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Oxaliplatin plus irinotecan and leucovorin-modulated 5-fluorouracil triplet regimen every other week: a dose-finding study in patients with advanced gastrointestinal malignancies

P. Comella[1]*, R. Casaretti[1], V. De Rosa[3], A. Avallone[1], F. Izzo[2], F. Fiore[3], L. Lapenta[4] & G. Comella[1]

[1]Division of Medical Oncology A, [2]Division of Surgical Oncology C, [3]Service of Radiology, [4]Service of Nuclear Medicine, National Tumour Institute, Naples, Italy

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Background: Oxaliplatin (OXA) and irinotecan (IRI) are active drugs in first-line as well as second-line treatment of advanced colorectal cancer patients, their toxicity profiles are not overlapping, and both drugs have shown synergism with folinic acid-modulated 5-fluorouracil (5-FU). We planned this phase I study to define the dose-limiting toxicities (DLTs), the maximum tolerated doses (MTDs), and the recommended doses (RDs) for a triplet regimen including OXA plus IRI on day 1, and 6S-folinic acid (LFA) plus 5-FU on day 2, every 2 weeks.

Patients and methods: At least three patients had to be treated at each dose level, and the trial proceeded if no more than 33% of patients showed a DLT after the first cycle. Starting from OXA 85 mg/m^2 (over 2 h) and IRI 150 mg/m^2 (over 1 h), an alternated escalation was planned up to 110 mg/m^2 and 200 mg/m^2, respectively. Thereafter, a fixed dose of LFA, 250 mg/m^2 (as 2-h infusion), plus an escalating dose of 5-FU (from 650 to 800 mg/m^2 as an intravenous bolus) was added on day 2 to the previous dose level of OXA and IRI.

Results: Forty-six patients, all but four affected by advanced colorectal primaries, entered this study. The MTDs for OXA and IRI given on the same day were 110 and 200 mg/m^2: these doses caused a DLT in three of six patients. The previous dose level (110 and 175 mg/m^2, respectively) on day 1 was safely followed on day 2 by LFA plus 5-FU up to 800 mg/m^2. Indeed, only one of three patients treated at this last level had a DLT. This cohort was then expanded including a total of 14 patients, and on the whole series five cases of DLT occurred: WHO grade 4 neutropenia (two patients), grade 3 or 4 diarrhoea (three patients). Cumulative toxicity was analysed in 43 patients for a total of 347 cycles: grade 4 neutropenia was detected in 13 patients (30%); it was not dose-related, nor was it exacerbated by the addition of modulated 5-FU. Febrile neutropenia occurred in four patients. Grade 3 or 4 diarrhoea was suffered by nine (21%) and five (12%) patients, respectively. Two complete and nine partial responses were reported on 40 evaluable patients (six patients were disease-free at study entry), giving a response rate of 27.5% (95% confidence interval 15% to 44%); nine of 18 (50%) assessable patients of the two last cohorts treated with the triplet regimen achieved a complete response (two patients) or a partial response (seven patients).

Conclusions: The RDs for this biweekly regimen were: OXA 110 mg/m^2 plus IRI 175 mg/m^2 on day 1, and LFA 250 mg/m^2 plus 5-FU 800 mg/m^2 on day 2. This regimen appeared active in pretreated gastrointestinal malignancies, and it is worthy of being evaluated in advanced colorectal carcinoma after failure of 5-FU-based adjuvant or palliative treatment.

Key words: biweekly regimen, colorectal carcinoma, 5-fluorouracil, irinotecan, oxaliplatin, triplet regimen

**Correspondence to:* Dr P. Comella, Division of Medical Oncology A, National Tumour Institute, Via M. Semmola, 80131 Naples, Italy. Tel: +39-081-5903227; Fax: +39-081-5903821; E-mail: pcomella@sirio-oncology.it

Introduction

In the last few years, the options of treatment for patients affected by advanced colorectal cancer have considerably increased. Indeed, besides 5-fluorouracil (5-FU), which still remains a cornerstone for the management of these patients [1], novel drugs have recently shown appreciable growth inhibitory effects in this disease.

