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A randomised phase II study of oxaliplatin alone versus oxaliplatin combined with 5-fluorouracil and folinic acid (Mayo Clinic regimen) in previously untreated metastatic colorectal cancer patients☆

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Abstract

The aim of this study was to examine the efficacy and safety of both oxaliplatin as a single agent and oxaliplatin in combination with daily×5 bolus 5-fluorouracil and folinic acid (5-FU/FA, Mayo clinic regimen) in the first-line treatment of metastatic colorectal cancer (CRC) patients. 73 advanced CRC patients were randomised to receive either oxaliplatin 85 mg/m^2 every 2 weeks (35 patients), or the same treatment combined with 5-FU 425 mg/m^2/day and FA 20 mg/m^2/day×5 days every 4 weeks (38 patients). Treatment was continued until disease progression or unacceptable toxicity. All patients had documented inoperable disease and no previous chemotherapy for advanced disease. Based on the investigators' assessment of best response, objective response rate was 9% (95% confidence interval (CI) 2–24%) in the oxaliplatin arm, and 45% (95% CI 27–64%) in the oxaliplatin + 5-FU/FA arm. Median progression-free survival (PFS) was 2 months (95% CI 1.7–2.4 months) in the oxaliplatin arm and 3.9 months (95% CI 2.9–5 months) in the oxaliplatin + 5-FU/FA arm. Severe neutropenia was seen in 23% of patients in the oxaliplatin + 5-FU/FA arm, and none in the oxaliplatin arm. There were two treatment-related deaths, both in the oxaliplatin + 5-FU/FA arm. In the oxaliplatin + 5-FU/FA arm, severe diarrhoea, vomiting and stomatitis were seen in 34, 14 and 14% of the patients, respectively. In conclusion, oxaliplatin at a dose of 85 mg/m^2 given every 2 weeks was well tolerated and has limited activity in metastatic CRC, while the combination of this treatment with the full-dose Mayo clinic regimen (5-FU bolus 425 mg/m^2/day + FA 20 mg/m^2/day×5 days every 4 weeks), although active, was unfeasible due to a high level of myelosuppression and gastrointestinal toxicity. Alternative lower dosing or other regimens are to be explored to ascertain the value of bolus 5-FU/FA combined with oxaliplatin.

Keywords: Colorectal; Chemotherapy; Oxaliplatin; Mayo Clinic regimen; Randomised

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1. Introduction

Colorectal cancer (CRC) is a major health problem, with approximately 150 000 new cases reported every year in the USA, and only approximately 50% of patients surviving beyond 5 years. Furthermore, the incidence of the disease in any region appears to be linked to its state of socio-economic development, and hence the worldwide frequency of the disease is expected to increase dramatically in the future [1]. 5-Fluorouracil (5-FU)-based regimens remain the standard chemotherapy, usually modulated with folinic acid (FA), although an optimal administration schedule has yet to be defined. 5-FU administered via continuous infusion (CIV) has shown activity and clinical benefit (improvement in symptoms) in patients progressing on or after 5-FU bolus regimens [2]. An adequate meta-analysis has elicited a statistically significant survival advantage of limited clinical relevance (1 month) for CIV when compared with bolus administration of 5-FU [3]. High-dose CIV schedules and hybrid regimens are commonly used in Europe, with consistently higher response rates and better progression and survival times than the bolus regimens. Nevertheless, it is worth bearing in mind that bolus infusion represents a reasonable and more economic treatment option, given the limited difference in therapeutic benefit expected from CIV in the first-line treatment of CRC patients [3] and the greater institutional burden of administering CIV schedules.

