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High-dose intensity oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX 7)☆

F. Maindrault-Gœbel [a], A. de Gramont [a,*], C. Louvet [a], T. André [b], E. Carola [c], M. Mabro [a], P. Artru [a], V. Gilles [a], J.P. Lotz [b], V. Izrael [b], M. Krulik [a] for the Oncology Multidisciplinary Research Group (GERCOR)

[a] *Service de Médecine Interne-Oncologie, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, 75571 Paris Cedex 12, France*
[b] *Service d'Oncologie Médicale, Hôpital Tenon, 4 rue de la Chine, 75970 Paris Cedex 20, France*
[c] *Hôpital de Senlis, Service de Médecine 2, 60109 Senlis Cedex, France*

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Abstract

This phase II study examined a regimen (FOLFOX7) of leucovorin (LV), high-dose intensity oxaliplatin, and 5-fluorouracil (5-FU), as second-line therapy for metastatic colorectal cancer. 48 patients were enrolled — 36 refractory and 12 resistant to prior therapy with LV–5-FU. Oxaliplatin (130 mg/m^2) was infused with LV (400 mg/m^2) over 2 h on day 1, followed by bolus 400 mg/m^2 and a 46-h infusion (2400 g/m^2) of 5-FU, every 2 weeks. Patients who responded or were stable received eight cycles. Patients were evaluated every 2 months. 20 patients (42%) had partial responses (95% confidence interval (CI): 28–56%), 19 (40%) had stable disease and 9 (19%) progressed. Median progression-free survival (PFS) was 6 months and median survival 16.1 months. Toxic effects of National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 3/4 were: peripheral neuropathy 15%, nausea 8%, diarrhoea 11%, neutropenia 9%, thrombocytopenia 11%. Overall, 38% of patients experienced grade 3/4 toxicities, and 64% received 90% or more of the scheduled oxaliplatin dose intensity during the first four cycles. FOLFOX7 was highly active, with good tolerability, in pretreated patients resistant to LV–5-FU.

Keywords: Oxaliplatin; 5-FU; Leucovorin; Metastatic colorectal cancer

1. Introduction

In vitro and *in vivo* preclinical studies on colorectal cancer have shown that oxaliplatin is active against colorectal cell lines and is synergistic with 5-fluorouracil (5-FU) [1]. In phase II trials, single-agent oxaliplatin has resulted in a 10% response rate, with mild toxicity, in patients whose disease had progressed on fluoropyrimidines [2]. Oxaliplatin has also been used in combination with leucovorin (LV) and continuous infusion of 5-FU. The first studies involved a 5-day chronomodulated regimen [3]. The FOLFOX (FOLinic acid, 5-FU, OXaliplatin) studies on patients whose cancers were resistant to LV–5-FU tested the 48-h bimonthly regimens (LV–5-FU2) in combination with oxaliplatin at different doses [4]. The feasibility study (FOLFOX1) used a bimonthly regimen of high-dose LV and high-dose 5-FU given as a continuous infusion (FOLFUHD; FOLinic acid, 5-FU High Dose), with oxaliplatin (130 mg/m^2) given every alternate cycle [5]. FOLFOX2 to FOLFOX5 employed variations in the dosages and timing of the administration of the component drugs [6–8]. With FOLFOX6, oxaliplatin (100 mg/m^2) was added to a new, simplified, bimonthly regimen which involved high-dose LV followed by bolus and 46-h continuous infusion of 5-FU every 2 weeks [4,9,10].

The higher response rate (46%) with FOLFOX2 (high-dose intensity of oxaliplatin) than with FOLFOX3 or FOLFOX4 (18–23%) and FOLFOX6 (26.7%) (in all

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* Corresponding author. Tel.: +33-1-4928-2336; fax: +33-1-4928-2344.

E-mail address: aimery.de-gramont@sat.ap-hop-paris.fr (A. de Gramont).