Oxaliplatin (OXA) has been extensively evaluated in colorectal cancer [2–10]. Although it has a demonstrated activity as a single agent [3, 4], OXA has been usually combined with leucovorin-modulated 5-FU [5]. Initial studies were carried out using both cytotoxic drugs in a 5-day chronomodulated infusion [6, 7]. However, comparable results were subsequently reported with OXA administered as a short infusion before a 5-day chronomodulated [8], or a 2-day flat infusion of 5-FU [9, 10]. In a randomised trial, this biweekly regimen was compared with the same 5-FU infusion without OXA: a significantly greater response rate, and a significantly longer time to progression, were reported for the combination arm [10].

Irinotecan (IRI) has also demonstrated a significant activity in colorectal cancer patients [10–16]. In first-line use, IRI alone was proven as effective as the standard leucovorin-modulated 5-FU monthly regimen [14]. Moreover, the addition of IRI to leucovorin-modulated 5-FU has been compared with modulated 5-FU in three randomised studies. All these studies reported a significantly greater response rate, and a significantly longer time to progression, for the combination arm [14–16]. Two of these trials also demonstrated a substantial survival gain by the addition of IRI [14, 15].

Therefore, for patients unexposed to 5-FU, or showing a late recurrence after previous 5-FU-based treatment, both doublets of either OXA or IRI combined with modulated 5-FU may be considered as suitable options, capable of improving the response rate and prolonging the time to progression in comparison with 5-FU alone. The choice between these two regimens depends more on considerations about their tolerability than on substantial differences in antitumour activity. In addition, a cross-over design at the time of first progression may represent a new strategy of management, which has been claimed to obtain an unprecedented median survival time in excess of 20 months [17].

On the contrary, the treatment options are much less effective for patients already exposed to 5-FU-based treatment showing an early relapse or progression. Both OXA and IRI have been employed in these refractory patients with only moderate benefit on survival [4, 9, 12, 13]. In detail, IRI as second-line treatment has been compared with a 5-FU infusional regimen or with best supportive care alone in two randomised trials, giving a median survival time of 9.8–10.8 months [12, 13]. As for OXA, it has usually been assessed in addition to leucovorin-modulated high-dose 5-FU infusion. Indeed, in a large series of patients progressing on bimonthly leucovorin–fluorouracil regimens, the addition of OXA to the same regimen produced a 10.8 months median survival time [9].

Another possible approach to overcome 5-FU resistance may be represented by the combination of OXA and IRI, with or without 5-FU, in consideration of their different target sites and non-overlapping toxicities. However, for the time being there is still uncertainty about the optimal schedule of this combination in cancer patients. Indeed, from a pooled analysis of two identical phase I studies, the recommended doses (RDs) for an every-3-week cycle were OXA 85 mg/m^2 and IRI 200 mg/m^2 [18]. On the other hand, Goldwasser et al. [19] have suggested OXA 85 mg/m^2 plus IRI 175 mg/m^2 in a biweekly cycle. Other investigators evaluated a different schedule, in which IRI was given on days 1, 8 and 15, and OXA on day 1 and 15, recycling every 4 weeks. These authors recommended OXA 85 mg/m^2 and IRI 80 mg/m^2 suggesting also the prophylactic use of granulocyte colony-stimulating factor (G-CSF) to avoid excessive neutropenia [20]. Moreover, US investigators have recommended a dose of 60 mg/m^2 for both drugs weekly for 4 consecutive weeks followed by 2 weeks of rest [21].

Many preclinical studies have tried to elucidate the interaction between OXA, IRI and 5-FU. Experiments on HT29 human colon cancer cell line have demonstrated a better growth inhibitory effect when OXA shortly preceded the exposure to SN-38 (the active metabolite of IRI) [22]. On the other hand, other authors have assessed the effect of SN38 and 5-FU exposures on several colon cancer cell lines, either sensitive (SNU-C4) or resistant (SW620 and HT29) to 5-FU. They reported that the sequential (with SN38 preceding 5-FU) rather than the simultaneous exposure produced a synergistic or at least an additive effect in all cell lines [23]. This schedule-dependent interaction was also confirmed in animal models, in which a much greater tumour regression was achieved when IRI preceded 5-FU [24]. A similar schedule-dependent interaction has been observed for OXA followed by 5-FU, which was more synergic than the reverse sequence in HT29 and LoVo colon cancer cell lines, either sensitive or resistant to 5-FU [25]. In addition, *in vitro* experiments on colon cancer cell lines have demonstrated that the OXA plus 5-FU combination is more cytotoxic when 5-FU is given as a short rather than prolonged exposure [26]

All these considerations prompted us to assess a novel triplet regimen, in which all these drugs are administered in close sequence in a 2-day schedule every 2 weeks. The aim of this study was to define the dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of this regimen, and to have preliminary evidence of its activity when used at the RD in pretreated colorectal cancer patients.