In the absence of consensus, the Mayo regimen (bolus 5-FU, at 425 mg/m^2 per day and low dose FA at 20 mg/m^2 per day for 5 days, given in a 28-day cycle) has become the reference in the treatment of metastatic CRC in the US. Nevertheless, concerns have been expressed about the toxicity of the Mayo regimen that is and the fact that no formal phase I trial seems to have been conducted to determine this dose level in a regimen that is recognised as having a narrow therapeutic index. In a retrospective analysis of 134 patients treated with this regimen, Tomiak and colleagues found that 35% ($\pm$8%) of patients experienced sufficient toxicity to have some kind of dose adjustment or delay, with 5 patients (4%) failing to complete their first cycle of treatment. The principal toxicity was mucositis, seen in 60% of patients, with febrile neutropenia reported in 6 patients, and implicated in at least one of the two toxic deaths [4].

Oxaliplatin (*trans-l*-diaminocyclohexane oxalatoplatinum) (DACPLAT, Searle, Argentina), is a new platinum derivative with a high level of antitumour activity. It acts by forming DNA intrastrand adducts and has been shown both *in vitro* and *in vivo* to be active against CRC cell lines and synergistic with 5-FU without complete cross-resistance [5,6].

Oxaliplatin is the first platinum compound to show activity as a single agent when used in the treatment of advanced CRC patients [7]. In two phase II studies involving patients with fluoropyrimidine-resistant advanced CRC, treated with oxaliplatin given as a single agent at 130 mg/m^2 over a 2-h infusion every 3 weeks, the objective response rates (ORR) were both 10% (95% CI: 0.04–0.16), with 24 and 40% of patients exhibiting disease stabilisation, and median overall survival times (OS) of 8.3 and 10 months [8]. In a phase II trial by Bécouarn and colleagues involving untreated CRC patients, oxaliplatin used as a single agent (130 mg/m^2/every (q) 3 weeks) produced a 27% ORR (95% confidence interval (CI) 13.8–44.1%), with a median response duration of 195 days (range 126–364+ days), median time to progression (TTP) of 127 days (range 22–364+ days), and median OS of 395 days (range 28–573+ days) [9]. Data for oxaliplatin as a single agent (or in combination with 5-FU/FA) in previously untreated CRC patients at the currently approved recommended dose of 85 mg/m^2 q 2 weeks are, to our knowledge, unavailable.

In a randomised phase III trial reported by Giacchetti and coworkers, 200 non-pretreated metastatic CRC patients were given a chronomodulated 5-FU/FA regimen either with or without the addition of oxaliplatin at 125 mg/m^2 q 3 weeks. The ORR was 53% in the oxaliplatin arm (95% CI 42–63%), and 16% in the oxaliplatin-free arm (95% CI 9–24%; $P<0.001$). The median progression-free survival (PFS) in the oxaliplatin and control arms were 8.7 months (range: 7.4–9.2) and 6.1 months (range: 4.1–7.4), respectively, and the OS was 19.4 months (range: 15.4–23.4) and 19.9 months (range: 14.0–25.7), respectively [10]. In another phase III randomised study, reported by de Gramont and colleagues and involving 420 previously untreated metastatic CRC patients, the intent to treat ORR was found to be 50% (95% CI 46.1–54.9) in the oxaliplatin-containing arm and 21.9% (95% CI: 17.9–25.9) in the control arm, with the median PFS being 9 months in the oxaliplatin arm and 6.2 months in the control and an OS of 16.2 and 14.7 months, respectively [11].

There is no fully reported experience of the combination of oxaliplatin with 5-FU/FA given according to the Mayo Clinic regimen, and it has been suggested that the combination of oxaliplatin with CIV 5-FU/FA might be better than with the bolus modality [12].

In the present multicentre phase II randomised study, we gave oxaliplatin as a single agent at 85 mg/m^2 every 2 weeks in one arm with patients in the other arm receiving the same regimen of oxaliplatin added to the Mayo regimen described above with the aim of further defining the activity and toxicity profiles of oxaliplatin given alone and in combination. To our knowledge, this is the first study to use either one of these two regimens in the treatment of CRC patients.

