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Original Paper

Oxaliplatin with High-dose Leucovorin and 5-Fluorouracil 48-hour Continuous Infusion in Pretreated Metastatic Colorectal Cancer

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Oxaliplatin has shown *in vivo* cytotoxic activity against colorectal cell lines. Preliminary studies suggest potentiation of fluorouracil (5-FU). To assess this issue, we performed a phase II study in pretreated patients with advanced colorectal cancer (CRC) resistant to leucovorin and 5-FU. The regimen (FOLFOX2) consisted of oxaliplatin 100 mg/m^2 as a 2-h infusion on day 1; leucovorin 500 mg/m^2 as a 2-h infusion, followed by 5-FU 24-h infusion 1.5–2 g/m^2 for two consecutive days every 2 weeks. The initial 5-FU dose was 1.5 g/m^2 for two cycles and increased to 2 g/m^2 in case of no toxicity>grade 2. 46 patients were treated, all with disease progression on leucovorin and 5-FU therapy for metastatic disease, or relapse less than 6 months after the end of adjuvant therapy. One complete response (CR) and 20 partial responses (PRs) were observed for an overall response rate of 46%. 22 patients had prior documented progression while receiving the same schedule of leucovorin and 5-FU as the one used in the FOLFOX2 regimen, and among them, 10 had PRs (45%). From the start of FOLFOX2, median progression-free survival was 7 months and median survival 17 months. WHO toxicity ⩾ grade 3 per patient was: peripheral neuropathy 9%, nausea 4%, diarrhoea 9%, mucositis 13%, neutropenia 39%, thrombocytopenia 11%, alopecia 9%, and allergy 2%. Overall, 21 patients (46%) experienced grade 3–4 toxicity. This combination of leucovorin, 5-FU and oxaliplatin achieves a high response rate in pretreated patients with CRC resistant to leucovorin and 5-FU. Limiting toxicities are neutropenia and peripheral neuropathy. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: oxaliplatin, 5-FU infusion, colorectal cancer, folinic acid (leucovorin)

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INTRODUCTION

5-FLUOROURACIL (5-FU) is the standard cytostatic agent in colorectal cancer treatment. Administered as a single agent, given as an intravenous (i.v.) bolus, 5-FU produces a 10–15% response rate and a median survival time of 6–9 months in metastatic cancers. Continuous i.v. administration increases the time that tumour cells are exposed to 5-FU, and also allows an increase in the total tolerated dose compared with bolus administration. Continuous infusion results in different toxicities from bolus injection, with a higher incidence of hand–foot syndromes but fewer cases of neutropenia [1]. Randomized studies, comparing bolus 5-FU with continuous 5-FU, have shown a higher response rate for continuous infusion which is generally considered as symptomatically beneficial, but no improvement in survival time [1]. 5-FU is potentiated by leucovorin (LV). Clinically, the first protocols used high-dose LV and 5-FU bolus monthly for five consecutive days or weekly for one day [2, 3]. Meta-analysis of the results of the randomised trials showed an increase in the response rate compared with those of 5-FU alone, but there was no survival benefit [4].

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LV can also potentiate continuous 5-FU. However, leucovorin does not appear to be very effective with a protracted infusion of 5-FU (>5 days) [5]. A bimonthly 48-h regimen that combines 5-FU bolus and continuous 5-FU allows the dose of 5-FU to be twice that of the LV–5-FU bolus regimen, with a higher response rate and less toxicity [6, 7]. Continuous 5-FU administration with high-dose leucovorin appears to give a better response rate, especially if 5-FU is given as a short high-dose infusion. Weekly 24-h 5-FU infusion allows the administration of very high doses of 5-FU at the beginning of treatment, up to 10 g/m^2/month [8].

Based on the initial bimonthly regimen [6], we carried out a phase I trial combining high-dose leucovorin and high-dose continuous 5-FU in order to study the optimal dose intensity that can be maintained over time and allows combination with other modulators or other drugs as a basis for our future protocols. This study showed that it was possible to administer 5-FU continuous infusion over 2 days every two weeks at a dosage of 1.8–2.1 g/m^2/24 h, i.e. 7.2–8.4 g/m^2/month with high doses of leucovorin [9]. This dose of 5-FU was twice that used in the bolus and continuous infusion regimen.