Patients and methods

Patient selection

Patients with histologically proven recurrent or metastatic carcinoma of the gastrointestinal tract were candidates for this study. All patients should have received at least one 5-FU-based regimen. Other eligibility criteria were: age between 18 and 75 years; performance status (PS) <2 on the Eastern Cooperative Oncology Group scale; life expectancy >3 months; discontinuation of any previous chemotherapy for at least 1 month; normal bone marrow reserve, with absolute neutrophil count (ANC) ≥2000/μl, and platelet (PLT) count ≥100 000/μl; and adequate hepatic (bilirubin serum level <1.5 mg/dl; aspartate aminotransferase and alanine aminotransferase <2 × upper normal limit), and renal function (creatinine clearance >60 ml/min). The study protocol was approved by the Independent Ethical Committee of the National Tumour Institute of Naples. All patients were informed of the investigational nature of this study, and each patient provided written consent before registration.

Study design

At least three patients were entered in each dose level. If one out of three patients experienced a DLT, three additional patients were enrolled at the same dose level. Doses of chemotherapy were assigned at registration, and no intrapatient dose escalation was permitted. The dose escalation was stopped if more than two out of three or four out of six patients experienced a DLT. This dose level was considered as the MTD, and the preceding dose level was identified as the RD for phase II study. DLT was defined as follows: ANC <500/μl lasting 7 days or more, or ANC <100/μl lasting 3 days or more; fever >38°C associated with neutropenia; PLT count <25 000/μl, or PLT count <50 000/μl with bleeding; any WHO grade ≥3 non-haematological toxicity (except for alopecia and vomiting); or a delay of more than 2 weeks in treatment recycling.

Dose-escalation plan

We assessed first the combination of OXA and IRI given on the same day, recycling every 2 weeks. The starting doses of OXA and IRI were 85 and 150 mg/m^2, respectively. Through four dose levels, we alternately increased OXA to 110 mg/m^2 and IRI to 200 mg/m^2. Thereafter, the previous dose level (OXA 110 mg/m^2 plus IRI 175 mg/m^2) was followed on day 2 by a fixed dose of 6S-folinic acid (LFA) 250 mg/m^2 plus 5-FU 650 mg/m^2. In the last cohort of patients, 5-FU dosage was further increased to 800 mg/m^2.

Administration of treatment

OXA was administered intravenously (i.v.) over at least 2 h. IRI was given after OXA i.v. over 1 h. LFA was administered i.v. over 2 h. 5-FU was given as an i.v. bolus at the end of LFA infusion. Patients received a standard antiemetic premedication, including 5-hydroxytryptamine type 3 receptor antagonists and steroids, on the first day of each cycle. Systematic prophylaxis for early cholinergic symptoms due to IRI was not performed. Similarly, no prophylaxis was given for late diarrhoea. However, patients were carefully instructed to take loperamide orally as soon as the first stool modification occurred. G-CSFs were not permitted except in the case of febrile neutropenia.

Recycling rules and dose reduction

Courses were repeated every 2 weeks in the presence of ANC ≥1500/μl and PLT count ≥100 000/μl, and recovery of any extra-haematological toxicity. Otherwise, treatment was postponed for 1 or 2 weeks until recovery. If recovery required more than 2 weeks, the patient went off study. In the presence of WHO grade 4 haematological toxicity, or in the presence of grade ≥3 non-haematological toxicity, the subsequent cycles were administered, after recovery of side-effects, with a 25% dose reduction of all cytotoxic drugs. In cases of grade 3 neurotoxicity according to the Lévi scale [7], OXA was reduced by 25%; if there was no recovery at the time of recycling after this dose reduction, treatment was discontinued.