2. Patients and methods

2.1. Eligibility criteria

Eligibility criteria included inoperable metastatic histologically-confirmed CRC, measurable disease, defined as the presence of at least one lesion larger than 2 cm evaluated by computer tomography (CT) scan, and having received no previous chemotherapy for metastatic disease. Patients who had been exposed to pelvic radiation were eligible if there was at least one measurable lesion outside the irradiated area. Other eligibility requirements were that patients be 75 years old or less, with a life expectancy of at least 3 months, World Health Organization (WHO) performance status $\leqslant 2$, neutrophils $>2000\times10^6$/l, platelets $>100\times10^9$/l, total bilirubin $\leqslant 1.5\times$ULN (upper limit of normal laboratory values), alkaline phosphatase $\leqslant 3\times$ULN, and creatinine $<1.5\times$ULN. Patients were excluded from the study if they had received any previous chemotherapy, except for adjuvant chemotherapy administered at least 1 year prior to the development of metastatic disease. The study did not include patients with non-measurable disease only, with central nervous system metastasis, or a second neoplasm (except for non-melanoma skin cancer or properly treated *in situ* cervical cancer). All patients provided written informed consent prior to inclusion.

2.2. Treatment allocation and administration

Patients were enrolled and randomised to receive either oxaliplatin single agent or the combination oxaliplatin + 5-FU/FA (Mayo clinic regimen). Randomisation was centralised, and was stratified according to performance status (PS $\leqslant 1$ versus PS = 2), and number of metastatic sites (one metastatic site versus at least two).

Patients in the oxaliplatin arm received oxaliplatin at a dose of 85 mg/m^2 as a 2-h intravenous (i.v.) infusion q 2 weeks, and patients in the oxaliplatin + 5-FU/FA arm also received oxaliplatin at a dose of 85 mg/m^2 as a 2-h i.v. infusion q 2 weeks but combined with the 5-FU-based Mayo Clinic regimen (5-FU bolus at 425 mg/m^2/day + FA bolus 20 mg/m^2/day$\times$5 days q 4 weeks). In cases of severe (WHO Grade 3 or 4) toxicities, including haematological, digestive and skin toxicities, the next administration could either be delayed for up to 2 weeks or the dose could be reduced to 370 mg/m^2/day for 5-FU and 65 mg/m^2 for oxaliplatin. In cases of neurosensory toxicity, the oxaliplatin dose was to be reduced first to 65 mg/m^2 and then to 50 mg/m^2. In cases of acute, severe pharyngolaryngeal dysesthesia, the oxaliplatin infusion time was to be increased to 6 h in subsequent cycles. The study treatment was to be continued until documented disease progression, but could also be stopped in cases of limiting toxicity.

2.3. Evaluation

Clinical, haematological, and neurological toxicities were graded according to the WHO scale. Peripheral neurosensory toxicity was evaluated using the oxaliplatin-specific scale [13].

Response was defined according to WHO criteria [14]. Complete response (CR) was defined as the disappearance of all known disease, partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the two largest perpendicular diameters of all measurable lesions; in addition, no manifestation of new lesions or progression of any pre-existing lesions could be observed. Stable disease was defined as a decrease in total tumour size of less than 50% or a less than 25% increase in the size of one or more measurable lesions. Response was assessed at the end of every 8-week period. We report the best response which is defined as the best response recorded by the investigators, since the confirmatory radiological evidence of response after 4 weeks was not consistently available. Progression-free survival is presented according to the Kaplan–Meier method.

3. Results

3.1. Patient characteristics

From 9 December 1996 to 15 September 1998, 73 patients were enrolled and randomised in 11 institutions in Argentina, with 3 of them enrolling 46% of the patients. 35 patients were assigned to the oxaliplatin arm and 38 to the oxaliplatin + 5-FU/FA arm. 3 patients randomised to the oxaliplatin + 5-FU/FA arm did not receive treatment and these patients were not included in either the efficacy or the safety analysis. Pretreatment characteristics of the patients are presented in Table 1 according to the treatment arm.