Oxaliplatin, *trans*-L-1,2-diminocyclohexane oxalatoplatinum, is a new platinum compound which has shown *in vitro* and *in vivo* preclinical activity, including colorectal cell lines such as HT29, colon 26 and colon 29 and cisplatin-resistant cell lines [10–12]. Oxaliplatin used as a single agent has shown, in phase II trials, a 10% response rate with mild toxicity in patients with progressive disease while under fluoropyrimidines [13, 14].

Synergy between oxaliplatin and 5-FU has been suggested in L1210 leukaemia cell culture transplanted into mice [15]. Oxaliplatin has been used as a continuous chronomodulated infusion in combination with leucovorin and 5-FU continuous infusion. In a phase II study, this regimen achieved a 58% response rate and a 15 months median survival [16]. In a randomised first-line phase III study, this chronomodulated regimen produced a 49.5% response rate versus 30% with the flat administration of the drugs [17].

A feasibility study of the bimonthly combination of leucovorin, 5-FU 48-h infusion and oxaliplatin in pretreated patients, where oxaliplatin was administered every other cycle as a 2-h infusion, as in the phase II trials of oxaliplatin alone, has produced four responses among 10 patients with measurable lesions. Limiting toxicities were neutropenia and mucositis [18].

In the present study (FOLFOX2), the initial 5-FU dose was reduced and a lower dose of oxaliplatin was administered at every 2-week cycle.

PATIENTS AND METHODS

Inclusion criteria

Eligibility criteria were: histologically verified adenocarcinoma of the colon or the rectum; progressive disease while treated with leucovorin and 5-FU; bidimensional measurable lesions; no central nervous system metastasis; no exclusive bone metastases; no second malignancy, except adequately treated *in situ* carcinoma of the cervix or nonmelanomic skin cancer; life expectancy of at least 3 months; age from 18 to 75 years; WHO performance status 0–2; metastases outside the irradiation field in patients who had previous radiation therapy; initial evaluation two weeks or less before inclusion; neutrophils >1500/mm^3; platelets >100 000/mm^3; serum creatinin level <300 μmol/l; partial thromboplastin time (PTT) >50%; and regular follow-up feasible. Written informed consent was obtained from all patients.

Chemotherapy

Leucovorin was given at 500 mg/m^2/day as a 2-h infusion followed by a 24-h infusion of 5-FU at 1500–2000 mg/m^2/day for two consecutive days (days 1–2). Oxaliplatin was administered at 100 mg/m^2 as a 2-h infusion (day 1) during leucovorin infusion without mixing. Initial 5-FU dose was 1500 mg/m^2/day for the first 2 cycles, to be increased for subsequent cycles to 2000 mg/m^2/day in the case of maximal toxicity less than WHO grade 2. Cycles were repeated at 2-week intervals (Figure 1).

This regimen was to be administered until progression when neutrophils were over 1500/mm^3, platelet count over 100 000/mm^3 and in case of tolerable toxicity (WHO grade 0–2). If persistent WHO grade 1 peripheral neuropathy occurred after 6 cycles, oxaliplatin was to be given only every two cycles; in case of persistent WHO neurological