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of which a lower dose intensity of oxaliplatin was administered) suggested that the dose intensity of oxaliplatin could be critical in the combination of oxaliplatin with 5-FU [11]. The toxicity profile of all the FOLFOX regimens was also similar, with two limiting toxicities: grade 3/4 neutropenia (FOLFOX2, 39%; FOLFOX3, 15 and 20% (two studies); FOLFOX4, 37%; FOLFOX6, 24%) and specific grade 2/3 sensory neuropathy (FOLFOX2, 29%; FOLFOX3, 13 and 27%; FOLFOX4, 16%; FOLFOX6, 16%). These results led us to undertake this study of oxaliplatin at a high-dose intensity, with a cessation of treatment after eight cycles in order to limit the neurosensory toxicity, and a lower dose of 5-FU to decrease the haematological toxicity. In the regimen reported here, (FOLFOX7), oxaliplatin (130 mg/m^2) was added to the new, simplified, bimonthly regimen of high-dose LV followed by bolus and 46-h continuous infusion of 5-FU every 2 weeks (Fig. 1).

2. Patients and methods

2.1. Inclusion criteria

Eligibility criteria were: histologically proven adenocarcinoma of the colon or rectum, progression while being treated with a bimonthly LV–5-FU regimen, bidimensionally measurable lesions, no central nervous system metastases, no exclusive bone metastases, no second malignancy other than adequately treated *in situ* carcinoma of the cervix or non-melanoma skin cancer, life expectancy of at least 3 months, age greater than 18 years and less than 80 years, World Health Organization (WHO) performance status 0–2, metastases outside the irradiation field in patients who had received prior radiation therapy, initial evaluation at or less than 2 weeks before inclusion, neutrophil count greater than 1500×10^6/l, platelet count greater than 100×10^9/L, alkaline phosphatase less than 3 times the upper limit of the normal value, serum creatinine less than 300 μmol/l.

Patients were divided into two groups. Group A (refractory) included patients who had documented progressive disease (PD) while treated with the simplified LV–5-FU regimen. In this group, oxaliplatin was added to the same LV–5-FU regimen. Group B (resistant) included patients who had documented PD while treated with other bimonthly LV–5FU regimens than simplified LV–5-FU (LV–5-FU2 or FOLFUHD). Written informed consent was obtained from all the patients.

2.2. Chemotherapy

The FOLFOX7 regimen (Fig. 1) consisted of oxaliplatin (130 mg/m^2) as a 2-h infusion during the 2-h infusion of LV (DL-racemic mixure 400 mg/m^2), without mixing, followed by 5-FU bolus (400 mg/m^2 on day 1) and a 46-h infusion of 2400 mg/m^2. Cycle 2 was administered at week 3; doses were adjusted according to the haematological nadir and the toxicity of cycle 1. If haematological toxicity was 3 or more according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), the 5-FU bolus was omitted, the 5-FU infusion dose was lowered from 2400 to 2000 mg/m^2, and the oxaliplatin dose was decreased to 100 mg/m^2. Subsequent cycles were repeated at 2-week intervals for all patients. Disposable pumps were used for outpatient therapy. When NCI-CTC neurosensory toxicity of grade 2 or greater persisted between cycles, with pain or functional impairment, oxaliplatin was discontinued. Patients who responded or were stable received eight cycles. Patients were then evaluated every 2 months and FOLFOX7 could be resumed in the responders if progression occurred and neurotoxicity was grade 1 or less.

2.3. Study parameters

Physical examination and complete blood counts were performed at each cycle. Assays for carcinoembryonic antigen (CEA), alkaline phosphatase, and lactate dehydrogenase (LDH), and computed tomography (CT) scans were repeated every four cycles, or earlier in the case of clinical deterioration. Only patients with bidimensionally measurable lesions (largest diameter 2 cm or greater) on CT scan could be evaluated for tumour response. Complete response (CR) was defined as the complete disappearance of all assessable disease for at least 4 weeks; partial response (PR) indicated a decrease of at least 50% in the sum of the products of the

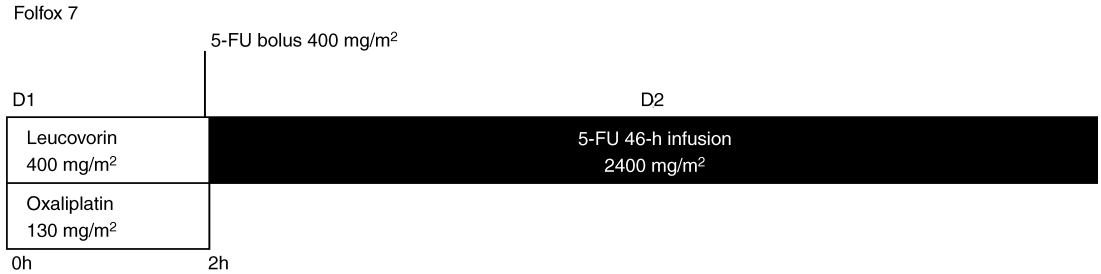

Fig. 1. FOLFOX7 regimen. Cycles were repeated every 2 weeks.