Evaluation of toxicity

For the assessment of acute haematological toxicity, blood cell counts were performed weekly, and twice a week in cases of grade 4 toxicity. Biochemistry was performed at each cycle. Patients were checked to detect any sign of neurotoxicity at initial treatment, and at every cycle thereafter. The acute toxicity was classified according to WHO toxicity criteria [27]. Neurological toxicity was graded according to a specific scale [7].

Evaluation of activity

Initial staging work-up included history and physical examination, routine biochemistry, blood cell count, carcinoembryonic antigen serum level determination, chest X-ray and abdominal ultrasound scan. Bidimensionally measurable indicator lesion(s) were assessed by computed tomography scan or magnetic nuclear resonance imaging. Subjective symptoms, body weight, physical examination and PS were recorded before each treatment cycle. All abnormal tests were repeated after every four cycles. Responses were classified according to standard WHO criteria [27]. To classify for response, the reduction of tumour burden should be confirmed 2 months apart.

Results

Patient characteristics

Between January 2000 and October 2001, 46 patients entered this trial (Table 1). All but four patients had a diagnosis of a colorectal carcinoma, while two patients were affected by gastric carcinoma, one patient had a gall bladder carcinoma, and one was affected by pseudomyxoma peritonei. On the basis of the previous exposure to chemotherapy, 18 patients (39%) were defined as chemosensitive, because they were relapsing later than 6 months from the ending of adjuvant chemotherapy (nine cases), or had achieved a major response with previous palliative chemotherapy, and/or the time to tumour progression had been longer than 6 months (nine cases); 15 patients (33%) were considered chemoresistant, because they had a recurrence within 6 months from the discontinuation of adjuvant chemotherapy (four cases), or the time to tumour progression had been shorter than 6 months (11 cases), while 13 patients (28%) were classified as chemorefractory, because of recurrence or progression of disease during adjuvant (two cases) or palliative chemotherapy (11 cases). In addition, five patients had already received an OXA-based regimen, three patients an IRI-containing regimen, and two patients other multidrug regimens. Six patients were entered in this study disease-free after surgical resection of liver metastases.

Table 1. Patients' main characteristics

Characteristics	No.	Per cent
Eligible patients	46	100
Males	22	48
Females	24	52
Median age in years (range)	56 (37–74)	–
ECOG PS		
0	25	54
1	20	44
2	1	2
Previous adjuvant chemotherapy	19	41
Previous palliative chemotherapy	35	78
Chemosensitivity		
Sensitive	18	39
Resistant	15	33
Refractory	13	28
No. of disease sites		
0	6	13
1	17	37
2	17	37
≥3	6	13
Involved sites		
Liver	23	50
Lung	13	28
Lymph nodes	12	26
Peritoneum	9	20
Unresected primary	9	20
Pelvic relapse	3	7
CEA >5 ng/ml	34	77[a]
Mean value (range)	136 (0.7–1410)	–

[a]No available basal value in one patient.
CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status.

Dose-escalation findings

The number of patients entered in each dose level, and the number and the type of DLTs encountered, are reported in Table 2. Alternated dose escalation safely proceeded through the first three dose levels. Indeed, at the initial dose level (OXA 85 mg/m^2 plus IRI 150 mg/m^2) diarrhoea affected two of six patients after the first course. Due to rapid case accrual, eight patients entered into the second dose level (OXA 85 mg/m^2 plus IRI 175 mg/m^2), but only one suffered from severe diarrhoea after the first cycle. In the next cohort, one of six patients treated with an increased dose of OXA (110 mg/m^2) had a neutropenic fever after the first cycle. The further increase of IRI dosage to 200 mg/m^2 caused in three of six patients a severe diarrhoea, which was associated with severe vomiting in two patients, and with severe bone marrow suppression in one patient. Therefore, this dose level was identified as the MTD for the doublet combination. Six subsequent patients were treated with the previous dose level of OXA and IRI, adding LFA (250 mg/m^2) plus a starting dose of 5-FU (650 mg/m^2) on day 2. This regimen produced severe diarrhoea and vomiting in two patients, requiring hospitalisation for rehydration in one. This patient went off study, while the other patient remained on treatment with reduced dosages of all three cytotoxic drugs. In the next step, an increased dose of 5-FU (800 mg/m^2) was assessed. Only two of the first six treated patients suffered from DLT, which was severe diarrhoea in one case, and grade 4 neutropenia in the other. Because at this step active doses of all cytotoxic drugs had already been reached, we decided to stop the dose escalation, and to expand the last cohort with the enrolment of eight further patients. Among these last patients, three DLTs occurred: two cases of severe diarrhoea, and one case of grade 4 neutropenia. Therefore, we concluded that this last dose level should be considered as the RD for further study.