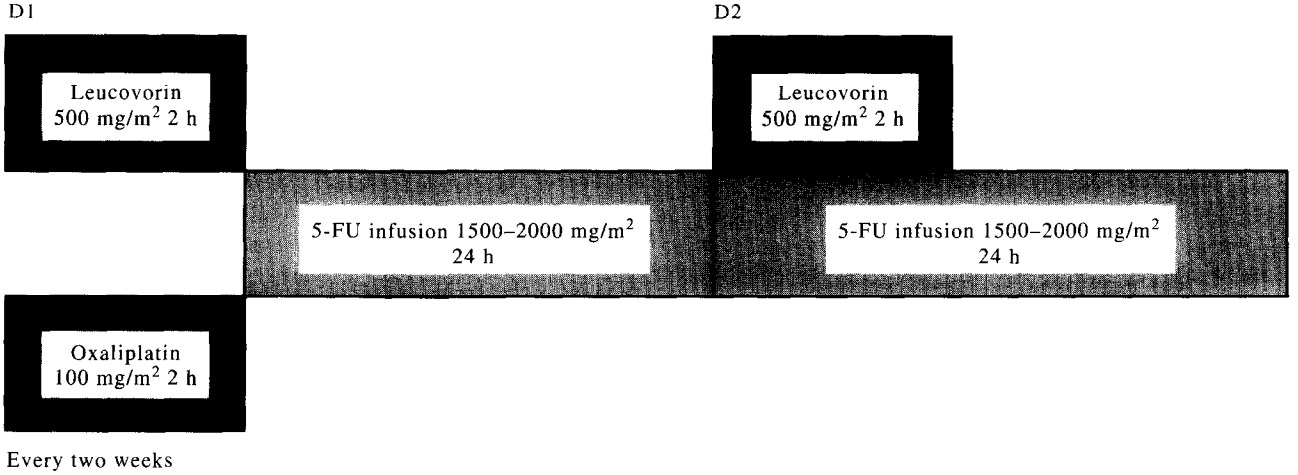

Figure 1. Bimonthly leucovorin, 5-FU continuous infusion and oxaliplatin (FOLFOX regimen).

toxicity ≥grade 2 with pain or functional impairment, oxaliplatin was to be discontinued. In case of other toxicity >grade 2, the 5-FU dose was to be reduced from 2000 mg/m^2/day to 1500 mg/m^2/day and in case of persistent toxicity, from 1500 mg/m^2/day to 1200 mg/m^2/day.

Study parameters

Physical examination and full blood counts were performed at each cycle. Carcinoembryonic antigen (CEA), alkaline phosphatases, LDH, chest X-ray, MRI, or CT scans were repeated every 12 weeks (i.e. every 6 cycles) or earlier in the case of clinical deterioration. Only patients with bidimensional measurable lesions on a CT scan or MRI were considered as evaluable for tumour responses.

Complete response (CR) was defined as complete disappearance of all evaluable disease for at least 4 weeks, while partial response (PR) as a decrease of at least 50% in the sum of the products of the diameters of measurable lesions for at least 4 weeks. Stable disease (SD) was defined as a decrease under 50% or an increase under 25% of the disease, and progressive disease (PD) was an increase of at least 25% or the appearance of a new neoplastic lesion [19]. Serosal effusions or CEA levels were not considered evaluable. For rectal cancers, evaluable metastases were to be outside the pelvis. An external review of all CT scans and MRI was performed.

Therapy was continued until disease progression or occurrence of non-tolerable toxicity. Disappearance of or improvement in tumour-related symptoms (e.g. pain, jaundice, fever) was considered relief from symptoms in patients who had baseline tumour-related symptoms. The definition of weight gain used was an increase in baseline weight greater than 2 kg. Normalisation of CEA levels or more than a 50% decrease in CEA levels was considered a biological effect in patients whose CEA levels were increased at baseline.

Statistical considerations

Response duration and survival were calculated using the Kaplan–Meier method from start of chemotherapy until 1 February 1996 [20]. Response duration and progression-free survival were calculated from the date of start of therapy to the date when progression was first observed.

RESULTS

Patient characteristics

From 6 February 1993 until 31 January 1995, 46 patients were included in the study. Patients' characteristics are shown in Table 1. 24 patients had disease progression while on different leucovorin and 5-FU regimens and 22 had progressed while receiving the same dose and schedule of 48-h bimonthly high-dose leucovorin and 5-FU: in this subset of fully refractory patients, the only change in therapy was the addition of oxaliplatin to the leucovorin and 5-FU regimen.