diameters of measurable lesions, for at least 4 weeks. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% in tumour size, and PD was an increase of at least 25% or the appearance of new neoplastic lesion(s). For rectal cancers, assessable metastases had to be outside the pelvis. External review of the CT-scan was not performed. Therapy was discontinued after eight cycles or when disease progressed or if neurosensory toxicity of grade 2 or greater occurred. Disappearance or attenuation of tumour-related symptoms (performance status, pain and/or fever) was assessed for patients who had these symptoms at baseline. Weight gain was defined as an increase of baseline weight greater than or equal to 2 kg. Decreased CEA concentration was considered a biological effect in patients whose CEA levels had been elevated at baseline.

2.4. Statistical considerations

Survival was calculated using the Kaplan–Meier method from the start of chemotherapy [12]; the endpoint was 1 December 1999. The response duration and progression-free survival (PFS) were calculated from the date therapy started to the date disease progression was observed.

Table 1
Patient characteristics

Characteristic	Group A *n* (%)	Group B *n* (%)	All patients *n* (%)
No. included	36 (75)	12 (25)	48 (100)
Male/female	22 (61)/14 (39)	8 (67)/4 (33)	30 (63)/18 (38)
Age (years)			
Median (Range)	67 (46–79)	63 (40–74)	66 (40–79)
Age 76–80 years	6 (17)	0 (0)	6 (13)
Primary tumour[a]			
Colon	29 (81)	9[a] (75)	38 (79)
Rectum	7 (19)	4[a] (33)	11 (23)
Site of metastases			
Liver	27 (75)	5 (42)	32 (67)
Lung	15 (42)	4 (33)	19 (40)
Peritoneum	5 (14)	4 (33)	9 (19)
Other	6 (17)	3 (25)	9 (19)
Involved sites			
1	22 (61)	9 (75)	31 (65)
$\geqslant 2$	14 (39)	3 (25)	17 (35)
WHO performance status			
0	23 (64)	7 (58)	30 (63)
1	8 (22)	4 (33)	12 (25)
2	5 (14)	1(8)	6 (13)
Tumour-related symptoms			
None	24 (67)	8 (67)	32 (67)
Present	12 (33)	4 (33)	16 (33)
Alkaline phosphatase			
Elevated <3 times normal range	9 (25)	1 (8)	10 (21)
Elevated $\geqslant$ times normal range	1 (3)	0 (0)	1 (2)
Elevated CEA			
Increased by >5 ng/ml	16 (44)	9 (75)	25 (52)
Increased by >100 ng/ml	14 (39)	0 (0)	14 (29)
Previous chemotherapy			
Bimonthly simplified LV–5-FU	36 (100)	0 (0)	36 (75)
Other bimonthly LV–5-FU (LV–5-FU2 or FOLFUHD)	0 (0)	12 (100)	12 (25)
Largest mass diameter			
<5 cm	19 (53)	12 (100)	31 (65)
$\geqslant 5$ cm	15 (42)	0 (0)	15 (31)
Not reviewed	2 (6)	0 (0)	2 (4)

WHO, World Health Organization; CEA, carcinoembryonic antigen; LV, leucovorin; 5-FU, 5-fluororacil.
[a] One double localisation.

3. Results

3.1. Patient characteristics

From 23 December 1997 to 29 March 1999, 48 patients were enrolled. Patient characteristics are shown in Table 1. 36 patients were assigned to group A and 12 to group B. 6 patients were over 75 years of age in group A.