Among the patients included in the study, 43% had synchronous metastatic disease at diagnosis. An imbalance approaching statistical significance existed between the arms, with 54% of the patients included in the oxaliplatin + 5-FU/FA arm having synchronous metastatic disease at diagnosis versus 31% in the oxaliplatin arm ($P = 0.058$).

The most common primary tumour location was the colon, accounting for 76% of patients included in the study, and there was again an imbalance between the arms, with 89% of patients in the oxaliplatin arm and 63% of those in the oxaliplatin + 5-FU/FA arm having the colon as the primary site ($P = 0.012$). 40 patients (57%) had two or more organs affected by metastatic disease.

The level of the carcinoembryonic antigen (CEA) tumour marker was known for 32 of the patients (13 in the oxaliplatin arm and 19 in the oxaliplatin + 5-FU/FA

Table 1
Patient characteristics

Demographic data	Treated patients (%)	
	Arm A: oxaliplatin ($n=35$)	Arm B: oxaliplatin + 5-FU/FA
Age (years) median (range)	61 (35–75)	60 (45–75)
Age by ranges of 10 years		
30–39	2 (6)	–
40–49	5 (14)	4 (11)
50–59	10 (29)	12 (34)
60–69	10 (29)	8 (23)
⩾70	8 (23)	11 (31)
Sex		
Male	21 (60)	23 (66)
Female	14 (40)	12 (34)
Performance Status (WHO)		
0	16 (46)	16 (46)
1	18 (51)	17 (49)
2	1 (3)	2 (6)
Primary tumour site		
Colon	31 (89)	22 (63)
Rectum	4 (11)	13 (37)
Original Astler & Coller's stage		
B1	1 (3)	2 (6)
B2	5 (14)	4 (11)
C1	5 (14)	2 (6)
C2	9 (26)	5 (14)
D	11 (31)	19 (54)
Missing data	4 (11)	3 (9)
Number of organs involved		
1	14 (40)	16 (46)
2	11 (31)	14 (40)
3	7 (20)	2 (6)
4	3 (9)	3 (9)
Organs involved		
Liver only	13 (37)	12 (34)
Liver + other	18 (51)	15 (43)
Lung only	–	3 (9)
Lymph nodes only	1 (3)	–
Other	3 (9)	5 (14)
Tumour marker CEA		
<5 ng/ml	1 (3)	–
>5–⩽10 ng/ml	2 (6)	0 (0)
>10 ng/ml	10 (29)	19 (54)
Unknown	22 (63)	16 (48)
Median (range) (ng/ml)	45 (0.6–5740)	104 (20–9000)
No. of patients with at least one tumour-related symptom	16	12

CEA, carcinoembryonic antigen; WHO, World Health Organization.

arm), and the median value of the level of this marker was higher in the oxaliplatin + 5-FU/FA arm (104 ng/ml) (range: 20–9000) than in the oxaliplatin arm (45 ng/ml) (range: 0.6–5470).

A longer median disease-free interval for the period between the last adjuvant chemotherapy and the randomisation was observed in the patients in the oxaliplatin arm (13.3 months) than those in the oxaliplatin + 5-FU/FA arm (7.3 months). This difference no doubt follows from the difference between the two arms in terms of the frequency of metastatic disease at diagnosis mentioned above.

Table 2
Assessment of best objective response according to the investigators

Best response	Oxaliplatin arm	Oxaliplatin + 5-FU/FA
Intent-to-treat	35	34
Assessable	34	31
Complete response	1	–
Partial response	2	14
Stable disease	8	6
Progressive disease	23	11
Objective response rate[a]	9%	41%
95% confidence interval	0–18%	24.5–57%

[a] Calculated on the basis of intent to treat.

