatin	Irinotecan		
First cohort (fixed regimen for LV5FU2)						
60/90	3/22	6 (4–12)	–	–	1 (11)	–
60/120	4/45	12 (9–12)	–	2 (4)	4 (32)	3 (51)
85/120	2/5	2.5 (2–3)	–	–	1 (33)	–
85/150	6/48	9.5 (1–12)	2 (8)	3 (8)	4 (52)	3 (48)
85/180	8/45	4 (1–12)	1 (4)	2 (7)	5 (49)	5 (44)
85/200	6/25	4 (1–8)	2 (8)	3 (16)	5 (42)	4 (44)
85/220	5/36	7 (3–12)	1 (6)	3 (11)	5 (32)	4 (53)
Second cohort [fixed simplified LV5FU scheme (85/180)]	7/51	8 (3–12)	3 (14)	2 (6)	4 (11)	2 (18)

LV, leucovorin; 5-FU, 5-fluorouracil; LV5FU2, full-dose LV and 5-FU regimen on days 1 and 2, every 2 weeks; LV5FU, simplified LV and 5-FU regimen; G-CSF, granulocyte colony-stimulating factor.

Table 3. Dose escalation for determination of maximum-tolerated dose (first cohort)

Dose level, oxaliplatin/ irinotecan (mg/m ²)	No. of patients	No. of cycles	No. of patients with at least one dose-limiting toxicity at the first cycle
60/90	3	22	—
60/120	4	45	—
85/120	2	5	—
85/150	3 + 3 ^a	48	2 (diarrhea grade 3, grade 4) ^a
85/180	5 + 3 ^a	45	2 (neutropenia grade 4 ≥ 7 days, febrile neutropenia with diarrhea grade 4)
85/200	6	25	2 (neutropenia grade 4 ≥ 7 days, stomatitis grade 4)
85/220	5	36	2 (neutropenia grade 4 ≥ 7 days, febrile neutropenia grade 4) ^b

^aPatients included after determination of maximum-tolerated dose.

^bTwo dose-limiting toxicities among the first four patients included at this dose level.

Toxicity

All treated patients were assessable for toxicity. No treatment-related death was reported by the investigators during the study. Table 3 lists the DLTs observed during the first cycle of the combination in the dose-escalation part of the study. Table 4 summarizes the main grade 3/4 toxicities encountered during treatment, overall and by dose level. The DLT of the association is clearly neutropenia, which was the most common toxicity in severity. Overall, 85% of patients experienced neutropenia and 78% had at least one grade 3/4 in 23% of cycles. Although the incidence of grade 3/4 toxicity per patient was high, episodes of severe neutropenia, febrile neutropenia or grade 4 lasting ≥ 7 days occurred only above the dose level 85/150 mg/m² and in less than 10% of cycles. It should be noted, however, that no patient received prophylactic G-CSF at cycle one, although overall, 51% of patients required G-CSF in 38% of cycles under treatment. In most cases, G-CSF was used because of no hematological recovery at day 15 with a neutrophil count < 1.5 × 10⁹/l. It is noteworthy that at dose level 85/180 mg/m² with the simplified LV5FU scheme (second cohort), the incidence of grade 3/4 neutropenia was lower (43% of patients and 10% of cycles) with a lesser use of G-CSF as already stated above: 29% of patients received G-CSF in 18% of cycles compared with 56% of patients of the first cohort (dose escalation) in 42% of cycles (Table 2). Grade 3/4 thrombocytopenia occurred in 6% of cycles and was reported as a serious adverse event for one patient with gastric cancer at two successive cycles. Grade 3/4 anemia was experienced in 5% of cycles and reported as a serious adverse event for one patient. This patient also had a gastric cancer and rapidly recovered after transfusion.