3.2. Toxicity

The incidence of the main toxic effects per patient according to the NCI-CTC grade scale [13] is listed in Table 2. 337 cycles could be evaluated in 47 patients. One patient received only one cycle and toxicity could not be recorded. 33 patients (69%) received the eight scheduled cycles. 15 patients (31%) stopped before eight cycles, either for progression (9 patients, 19%) or toxicity (4 patients, 8%) or for personal reasons (2 patients, 4%). Neutropenia reached grade 3 in 9% of the patients, without febrile neutropenia, and was never the reason for discontinuing therapy. Neutropenia did not recur after dose reduction in the patients who experienced grade 3 neutropenia on the full 5-FU dose. Asymptomatic grade 3 thrombocytopenia developed in 5 of the evaluable patients (11%). None of them needed tranfusion.

Grade 3 sensory neuropathy occurred in 2 if the evaluable patients (4%). At the time of the analysis, functional impairment had disappeared in both of these patients 3 months after oxaliplatin withdrawal. A late grade 3 neurosensory toxicity developed in 5 other evaluable patients (11%) within 6 weeks of the end of treatment.

The other grade 3 toxicities observed were nausea in 3 of the evaluable patients (6%) (plus 1 patient with grade 4, 2%) and diarrhoea in 5 of the evaluable patients (11%). No grade 3 mucositis was observed. Laryngospasm was observed in 5 patients: oxaliplatin was reintroduced and symptoms did not recur when perfusion lasted 6 h instead of 2 h. 64% of the patients received at least 90% of the scheduled oxaliplatin dose intensity during the first four cycles and 85% a dose intensity $\geqslant 100$ mg/m^2/cycle. Overall, 20 patients (42%) had at least one cycle delayed for toxicity. At the time of this report, 8 patients resumed FOLFOX after a median time without therapy of 3 months.

Table 2
Percentage toxicities per patient (maximum NCI-CTC grade) evaluated for 337 cycles given to 47 patients

	NCI–CTC grade (%)			
Side-effect	1	2	3	4
Nausea/vomiting	36	28	6	2
Mucositis	40	2	0	0
Diarrhoea	26	26	11	0
Sensory neuropathy	70	23	4[a]	0
Hand–foot syndrome	34	6	0	0
Anaemia	32	11	2	0
Neutropenia	19	15	9	0
Thrombocytopenia	30	30	11	0
Alopecia	17	0	–	–
Maximum toxicity	9	53	32	6

NCI–CTC, National Cancer Institute–Common Toxicity Criteria.
[a] 11% of the patients developed grade 3 sensory neuropathy after completion of chemotherapy.

3.3. Objective tumour responses

The objective response rate (ORR) for all patients was 42% (95% confidence interval (CI): 28–56%) (Table 3). For group A, the ORR was 44% (95% confidence interval: 27–62%) and for group B, the ORR was 33% (95% confidence interval: 7–60%). The response rate of liver metastases was 50%. Among the 6 patients more than 75 years old, 4 had a partial response. Median response duration was 6.9 months (95% CI: 6.2–7.8 months). Stable disease was observed in 40% of patients, and progressive disease in 19% of the patients. 2 patients had curative surgery: 1 of them remained disease-free and 1 relapsed.

3.4. Palliative and biological effects

Tumour-related symptoms present at inclusion regressed or disappeared in 12 out of 16 patients (75%) who had been symptomatic at study entry. A weight increase of $\geqslant 2$ kg was observed in 4 patients (8%). Performance status improved for 6 of the 18 patients (33%) with a baseline performance status $\geqslant 1$. CEA levels decreased in 53% of the patients ($n = 25$) and the decrease was $> 50\%$ in 26% of the patients with elevated CEA levels at baseline (10 out of 39).

3.5. Survival

Survival curves are shown in Fig. 2. The median PFS was 6 months (95% CI: 5.5–6.2 months) and the median

Table 3
Objective response rates (ORR)

	Group A[a] ($n = 36$)	Group B[a] ($n = 12$)	All ($n = 48$)
	n (%)	n (%)	n (%)
Complete response	0 (0)	0 (0)	0 (0)
Partial response	16 (44)	4 (33)	20 (42)
Stable disease	13 (36)	6 (50)	19 (40)
Progressive disease	7 (19)	2 (17)	9 (19)

LV, leucovorin; 5-FU, 5-fluorouracil.
[a] Group A included patients refractory to the bimonthly, simplified LV–5-FU regimen. Group B included patients resistant to other bimonthly regimens.