3.2. Treatment exposure

A total number of 208 treatment cycles were administered, 96 to patients in the oxaliplatin arm and 112 to patients in the oxaliplatin + 5-FU/FA arm. The median number of cycles per patient in the oxaliplatin arm was two (range 1–6 cycles) and three in the oxaliplatin + 5-FU/FA arm (range 1–8 cycles).

Similar numbers of patients in both arms experienced delays $\geqslant$4 days; 15 of the 35 patients (43%) who received more than one cycle of treatment in the oxaliplatin arm, and 18 of the 35 patients (51%) who received more than one cycle of treatment in the oxaliplatin + 5-FU/FA arm. Nevertheless, in the combination treatment arm, there was a significant difference in the number of dose delays occurring in the second part of the 4-week cycle (days 15–28), which represents the administration of oxaliplatin alone following the administration of the combination in the oxaliplatin + 5-FU/FA arm. Thus, while there were a total of 18 delays in the 151 administrations (12%) of the single agent in the oxaliplatin arm, 22 out of the 104 oxaliplatin single-agent administrations (21%) in the oxaliplatin + 5-FU/FA arm were delayed ($P = 0.05$).

3.3. Response and efficacy

Out of the initial 70 patients that were treated, 1 in the combination arm was deemed not to be eligible for assessment of efficacy due to unconfirmed metastatic disease, while 4 patients died before cycle 2 (1 patient in the oxaliplatin arm and 3 patients in the oxaliplatin + 5-FU/FA arm). Patients who died before cycle 2 were retained for the intent-to-treat analysis. The analysis of antitumour activity was based on patients' best objective responses. Thus, 14 patients in the oxaliplatin + 5-FU/FA arm and 3 patients in the oxaliplatin arm achieved an objective response, giving an objective response rate of 41% (95% confidence interval (CI) 24.5–57.5%) in the oxaliplatin + 5-FU/FA arm, and 9% (95% CI 0–18.5%) in the oxaliplatin arm. Details of the responses in both arms are presented in Table 2.

The median follow-up was 19 months (range 9–30 months). The median PFS in the oxaliplatin arm was 2 months (95% CI 1.7–2.4 months), and the median PFS in the oxaliplatin + 5-FU/FA arm was 3.9 months (95% CI 2.9–5 months). The Kaplan–Meier curves for PFS are presented in Fig. 1.

Table 3
Severe (WHO Grade 3–4) toxicity by patient and cycle

	Oxaliplatin arm		Oxaliplatin + 5-FU/FA	
	% of patients ($n = 35$)	% of cycles ($n = 96$)	% of patients ($n = 35$)	% of cycles ($n = 112$)
Haematological				
Anaemia	6	4	6	3
Leucopenia	–	–	14	6
Neutropenia	–	–	23	8
Thrombocytopenia	–	–	6	2
Gastrointestinal				
Nausea	3	1	14	4
Vomiting	–	–	14	5
Diarrhoea	–	–	34	16
Stomatitis	–	–	14	4
Neurotoxicity[a]				
Paresthaesia with pain	3	1	3	1
Paresthaesia with functional impairment	3	1	6	2

WHO, World Health Organization.
[a] Assessed according to an oxaliplatin-specific scale [13].

3.4. Safety

Table 3 summarises the incidence and severity of non-neurological and neurological adverse events according to patient and cycle. Grade 3–4 neutropenia affected 23% of patients in the oxaliplatin + 5-FU/FA arm, while no Grade 3–4 neutropenia was observed in the oxaliplatin arm ($P < 0.01$). 2 patients in the oxaliplatin + 5-FU/FA arm (6%) presented Grade 4 thrombocytopenia each in only one cycle, while only mild thrombocytopenia was observed in the oxaliplatin arm.