Cumulative toxicity

A total of 347 cycles were administered, with a median of eight (range 1–12) courses per patient. One fatality occurred in a patient recruited in the first dose level. This 50-year-old male, affected by a pelvic relapse and multiple lung metastases from rectal carcinoma, after the second course of OXA plus IRI had a transient intestinal occlusion that required hospitalisation. He was discharged after recovery of bowel function, but he subsequently suffered at home from severe diarrhoea complicated by dehydration, and he eventually died of cardiac failure. Table 3 reports the main adverse events registered during treatment, according to the dose level tested. Neutropenia affected 41 patients (89%). In detail, grade 3 neutropenia was detected in 17 patients (38%), and grade 4 neutropenia in 14 patients (30%). This side-effect did not seem dose-related, because it occurred from the initial dose level, nor did it appear to be exacerbated by the addition of modulated 5-FU. Of course this observation should be considered with caution, given the small number of patients treated at each dose level. Anyway, neutropenia was usually short-lasting and rarely complicated; indeed, neutropenic fever or infections during treatment affected only four patients. Other haematological toxicities were mild: anaemia was detected in 11 patients (24%), but it was of grade 3 in only one. Seven patients (15%) were affected by thrombocytopenia: among these, three patients had a grade 3, and one patient a grade 4.

As for non-haematological side-effects, diarrhoea of any grade affected 40 patients (89%): 18 (40%) of them had severe diarrhoea. This side-effect occurred from the initial dose level, and seemed not to be exacerbated by the addition of modulated 5-FU. Severe vomiting requiring further antiemetic treatment was never encountered in the three initial cohorts, it

Table 2. Results of the dose escalation

Level	OXA	IRI	LFA	5-FU	No. of patients	Dose-limiting toxicity	
						No.	Type (no. of patients)
1	85	150	0	0	6	2	Diarrhoea (2)
2	85	175	0	0	8	1	Diarrhoea (1)
3	110	175	0	0	6	1	Neutropenia (1)
4	110	200	0	0	6	3	Diarrhoea (3), neutropenia (1), thrombocytopenia (1)
3b	110	175	250	650	6	2	Diarrhoea (2)
4b	110	175	250	800	14	5	Diarrhoea (3), neutropenia (2)

5-FU, 5-fluorouracil; IRI, irinotecan; LFA, 6S-folinic acid; OXA, oxaliplatin.

Table 3. Main worst toxicities (WHO scale) reported by patients according to dose level

Dose level	No. of patients	No. of cycles	Neutropenia				Diarrhoea				Vomiting				Stomatitis				Neurological				Cholinergic			
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1	6	44	0	1	2	1	0	4	2	0	3	0	0	0	0	1	0	0	3	0	0	0	0	2	0	0
2	8	62	1	1	1	5	1	4	2	0	5	2	0	0	2	0	0	0	4	0	0	0	1	0	0	0
3	6	60	1	1	4	0	2	2	1	4	1	3	0	0	0	2	0	0	5	0	0	0	2	0	0	0
4	6	38	0	2	1	1	0	2	1	2	1	1	3	0	0	0	0	0	0	1	2	0	0	1	1	0
3b	6	42	0	1	5	0	0	3	1	1	2	1	1	1	0	1	0	0	0	1	0	0	0	1	0	0
4b	14	101	1	1	4	7	1	3	3	1	3	1	3	2	1	2	1	0	3	1	0	0	0	2	2	0

rarely appeared in the next two cohorts, while it was troublesome in the last one, affecting five of 14 patients (36%). Stomatitis was seldom complained of by patients at all dose levels. Thirty-two patients received at least eight courses, and six patients were given 12 courses of treatment, for an OXA mean cumulative dose of 1035 mg/m^2 (range 780–1224). Grade 3 peripheral neuropathy affected only one patient after three courses (OXA cumulative dose 308 mg/m^2), and another one after five courses (OXA cumulative dose 617 mg/m^2). However, these two patients were submitted to further cycles at reduced doses, reaching a cumulative dose of 812 and 1046 mg/m^2, respectively. Surprisingly, among the remaining patients, only grade 1 (14 cases, 33%) or 2 toxicity (two cases, 5%) was reported.