Toxicity

The incidence of main toxicities per patient is summarised in Table 2. 502 cycles were evaluable. The median number of cycles per patient was 10. Limiting toxicities were neutropenia and peripheral neuropathy. Neutropenia reached grade 3–4 in 18 patients (39%), including 4 patients (9%) who had febrile neutropenia. Therapy was discontinued in 4 patients (9%) for haematological toxicity. Neutropenia did not recur after 5-FU dose reduction in the other patients who had grade 3–4 neutropenia. Peripheral neuropathy of WHO grade 2 or 3 occurred in 33% of the patients. Partial or complete regression of the paresthesias was observed. Oxaliplatin could be re-introduced after regression of the paresthesias in 3 out of 11 patients who had to stop oxaliplatin. The other grade 3 toxicities observed were thrombocytopenia in 11%, nausea in 4%, diarrhoea in 9%, mucositis in 13% and alopecia in 9% of the patients. Hypersensitivity reaction (anaphylaxis) was observed at the 6th cycle in one patient, leading to oxaliplatin discontinuation. Angina pectoris, possibly due to 5-FU, occurred after

Table 1. Baseline patients' characteristics

No. included	46	
Median age (years)	59.4 (28–75)	
Male/female	29/17	
Primary tumour		
colon	24	52%
rectum	22	48%
Site of metastases		
liver	39	85%
lung	13	28%
peritoneal carcinomatosis	4	9%
other	14	30%
No. of involved sites		
one	31	67%
two (liver and other)	9	20%
>two	6	13%
WHO performance status		
0	22	48%
1	19	41%
2	5	11%
Pre-existing symptoms		
none	22	48%
yes	24	52%
Alkaline phosphatases		
within normal range	27	59%
increased	19	41%
LDH		
within normal range	27	59%
increased	19	41%
CEA		
within normal range	8	17%
increased	38	83%
Type of previous chemotherapy		
LV-5-FU bolus + continuous bimonthly alone or in combination	18	39%
LV-5-FU bolus monthly	5	11%
LV-5-FU high dose continuous bi-monthly +/– interferon: refractory patients	22	48%
LV-5-FU other schedule	1	2%
No. of prior regimens of chemotherapy		
1	33	72%
≥2	13	28%
Interval between progression and start of FOLFOX2		
≤2 months	32	70%
>2 months	14	30%

LV-5-FU: 2-day bimonthly regimen of leucovorin and 5-fluorouracil. FOLFOX2: 2-day bimonthly regimen of folinic acid, 5-fluorouracil and oxaliplatin.

Table 2. Toxicity per patient (maximum WHO grade)

	Grade									
$n = 46$	0		1		2		3		4	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Peripheral neuropathy	3	7	28	61	11	24	4	9	0	0
Neutrophils	19	41	3	7	6	13	9	20	9	20
Platlets	29	63	10	22	2	4	5	11	0	0
Anaemia	44	96	1	2	1	2	0	0	0	0
Nausea	13	28	20	43	11	24	2	4	0	0
Diarrhoea	18	39	12	26	12	26	4	9	0	0
Mucositis	17	37	17	37	6	13	6	13	0	0
Alopecia	23	50	11	24	8	17	4	9	0	0
Cutaneous*	29	63	14	30	3	7	0	0	0	0

*Hand-foot syndrome.

6 cycles in another patient. One case of transient grade 3 hepatic toxicity was also observed, but was not clearly related to chemotherapy, in a patient who received concomitant therapy for major depression. Mild toxicities also included drug-induced fever in 3 patients (7%) and conjunctivitis in 5 patients (11%). Overall 9 (20%) of the patients reached a grade 4 toxicity, 12 (26%) a grade 3, 17 (37%) a grade 2 and 8 (17%) a grade 1. Only 33% could receive the maximal 5-FU dose scheduled, i.e. 2000 mg/m^2/day. Six patients (13%) had further grade 3 or 4 toxicities with 5-FU 1500 mg/m^2/day. 11 patients (24%) had to stop oxaliplatin for neurological toxicity before evidence of disease progression, and 6 (13%) stopped therapy for other toxicities (neutropenia 4, anaphylaxis 1, angina pectoris 1). Another two patients (4%) asked for discontinuation of therapy before evidence of tumour progression.