All severe (Grade 3–4) gastrointestinal toxicities were observed in the oxaliplatin + 5-FU/FA arm, except for one cycle of Grade 3 nausea in the oxaliplatin arm, which supports the relationship between this toxicity

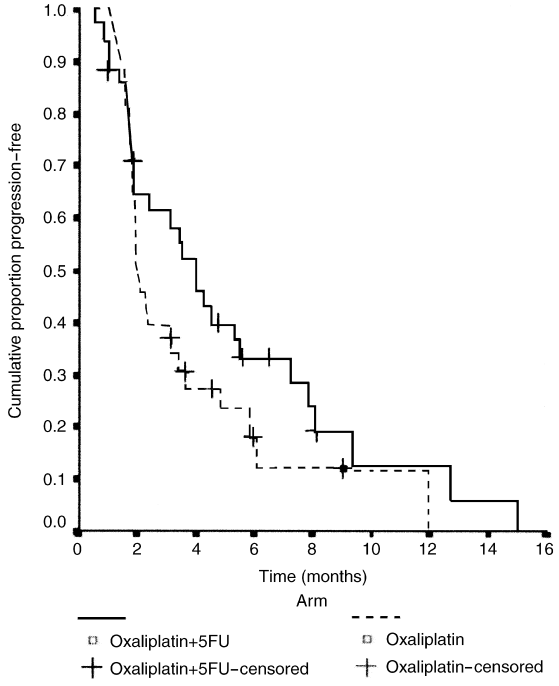

Fig. 1. Kaplan–Meier curve of progression-free survival by treatment arm.

Table 4
Occurrence of severe toxicities in oxaliplatin + 5-FU/FA arm according to treatment period

	NCI–CTC Grade 3			NCI-CTC grade 4		
	All 14-day periods $n = 206$	Days 1–14	Days 15–28[b]	All 14-day periods $n = 206$	Days 1–14[a]	Days 15–28[b]
Haematological						
Neutropenia	6	5	1	3	2	1
Gastrointestinal						
Vomiting	4	3	1	2	1	1
Diarrhoea	15	11	4	4	3	1
Stomatitis	8	5	3	–		

NCI-CTC, National Cancer Institute–Common Toxicity Criteria.
[a] Days 1–14, oxaliplatin administered with 5-FU and FA.
[b] Days 15–28, oxaliplatin administered alone.

and the administration of bolus 5-FU/FA. Diarrhoea was the most frequent severe non-haematological toxicity, reported in 34% patients and 16% of cycles in the oxaliplatin + 5-FU/FA arm, and not seen in the oxaliplatin arm. Likewise, severe vomiting and stomatitis, were each seen in 14% of patients in the oxaliplatin + 5-FU/FA arm. 2 patients in the oxaliplatin + 5-FU/FA arm (6%) and 1 in the oxaliplatin arm (3%) reported experiencing paraesthesia with functional impairment, a characteristic toxicity seen with oxaliplatin [13]. When the 28-day cycle of oxaliplatin + 5-FU/FA is divided into two halves, a first half where the full combination is administered (days 1–14) and the second where oxaliplatin is administered alone, and the severe toxicities are analysed separately in the two halves, the frequency of all severe toxicities (other than neurotoxicity) was consistently higher in the first half of the treatment cycle, suggesting that they resulted from the combination of drugs rather than oxaliplatin alone (Table 4).

6 patients, all in the oxaliplatin + 5-FU/FA arm, experienced diarrhoea or stomatitis (Grades 2–4) concomitant with a haematological toxicity (neutropenia or thrombocytopenia, Grades 2–4), a potentially dangerous, although usually manageable, combination of side-effects. 3 of these patients received no further treatment after the occurrence of these concomitant toxicities, 2 due to the investigators' assessment of disease progression. 5 treated patients died during the study, four before cycle 2. Two deaths were considered related to the study treatment, both occurring in the oxaliplatin + 5-FU/FA arm: 1 patient died after a general deterioration in her condition, related to severe gastrointestinal toxicity and disease progression, and the other died with severe biochemical abnormalities, also related to gastrointestinal toxicity and dehydration.