Activity

Among 40 patients with measurable disease, two complete responses (CRs) and nine partial responses (PRs) were achieved, giving an overall response rate of 27.5% (95% confidence interval 15% to 44%) according to an intention-to-treat analysis. In addition, 18 patients achieved a sustained stable disease for ≥3 months (Table 4). All but one major response were achieved in patients with colorectal primaries. Duration of major responses ranged from 2.2+ to 14.5 months (median 7.6), while the stabilisation of disease had a median length of 5.4 months (range 4–11.7). Activity of this regimen seemed unrelated to previous cytotoxic drug exposure. Indeed, five of 15 (33%) chemoresistant patients, and three of 13 (23%) chemorefractory patients achieved a major response. On the other hand, nine of 11 responses were reported among patients treated with the triplet combination. In detail, nine of 18 (50%) assessable patients of the two last cohorts achieved a CR (two patients) or a PR (seven patients). Moreover, two of three refractory patients treated with the triple-drug combination showed a major response. As for the extent of disease, while only four of 22 (18%) patients with two or more involved sites attained a major response with the doublet, this result was achieved with the triplet in three of six patients (50%) with such disseminated spread. At the time of this report, after a median follow-up of 18 months, 32 patients (70%) had shown a further tumour progression, and 27 (59%) had died. The median progression-free survival time was 7.3 months (range 2.2–27.4) for the whole series, and 5.2 months (range 3.8–11.3) for 13 refractory patients. The corresponding median survival times were 15.6 (range 1.3–27.4) and 11.0 (range 5.2–19.0) months, respectively.

Discussion

This study aimed at determining the MTD of a triplet regimen including OXA, IRI and modulated 5-FU in patients with gastrointestinal malignancies. This combination seemed worth evaluating, especially for treating advanced colorectal cancer patients, for a number of reasons: the different mechanism of action of each cytotoxic drug, their proven activity as single agents in this disease, the synergistic or at least additive effect

Table 4. Activity reported on 40 assessable patients according to dose level

Dose level	CR	PR	NC	PD	NA	Total
1	0	0	1	2	1	4
2	0	0	5	3	0	8
3	0	1	3	0	0	5
4	0	1	2	0	2	5
3b	1	2	1	1	1	6
4b	1	5	6	0	0	12
Total	2	9	18	6	4	40

CR, complete response; NA, not assessed; NC, no change; PD, progressive disease; PR, partial response.

reported in preclinical studies with each doublet, and their partially non-overlapping toxicity profiles.

The schedule for this study was defined on the basis of preclinical experiments on the interaction between OXA and SN38 [22], SN38 and 5-FU [23, 24], and OXA and 5-FU [25, 26]. From these studies, we inferred that the optimal schedule should allow for a 24-h interval between OXA plus IRI exposure and 5-FU administration. Furthermore, *in vitro* studies on colon cancer cell lines showed that, in combination with OXA, a short exposure to a high 5-FU concentration achieved a better antiproliferative effect than an intermediate or protracted exposure to much lower 5-FU concentrations [26]. On these premises, and taking into account our previous experience with a 2-day regimen including IRI on day 1 and leucovorin-modulated 5-FU bolus on day 2 [16], we decided to assess also in the present study the bolus rather than infusional administration of 5-FU after the OXA plus IRI exposure.

The activity and toxicity of a doublet of OXA plus IRI with different schedules has already been explored by several investigators. Scheithauer and co-workers [20] have reported a 42% response rate with their regimen, which entailed IRI on days 1, 8 and 15 and OXA on days 1 and 15 recycling every 4 weeks, in pretreated colorectal cancer patients. However, 81% of patients required the prophylactic administration of G-CSF to maintain the planned schedule. The same investigators assessed the doublet regimen with both drugs given on one day every 2 weeks in chemonaïve patients [28]. Although they planned to administer OXA 85 mg/m^2 with IRI 175 mg/m^2, they were forced to reduce IRI dosage to 150 mg/m^2 for excessive toxicity encountered in the first 20 treated patients. Despite this dose reduction, a 42% response rate was reported in a total of 38 treated patients. Another experience with an every-3-week schedule, including OXA 85 mg/m^2 and IRI 200 mg/m^2, seemed more tolerable, because only one of 30 patients (3%) experienced febrile neutropenia. Also this regimen appeared active, producing a 23% response rate in patients already exposed to adjuvant or palliative 5-FU-based chemotherapy [29]. A similar response rate (12 of 47, 25%) has been reported in heavily pretreated patients with the concurrent administration of both drugs in a weekly-times-four regimen by Kemeny et al. [21].