The most frequent and severe non-hematological adverse events were gastrointestinal toxicities, peripheral neuropathy and asthenia with the overall following occurrences of related grade 3/4 by patient: 27% diarrhea (5% of cycles); 24% nausea/vomiting (5% of cycles); 37% peripheral neuropathy (20% of cycles); and 41% asthenia (9% of cycles). All these toxicities are detailed by dose levels in Table 4. Overall, acute toxicity was mild under dose level 85/150 mg/m², except for peripheral neuropathy grade 3 (specific oxaliplatin Lévi scale) observed at almost all dose levels. Its severity was generally preceded by progres-

sively persistent paresthesias between cycles. Severe digestive toxicities, such as grade 3/4 delayed diarrhea, nausea/vomiting, occurred from dose level 85/150 mg/m² and never exceeded 10% of cycles with the exception of the MTD level 85/220 mg/m². Most of these toxicities were only experienced at one cycle per patient (50% at first cycle) and subsequent dose reduction and/or prophylactic anti-emetic therapy improved the gastrointestinal tolerance of these patients. The main other non-hematological toxicity was asthenia, which occurred above the dose level 60/120 mg/m². Of note, the severity of main toxicities appears lower in patients treated in the second cohort with the simplified LV5FU regimen, except for neurotoxicity. At this dose level the median cumulative dose for oxaliplatin was 537 mg/m².

The other frequently reported non-hematological toxicities related to study treatment were alopecia experienced by 61% of patients (27% grade 2), anorexia, which occurred in 59% of patients and 20% of cycles (4% of cycles grade 3/4), and stomatitis in 59% of patients and 23% of cycles, with two patients experiencing a grade 3 and 4, respectively, leading to 5-FU dose reductions. The occurrence and severity of those toxicities were not clearly dose-dependent and seemed rather more patient-related.

Efficacy

Patients were considered to be assessable for response if they had measurable lesions and had received at least four cycles of the study treatment or showed evidence of early progression. Seven treated patients were non-evaluable for efficacy: one patient could not be evaluated because he had no disease (error of diagnosis at study entry) and six came off the study before first evaluation, without evidence of early progression according to the investigator. Of 34 patients evaluable for efficacy, three complete responses (one pancreas, two colorectal cancers) and eight partial responses (three colorectal cancers, two cholangiocarcinoma, one pancreas, one gastric and one renal carcinomas) were observed, resulting in 11 objective responses. Among these responses, 10 concerned gastrointestinal tumors. All responders with CRC had received prior chemotherapy with 5-FU and had liver metastases. Two of them were able to have hepatic resection after response. The five other objective responses observed in

Table 4. Main grade 3/4 toxicities: total and by dose levels (values are no. of patients/cycles)

Dose level, oxaliplatin/ irinotecan (mg/m ²)	Total no. of patients (cycles)	Neutropenia		Diarrhea (grade 3/4)	Nausea/vomiting (grade 3/4)	Asthenia (grade 3/4)	Peripheral neuropathy [grade 3, (specific oxaliplatin Lévi scale)]
		Grade 3/4	With febrile neutropenia or neutropenia ≥7 days				
First cohort (fixed regimen for LV 5FU2)							
60/90	3 (22)	2 (9%)	–	–	–	–	2 (32%)
60/120	4 (45)	4 (29%)	–	–	–	–	–
85/120	2 (5)	2 (40%)	–	–	–	1 (20%)	1 (40%)
85/150	6 (48)	5 (28%)	3 (6%)	4 (8%)	2 (6%)	5 (10%)	4 (31%)
85/180	8 (45)	7 (27%)	2 (4%)	2 (4%)	4 (9%)	3 (7%)	1 (9%)
85/200	6 (25)	4 (36%)	1 (4%)	1 (4%)	–	3 (28%)	2 (12%)
85/220	5 (36)	5 (25%)	2 (8%)	2 (11%)	3 (17%)	4 (22%)	2 (22%)
Second cohort [fixed simplified LV5FU scheme (85/180)]							
	7 (51)	3 (10%)	1 (2%)	2 (4%)	1 (2%)	1 (4%)	3 (31%)
Total	41 (277)	32 (23%)	9 (4%)	11 (5%)	10 (5%)	17 (9%)	15 (20%)

LV5FU2, full-dose leucovorin (LV) and 5-fluorouracil (5-FU) regimen on days 1 and 2, every 2 weeks; LV5FU, simplified LV and 5-FU regimen.

digestive malignancies were obtained in diseases with a usually very poor prognosis. In those cases, response duration was ≥5 months except for one patient with one cholangiocarcinoma who went off the study after eight cycles because the response obtained enabled resection of the hepatic tumor. Furthermore, 13 patients (38%) had stable disease among whom four patients had a minor response. Responses were observed at nearly all dose levels (Table 5). With a median follow-up of 16 months, the median duration of response was 9 months (95% CI 6–18 months), the median duration of stabilization was 7 months (95% CI 6–12 months), the median time to progression was 7 months (95% CI 5–9 months) and the survival time ranged from 1.1 to 24.5 months.