4. Discussion

The per protocol analysis of the best response, as determined by the investigators, gave an ORR of 9% (95% CI 2–24%) in the oxaliplatin arm and 45% (95% CI 27–64%) in the oxaliplatin + 5-FU/FA arm, similar to the ORR given in other reports of studies using oxaliplatin + FU ± FA in the first-line treatment of CRC patients. Furthermore, it should be noted that there were some imbalances between the two treatment arms, with more patients allocated to the oxaliplatin + 5-FU/FA arm being diagnosed with rectal cancer and having stage D disease at diagnosis (Table 1).

With a median follow-up of 19 months (range 9–30 months), the median PFS was 2 months (95% CI 1.7–2.4 months) in the oxaliplatin arm and 3.9 months (95% CI 2.9–5) in the oxaliplatin + 5-FU/FA arm. Of note, the time to progression in the combination arm is well below those usually reported for oxaliplatin + 5-FU combinations [10]. It should be noted that the median number of cycles administered was low; two in the oxaliplatin arm and three in the oxaliplatin + 5-FU/FA arm. 49 out of 70 patients treated (70%) were withdrawn from the study due to the investigators' clinical determination of progressive disease; although 9 out of these 49 (18%) patients were considered to have stable disease by the external expert committee. This evidence suggests that investigators may have prematurely assessed patients as having progressive disease, perhaps due to the toxicities encountered. The perception of the poor tolerance of the combination treatment might also have influenced the assessment of its efficacy, with investigators failing to confirm objective responses or evaluating stable disease as disease progression.

The safety results showed a high overall incidence of haematological and gastrointestinal toxicity, such as neutropenia, diarrhoea, stomatitis and vomiting in the oxaliplatin + 5-FU/FA arm, with, for example, 23% of patients experiencing Grade 3–4 neutropenia. These high levels of myelosuppression and digestive toxicity suggest that the study treatment combination of oxaliplatin with the full-dose Mayo clinic regimen arm is unfeasible. Nevertheless, the problem may well exist with the Mayo clinic regimen itself, which has been associated with elevated toxicity. When the South-West

Oncology Group (SWOG) organised a screening trial of seven 5-FU regimens to assess efficacy and toxicity, they found that severe toxicities occurred most frequently in the 5-FU bolus arm [15]. A randomised trial conducted by de Gramont and colleagues compared the full-dose Mayo clinic regimen versus bimonthly bolus and continuous-infusion 5-FU plus high-dose FA, and showed that the patients receiving the Mayo clinic regimen experienced severe neutropenia, diarrhoea, and mucositis more frequently, confirming its high toxic profile [16]. Table 5 shows the rates of severe toxicities reported in randomised trials that used a variety of 5-FU + FA regimens alone, or combined with oxaliplatin, including the present trial. When the toxicities of the three combinations of oxaliplatin + 5-FU/FA are compared, the combination in the present study shows the highest rate of mucositis, and the rates of vomiting and diarrhoea in the present study are close to those seen when oxaliplatin was added to a triweekly chronomodulated 5-FU/FA regimen [10].

Although the differences in the rates of toxicity for similar regimens might be partially due to differences in assessment methodology or grading systems, the toxicity reported depends on the 5-FU delivery modality, with continuous infusion being less haematotoxic but having a higher rate of hand–foot syndrome and diarrhoea than bolus administration [17,18]. Nevertheless, it is of note that although several high-dose continuous infusion 5-FU-based regimens have been studied in combination with oxaliplatin, customary prescription patterns, as well as financial and practical issues constrain the feasibility of continuous infusion treatments in many countries, including, and foremost, in the United States. Moreover, continuous infusion has been shown to have only a modest impact in terms of extending survival [3]. Thus, the pharmacodynamic profile of the oxaliplatin + 5-FU/FA combination may be optimised by CIV administration of 5-FU/FA. The present study was a formal attempt to explore the more widespread bolus delivery modality, which could then provide a basis for the controlled investigation of any differences between the modes of delivery.