After the start of the present trial, an *in vitro* study on two human colon cancer cell lines (SW620 and WIDR) was published reporting the interaction of different simultaneous exposures to OXA, SN38 and 5-FU modulated by FA (FUFA) [30]. In this study, the OXA plus FUFA combination was always synergistic, OXA plus SN38 was either additive (when SN38 was applied after OXA) or antagonistic (when SN38 was applied first), and SN38 plus FUFA was always antagonistic, while the triple exposure (OXA plus SN38 plus FUFA) was additive. Furthermore, the relative contribution of each drug to the overall cytotoxicity of the triplet combination was analysed. From this analysis, the greatest contribution came from OXA, while SN38 appeared to bring a relatively modest addition to the combination effect.

Other investigators have recently reported their preliminary experience with the triplet combination in colorectal cancer using a biweekly schedule. In all these trials, short-term infusional 5-FU has been used. In detail, Masi et al. [31] administered OXA 100 mg/m^2 together with IRI 175 mg/m^2 plus leucovorin 200 mg/m^2 and a 48-h infusion of 5-FU 3800 mg/m^2. An exciting 67% response rate has been reported on mainly chemonaïve patients. However, grade 4 neutropenia was detected in 55% of patients, 12% of whom also had febrile neutropenia. In addition, grade 3 diarrhoea affected 21% of patients. Similarly, Calvo et al. [32] reported a 69% response rate on 26 patients treated with a single-day regimen including OXA 120 mg/m^2, IRI 250 mg/m^2 and LFA 500 mg/m^2 plus 5-FU 2600 mg/m^2 over 24 h. Moreover, the administration of IRI 150 mg/m^2 on day 1, OXA 65 mg/m^2 on day 2, followed by standard 'De Gramont' leucovorin-modulated bolus plus 24-h infusional 5-FU for 2 consecutive days every 2 weeks has been assessed by Souglakos et al. [33] on 35 previously untreated patients, achieving a 57% response rate.

Therefore, to our knowledge, the present study is the first one in which a leucovorin-modulated 5-FU i.v. bolus has been combined with OXA plus IRI in cancer patients. The results of our dose-finding study confirm that these three cytotoxic drugs can be combined in close sequence on a 2-day cycle. The RDs for each drug of this triplet regimen are very close or even greater than those utilised alone or in doublet combinations [10, 15, 29]. The main DLT of our triplet regimen was diarrhoea, which accounted for 11 of 14 DLTs encountered after the first cycle. However, neutropenia was the most common cumulative toxicity. The occurrence of severe neutropenia was similar to that reported with doublet regimens of OXA and IRI [18–20, 28], suggesting that the addition of FAFU did not worsen the bone marrow suppression. Unexpectedly, peripheral neuropathy seemed mild with this regimen. Of course, we have to remember that the mean cumulative dosage of OXA was relatively low in our series, with only 11 patients receiving a dosage >800 mg/m^2. As for the activity, we would underline that, when used at the RDs,

our triplet regimen produced a response rate that favourably compared with that reported by Scheithauer et al. with OXA plus IRI doublet in pretreated patients [20], and it is consistent with other experiences with similar three-drug combinations [31–33].

In conclusion, the toxicity profile of our OXA plus IRI plus FAFU biweekly regimen was substantial but manageable. However, due to the limited number of patients treated at the RDs, the safety of this regimen deserves to be confirmed in a larger series. In addition, a careful monitoring of bone marrow suppression with a weekly blood cell count assessment, and special care in instructing patients how to prevent and manage delayed diarrhoea, are mandatory. With such a cautious approach, this regimen could represent an effective salvage treatment for patients with early recurrence after adjuvant or palliative 5-FU-based chemotherapy.

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