Discussion

The objectives of this open-label, non-randomized, dose-escalation study were to determine the MTD, the DLT and the recommended dose for irinotecan and oxaliplatin given together with the LV5FU2 regimen as a triple combination every 2 weeks in patients with advanced solid tumors.

Forty-one patients were treated and evaluated for safety. Thirty-four patients were included in the dose-escalation cohort and the MTD was determined to be the dose level 85 mg/m² for oxaliplatin and 220 mg/m² for irinotecan with the LV5FU2 regimen. The DLT at this dose level was severe neutropenia. Therefore, the recommended dose should have been 85/200 mg/m². However, at this dose level, >30% of cycles had a dose reduction, with 16% of cycles requiring a dose reduction of irinotecan, mainly because of hematological toxicity. Thus, the 180 mg/m² irinotecan dose level was considered the best compromise between dose intensity and safety for designing further multi-center phase II or III studies. Our choice was also supported by the already determined recommended and currently used doses for the bi-therapy associations: irinotecan 180 mg/m² or oxaliplatin 85 mg/m² for combinations with LV5FU2 regimen given every 2 weeks [12, 13, 21, 22] and irinotecan 175 mg/m² or 200 mg/m² plus oxaliplatin 85 mg/m² for the association of the two new drugs given every 2 or 3 weeks [24, 26, 28]. Furthermore, recently published data suggesting the lower hematological toxicity of the simplified LV5FU regimen, alone or in combination with irinotecan [29–31], led us to treat a second cohort of patients at the dose level 85 mg/m² for oxaliplatin and 180 mg/m² for irinotecan with the simplified LV5FU regimen. Results obtained showed that the recommended dose level with this scheme could be safely administered with preservation of a good biweekly dose intensity, since nearly 90% of cycles could be administered every 2 weeks according to the protocol.

Overall, the most frequent adverse events observed were consistent with those expected in patients treated with either irinotecan or oxaliplatin combined with a 5-FU-based regimen, or by the two new drugs given together.

The main grade 3/4 toxicity in this study was neutropenia, observed in 78% of patients and 23% of cycles, with severe neutropenia (febrile neutropenia or grade 4 lasting ≥7 days) observed above the dose level 85/150 mg/m² in less than 10% of

Table 5. Antitumor activity by dose level (values are no. of patients)

Response (<i>n</i> = 34)	Initial planned dose level, oxaliplatin/irinotecan (mg/m ²)							Second cohort	Total
	60/90	60/120	85/120	85/150	85/180	85/200	85/220		
Complete response	1	1	–	–	–	–	1	–	3
Partial response	–	1	–	1	1	2	1	2	8
Stable disease	1	2	–	3	3	1	1	2	13 ^a
Progressive disease	1	–	1	1	2	2	1	2	10

^aIncluding four minor responses.

cycles. In all studies (phase I, II or III) combining every 2 weeks either irinotecan or oxaliplatin with LV5FU2, or the two new drugs together, the occurrence of grade 3/4 neutropenia varied from about 37 to 64% of patients [12, 13, 21, 22, 26, 27]. Furthermore, the occurrence of complicated neutropenia (22% of patients) appears more frequently with the association of the three drugs. These results may be because of the overlapping hematological toxicity of each drug, especially irinotecan and 5-FU. Yet they could also be explained by the patient's characteristics in our study including patients with various solid tumor types who, for the most part, had already been treated before inclusion. One important finding about the hematological safety profile of the association of the three drugs is that the use of growth factors seems necessary in order to allow dose intensity of the biweekly schedule, since, overall, 51% of patients required G-CSF. However, we noticed that at dose level 85/180 mg/m² with the simplified LV5FU scheme, the incidence of grade 3/4 neutropenia was lower (43% of patients and 10% of cycles) with less use of G-CSF: 29% of patients received G-CSF in 18% of cycles compared with 56% of patients of the first cohort (dose escalation) in 42% of cycles. These results are consistent with the already known hematological toxicity of 5-FU bolus compared with 5-FU infusional administration [34, 35] and confirm the lower hematological toxicity of the simplified LV5FU regimen compared with the LV5FU2 regimen [29, 36], which has also been observed in association with oxaliplatin (FOLFOX 6 schedule) or irinotecan (FOLFIRI scheme) [37–39]. Thrombocytopenia was not enhanced either in frequency or in severity with the triple combination as compared with combinations studies of oxaliplatin or irinotecan with LV5FU2 [21–25].