Objective tumour responses (Table 3)

The objective response rate in all patients was 46% (95% confidence interval was 31–60%). One CR lasted 8 months and the median duration of PR was 8.5 months. The median interval between the start of chemotherapy and the response was 84 days. 46% of patients had stable disease: among these patients, two had tumour regression over 50% which was not confirmed 4 weeks apart. 7% had progressive disease. One patient was not evaluated (2%, refusal). In patients resistant (refractory) to the same schedule of leucovorin and 5-FU, 10 responded: 45%, the 95% confidence interval was 24–67%. The response rate in liver metastases was 44% and in lung metastases 46%.

Table 3. Tumour responses

	All patients ($n = 46$)		Patients resistant to the same prior LV-5-FU schedule ($n = 22$)	
	No.	%	No.	%
Complete response	1	2	0	0
Partial response	20	43	10	45
Stable	21	46	10	45
Progression	3	7	2	9
Non-evaluable	1	2		
Response rate		46		45
(95% CI)		(31–60)		(24–67)

Palliative and biological effects

Pre-existing symptoms regressed or disappeared in 12 patients, 50% of those who were symptomatic at study entry. A weight increase of 2 kg or more was observed in 7 patients (15%). Performance status improved in 6 out of 24 (25%) patients with a baseline performance status ≥ 1. CEA normalised in 3/38 patients (8%) or decreased >50% in 17 patients (45%), among those with increased CEA at start of therapy. Two out of eight patients with a normal baseline CEA had an increased level during treatment.

Survival

Median progression-free survival was 7 months and median survival 17 months from the start of FOLFOX2. In the 22 patients resistant (refractory) to the same schedule of leucovorin and 5-FU, median progression-free survival was 6 months and median survival 16 months. The survival curves are shown in Figure 2.

DISCUSSION

Second-line therapy after first-line treatment with LV-5-FU is a new challenge in advanced colorectal cancer. Limited results have been achieved with 5-FU infusion after progression on LV-5-FU bolus treatment [21] or with further modulation of LV-5-FU [22]. Among new drugs,

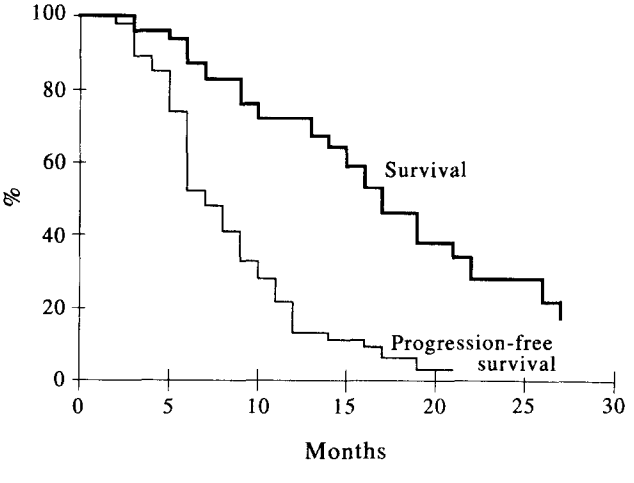

Figure 2. Survival and progression-free survival with oxaliplatin, leucovorin and 5-FU in pretreated advanced colorectal cancer.

CPT11 has achieved a 16–19% response rate in pretreated patients with 5-FU modulation [23].

Oxaliplatin is a new platinum compound which has neither renal nor haematological toxicity. The dose-limiting toxicity is a cumulative sensoric neuropathy [24]. Used alone in patients with metastatic colorectal cancer resistant to leucovorin and 5-FU, oxaliplatin has given a 10% response rate, a 5 month median progression-free survival and an 8.2 month median survival when administered either as a 2-h infusion or with chronomodulation [13, 14, 25, 26]. Oxaliplatin has shown *in vitro* synergy with 5-FU [15, 27, 28]. Further *in vitro* studies are ongoing to investigate further this potential therapeutic challenge.

Most clinical studies of oxaliplatin in combination with leucovorin and 5-FU have used chronomodulation administration of the drugs [16, 17, 29–31]. This combination has achieved high response rates: 49.5–61.5% when used as first-line therapy, and 29–55% when used as second-line therapy (Table 4). In a series of 25 patients who were already resistant to leucovorin and 5-FU given with chronomodulation, 29% of the patients responded to the addition of oxaliplatin [31].