In light of the poor tolerance seen when the oxaliplatin is added to the full-dose Mayo Clinic regimen, it is worth reconsidering the use of the weekly bolus administration of 5-FU (500 mg/m^2 weekly) with FA to combine with the fortnightly or triweekly administration of oxaliplatin [16]. A recent report with weekly bolus 5-FU

Table 5
Randomised trials with 5-fluorouracil (5-FU) and folinic acid (FA)

Study [Ref.]	Regimen doses (mg/m^2)	Toxicity						
		No. of patients	Neutropenia (%)	Thrombocytopenia (%)	Vomiting (%)	Diarrhoea (%)	Mucositis (%)	Toxic death (%)
Buroker [16] (NCCTG)	5-FU 425 (BS) + LV 20 (BS) ×5 days q 4 w[a]	183	29	3	8	18	24	3
	5-FU 600 (BS) + LV 500 (BS) weekly (6/8 weeks)	179	5	1	5	32	2	1
Leichman [15] (SWOG)	5-FU 425 (BS) + LV 20 (BS) ×5 days q 4 w[a]	85	47	2	6	12	14	2
De Gramont [20]	5-FU 425 (BS) + LV (BS) 20 ×5 days q 4 w	216	7	<1	3[b]	7	13	<1
	5-FU (400 (BS) and 600 (CI)] + LV 200 (BS)×2 days q 2 w	217	2	1	4	3	2	0
Giachetti [10]	5-FU 700 (CM) + FA 300 (CM) ×5 days q 3 w	100	<2	<2	2	5	4	1
De Gramont [11]	5-FU (400 (BS) and 600 (CI)) + LV 200 (BS)×2 days q 2 w	210	5	<1	2	5	1	NR
Randomised trials involving the addition of oxaliplatin to a 5-FU/FA regimen								
Giachetti [10]	5-FU 700 (CM) + FA 300 (CM) ×5 days q 3 w + oxaliplatin 125 (CI) q 3 w	100	2	1	25	43	10	1
De Gramont [11]	5-FU (400 (BS) and 600 (CI)) + LV 200 (BS)×2 days q 2 w + oxaliplatin 85 (CI) q 2 w	210	42	2	6	12	6	NR
ROC 95 (present study)	5-FU 425 (BS) + FA 20 (BS) ×5 days q 4 w + oxaliplatin 85 (CI) q 2 w	35	23	6	14	34	14	6

5-FU, 5-fluorouracil; LV, leucovorin; FA, folinic acid; BS, intravenous bolus; CI, intravenous continuous infusion; CM, intravenous, chronomodulated infusion; w, week; NR, not reported; q, every, SWOG, South-West Oncology Group.

[a] q 5 w after the first two administrations.

[b] Only nausea was reported.

and low-dose leucovorin combined with bimonthly oxaliplatin shows this regimen to be feasible and active [19]. In effect, the toxicity and morbidity associated with the Mayo clinic regimen has led to the increased use of continuous infusional regimens [20] and weekly bolus 5-FU/FA regimens have been chosen for combination with other new agents [21–23].

We conclude that the administration of fortnightly oxaliplatin at the dose of 85 mg/m^2 as a 2-h i.v. infusion is safe and well tolerated. Antitumour activity in previously untreated advanced CRC patients as judged by the assessment of patients' best responses was in the range of the activity reported in previous studies with single-agent oxaliplatin. However, the combination of fortnightly oxaliplatin with the full-dose Mayo clinic regimen is not feasible due to poor tolerance and enhanced 5-FU-related toxicity, limiting treatment compliance.

In the light of the present study, the further assessment of a different regimes combining oxaliplatin with a bolus 5-FU/FA administration, such as weekly 5-FU, at reduced doses over 5 days, or a shortened administration (3 or 4 days instead of 5), combined with the fortnightly administration of oxaliplatin (probably still at 85 mg/m^2) should be considered among the viable possibilities left to explore.

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