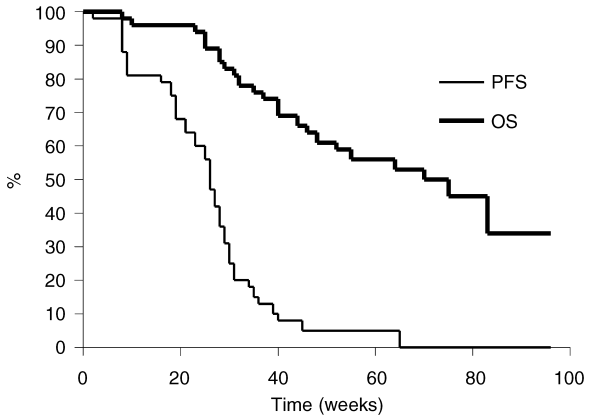

Fig. 2. Survival (OS) and progression-free survival (PFS) curves in the intention-to-treat population.

survival was 16.1 months (95% CI: 14.6–18.9 months) from the start of FOLFOX7. Group A patients had a median PFS of 6.0 months and a median survival of 17.2 months. For group B, median PFS was 5.7 months and median survival 12.6 months.

4. Discussion

Second-line metastatic therapy is a new challenge in advanced colorectal cancer. Limited responses have been achieved with 5-FU infusion, after progression on a LV–5-FU bolus treatment [14], or with further 5-FU modulation by LV [15]. Among new drugs, irinotecan prolonged the survival of patients with 5-FU-resistant colorectal cancer [16,17] and has shown a higher antitumour activity than LV–5-FU alone [18].

Oxaliplatin also improved the response rate to LV–5-FU and prolonged PFS in the treatment of advanced colorectal cancer [19,20]. The FOLFOX trials have tested the bimonthly regimens with oxaliplatin at three different doses: 85, 100 or 130 mg/m^2. The FOLFOX7 study used the simplified, bimonthly LV–5-FU regimen which combined high-dose LV, 5-FU bolus on day 1 only and high-dose 5-FU infused over 46 h with a disposable pump for outpatient therapy. This regimen was more comfortable for patients, less costly and at least as active, with lower toxicity, than the previous bimonthly regimens in which LV infusion had been repeated for 2 consecutive days [9]. An oxaliplatin dose of 130 mg/m^2 was chosen because the results obtained in previous studies suggested that there might be a dose-intensity effect on the response rate [11], while the toxicity profile of all regimens was very similar, with neutropenia and cumulative sensory neuropathy as the limiting toxicities.

The high response rate observed with FOLFOX7 again showed that the combination is active, even in the subgroup of patients resistant to regimens containing a similar combination of compounds. The overall results reproduced the FOLFOX2 results: median PFS 7 months and median survival 17 months, ORR 46% [6]. The high-dose intensity of oxaliplatin is the main explanation for these results. In a retrospective review of oxaliplatin dose intensity, 89% of the patients in the FOLFOX2 study received a dose intensity of 85 mg/m^2/2 weeks or greater for the first four cycles, as did 85% of those included in FOLFOX7. No other parameter such as age, performance status, mean age, localisation, number of metastatic sites, CEA level, increase in alkaline phosphatase, increase in LDH, 5-FU dose, or response to first-line therapy, could explain the good response rate [11]. With fewer cycles than FOLFOX2, it is notable that PFS and overall survival did not change. The high oxaliplatin dose intensity and the low rate of non-neurological toxicity, especially neutropenia, are explained by better adjustment of the 5-FU dose, which resulted in fewer delayed cycles.

Neurosensory toxicity was observed in only 4% of the patients during the study and 11% after the study. This low rate of neurosensory toxicity despite the higher dose of oxaliplatin is explained by the interruption of treatment after eight cycles. A previous study has shown the onset of grade 3 neuropathy occurred after a median time of 23 weeks of treatment with oxaliplatin, i.e. 11 cycles at 85–100 mg/m^2 [21]. Furthermore, the break in treatment could improve the quality of life for patients, and oxaliplatin could be resumed if there was progression and no residual neuropathy. We could only find two negative effects of high-dose oxaliplatin: an increased incidence of thrombocytopenia (11% grade 3/4), which might be the limiting toxicity, and of laryngospasm (11%).

Based on these results, FOLFOX7, an effective and well-tolerated regimen, is currently being compared with the FOLFOX4 regimen as first-line therapy in the OPTIMOX randomised study.

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