The other principal adverse events were gastrointestinal toxicities, cumulative oxaliplatin-related peripheral neuropathy and asthenia, with the following occurrence of grade 3/4: diarrhea in 27% of patients, nausea/vomiting in 24% of patients and grade 3 peripheral neuropathy in 37% of patients (specific Lévi scale grading). The incidence of these toxicities did not increase significantly in our study compared with the published phase I/II bi-therapy studies. At the recommended dose for combining irinotecan and LV5FU2 (180 mg/m²), grade 3/4 diarrhea occurred in 27% of patients in phase I/II [12] and 13% in phase III [13]. In phase I/II studies combining irinotecan and oxaliplatin every 2 or 3 weeks, grade 3/4 diarrhea was experienced by 17–30% of patients [24–26]. In these studies, the only overlapping toxicity between the two drugs was nausea/vomiting reported in 30–40% of patients overall. As ascertained before and in our

study, this toxicity can be managed by systematic prophylactic anti-emetics at each cycle, and moreover it never led to treatment discontinuation. The occurrence of severe peripheral neuropathy in our study (overall, 37% of patients in 20% of cycles) is of the same order as the one reported in the phase I study of oxaliplatin combined with irinotecan given as a 2-week schedule [26], although the median cumulative dose of oxaliplatin was lower: 359 mg/m² (537 mg/m² at the recommended dose with the simplified LV5FU scheme) compared with 765 mg/m² in the Goldwasser study [26].

Recently, four phase I studies evaluated various schedules of combination of the three drugs, irinotecan, oxaliplatin and 5-FU. All of these trials were conducted in MCRC patients, with a lesser dose intensity of the two new drugs and without 5-FU bolus. However, their preliminary results are consistent with ours, reporting neutropenia and diarrhea as the main DLTs [40–43].

Although tumor response was not the primary end point of this study, it should be noticed that 11 objective responses among 34 evaluable patients were observed at all dose levels and 71% of patients experienced a tumor growth control (complete response plus partial response plus stable disease) according to the investigators' assessment. Most objective responses were observed in digestive malignancies, since 10 of 11 were obtained in five colorectal cancers, two pancreatic cancers, two cholangiocarcinoma and one gastric cancer. With a median follow-up of 16 months, the median duration of responses was 9 months (95% CI 6–18 months) and the survival time ranged from 1.1 to 24.5 months. These results confirm the efficacy of the three drugs in the treatment of CRC, although this had already been demonstrated in bi-therapy studies of either irinotecan or oxaliplatin combined with 5-FU/LV or of the two new drugs combined together. Nevertheless, it is worth noting that two CRC patients who achieved a partial response were able to have hepatic resection after treatment by the triple combination. Furthermore, this also appears of particular interest in gastrointestinal malignancies such as cholangiocarcinoma, pancreatic and gastric cancer, as one patient with cholangiocarcinoma became resectable after eight cycles of treatment. Each patient with one of these diseases that was responsive under treatment (*n* = 5) was still alive 12 months after initial diagnosis.

In conclusion, this phase I study has shown both the lack of clearly overlapping toxicities when the three drugs are combined together and the feasibility of the triple association given every 2 weeks with the simplified LV5FU regimen administered together with the recommended doses of 85 mg/m² for oxaliplatin

and 180 mg/m² for irinotecan. At this dose, it should be noticed that G-CSF was administered in 18% of cycles in cases of severe neutropenia or to maintain a biweekly schedule. **Although the use of G-CSF is not recommended in routine palliative chemotherapy, it should be considered in the light of efficacy results.** Those obtained in our study warranted further investigation of the regimen, especially in the case of gastrointestinal malignancies, where 10 out of the 11 objective responses were observed. **The use of the triple combination with G-CSF support, if necessary, should be justified in front-line therapy for disease where no effective treatment is available, or to allow a secondary radical surgical approach on metastases in colorectal patients.** Thus, our results led to two ongoing phase II studies using this combination in advanced pancreatic adenocarcinoma and in metastatic colorectal patients with non-resectable liver metastasis. In this latter case, chemotherapy with the triple association can be justified, since it may increase the proportions of R0 surgical resections, which is the only effective treatment providing long-term survival in this disease [44, 45].

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