However, chronomodulation has not yet been investigated in comparison with the standard regimen for advanced cancer and there is no evidence for prolonged survival. Furthermore, in the flat arm of the recent randomised trial of Lévi and associates [17], the response rate in first-line therapy was only 30% which suggests that optimal synergy between leucovorin, 5-FU and oxaliplatin is not achieved when the drugs are administered as a 5-day continuous infusion.

The present study which combined the 2-h infusion of oxaliplatin with a high dose of leucovorin and 5-FU 48-h continuous infusion has shown an unusual response rate, 46%, and a median progression-free survival of 7 months in patients who progressed while on leucovorin and 5-FU therapy. In our study, a clinical synergy between the drugs was seen in the 22 refractory patients who progressed on the same leucovorin and 5-FU regimen, for whom we observed a 45% response rate (confidence interval 24–67%). In such patients, the expected response rate in the absence of synergy was 10% as shown in trials in which oxaliplatin was used as single agent. The rate of the decrease of CEA level was in the same range as the response rate. In several patients, improvement in performance status, weight and symptoms were observed. Furthermore, the 17 months median overall survival from start of second-line therapy was unusual for patients with such advanced disease, and even in the range of first-line leucovorin and 5-FU therapy for metastatic colorectal cancer. Patient selection is unlikely to explain these results: in a previous series of 32 patients having the same inclusion criteria and treated with oxaliplatin alone in our institution, progression-free survival was 5 months and median survival only 7.7 months.

Two limiting toxicities were observed. The haematological toxicity, including 39% grade 3–4 neutropenia (grade 4, 20%), was manageable and due to 5-FU. It could be avoided in most patients as it occurred in almost all cases after 5-FU dose escalation and did not recur after dose adaptation. We did not use haematopoietic growth factors.

Neurological toxicity was more cumbersome. We observed 33% grade 2–3 neuropathy (grade 3, 9%). It has two different features which have been previously described [32]: a cold-induced dysesthesia which is acute, always reversible and does not result in the discontinuation of therapy, and a peripheral sensitive neuropathy characterised by paresthesias which can interfere with function and result in oxaliplatin discontinuation. Paresthesias are also reversible but may last

Table 4. Clinical trials with folinic acid, 5-fluorouracil and oxaliplatin

		No. of patients	Response rate	Median OS (PFS)
Chronomodulation studies				
Lévi, 1992 [16]	phase II			
5 days every 3 weeks	first-line	46	59%	15 months (11 months)
5 days every 3 weeks	second-line	42	55%	13 months (10 months)
Brienza, 1993 [29]	phase II			
4 days every 2 weeks	second-line	57	38%	13 months (10 months)
Lévi, 1994 [17]	phase III			
5 days every 3 weeks	first-line	93	49.5%	
Bertault-Citkovic, 1994 [30]	phase II			
4 days every 2 weeks	first-line	13	61.5%	
4 days every 2 weeks	second-line	37	40.5%	
Garufi, 1995 [31]	phase II			
5 days every 3 weeks	second-line refractory	25	29%	12 months (5.8 months)
Studies without chronomodulation				
Lévi, 1994 [17]	phase III			
flat arm 5 days every 3 weeks	first-line	93	30%	
de Gramont, 1994 [18]	phase I-II			
2 days every 2 weeks (ox. every other cycle)	second-line	13	40%	
Present study	phase II			
2 days every 2 weeks (ox. every cycle)	second-line resistant	24	46%	17 months (8 months)
2 days every 2 weeks (ox. every cycle)	second-line refractory	22	45.5%	16 months (6 months)

OS, overall survival; PFS, median progression-free survival; ox., oxaliplatin.

for months. This neuropathy usually starts after 10–15 cycles of oxaliplatin. To decrease the intensity of this toxicity and to administrate oxaliplatin for longer, we are presently studying a lower dose of oxaliplatin (i.e. 85 mg/m^2).

To assess further the role of oxaliplatin in metastatic colorectal cancer, a multicentre randomised first-line trial is ongoing. It compares the bimonthly 48-h combination of leucovorin and 5-FU bolus continuous infusion alone or with the addition of oxaliplatin.

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