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First-line treatment of metastatic colorectal cancer with irinotecan, oxaliplatin and 5-fluorouracil/leucovorin (FOLFOXIRI): results of a phase II study with a simplified biweekly schedule

G. Masi[1], G. Allegrini[1], S. Cupini[1], L. Marcucci[1], E. Cerri[1], I. Brunetti[2], E. Fontana[2], S. Ricci[2], M. Andreuccetti[1] & A. Falcone[1]*

[1]*Division of Medical Oncology, Department of Oncology, Hospital of Livorno and University of Pisa;* [2]*Division of Medical Oncology, Department of Oncology, S. Chiara Hospital, Pisa, Italy*

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Background: In a previous phase I–II study we demonstrated that the FOLFOXIRI regimen [irinotecan 125–175 mg/m^2 day 1, oxaliplatin 100 mg/m^2 day 1, l-leucovorin (l-LV) 200 mg/m^2 day 1, 5-fluorouracil (5-FU) 3800 mg/m^2 as a 48-h chronomodulated continuous infusion starting on day 1, repeated every 2 weeks] has promising activity and efficacy in metastatic colorectal cancer. However, this regimen required a chronomodulated infusion of 5-FU, and because neutropenia occurred in 32% of cycles, granulocyte colony-stimulating factor (G-CSF) was used and the delivered dose intensity was only ~78% of planned. Therefore, we conducted the present phase II study in order to develop a simplified FOLFOXIRI regimen that could be more easily administered in clinical practice as well as in multicenter settings.

Patients and methods: A total of 32 patients with unresectable metastatic colorectal cancer received irinotecan 165 mg/m^2 day 1, oxaliplatin 85 mg/m^2 day 1, l-LV 200 mg/m^2 day 1 and 5-FU 3200 mg/m^2 as a 48-h continuous (not chronomodulated) infusion starting on day 1, repeated every 2 weeks.

Results: All 32 patients were evaluated for safety and the incidence of grade 3–4 toxic effects, and the use of G-CSF seemed to be lower than with the previous FOLFOXIRI regimen: grade 4 neutropenia (34%), grade 3 diarrhea (16%), grade 3 stomatitis (6%) and grade 2–3 peripheral neurotoxicity (37%) were reported, and G-CSF was used in 23% of cycles. Delivered dose intensity was 88% of that planned, and no toxic deaths occurred. The intention-to-treat analysis for activity showed four complete responses, 19 partial responses, seven stable disease and two progressive disease, for an overall response rate of 72% (95% confidence interval 53% to 86%). Eight (25%) patients with residual liver or lung metastases were radically resected after chemotherapy. After a median follow-up of 18.1 months, the median progression-free survival is 10.8 months and median survival is 28.4 months.

Conclusions: This simplified FOLFOXIRI combination can be delivered easily in outpatient settings, with manageable toxic effects, and has very promising antitumor activity. While the safety profile seems to be improved in comparison with our previous FOLFOXIRI regimen, antitumor activity and efficacy appear to be maintained.

Key words: colorectal cancer, 5-fluorouracil, irinotecan, oxaliplatin

Introduction

5-Fluorouracil (5-FU) has been the most commonly used agent in metastatic colorectal cancer [1]. Irinotecan and oxaliplatin are newer agents with antitumor activity in this disease [2, 3], and experimental studies have shown a synergic or additive interaction between SN-38 (the active metabolite of irinotecan), oxaliplatin and 5-FU [4–7]. Moreover, these agents have different mechanisms of action and dose-limiting toxic effects; therefore, the combinations of 5-FU and irinotecan, 5-FU and oxaliplatin, and irinotecan and oxaliplatin have been extensively explored in clinical trials [8]. In particular, the combinations of irinotecan + 5-FU/leucovorin (LV) (FOLFIRI and IFL) and oxaliplatin + 5-FU/LV (FOLFOX) have demonstrated

**Correspondence to*: Dr A. Falcone, U. O. Oncologia Medica, Ospedale Civile, Viale Alfieri 36, 57124 Livorno, Italy. Tel: +39-0586-223458; Fax: +39-0586-223457; E-mail: a.falcone@med.unipi.it

increased antitumor activity and efficacy compared with 5-FU/LV alone in phase III randomized studies [9–12]. Of interest, phase III studies comparing irinotecan + 5-FU/LV with 5-FU/LV alone suggested that more active treatment upfront can prolong survival, even if active second-line therapies are offered to patients progressing on 5-FU/LV. However, it should be remembered that salvage treatment was not a prospective part of these studies. Furthermore, studies with oxaliplatin + 5-FU/LV have indicated that a highly active first-line chemotherapy regimen may permit, in a small subgroup of initially unresectable metastatic colorectal cancer patients, a radical surgical approach to metastases after response to chemotherapy, and that approximately 30% to 40% of operated patients will survive without evidence of disease for >5 years [13, 14]. Therefore, these data indicate that, in metastatic colorectal cancer, a more active first-line treatment can be more effective, and a meta-analysis of 25 randomized trials of first-line treatment with standard bolus intravenous fluoropyrimidines versus experimental treatments (fluorouracil plus leucovorin, fluorouracil plus methotrexate, fluorouracil continuous infusion or hepatic-arterial infusion of floxuridine) also supports the relationship between tumor response to first-line chemotherapy and survival [15].

More recently, a randomized study by the GERCOR [16] assigned 220 untreated metastatic colorectal cancer patients to receive first-line FOLFIRI [irinotecan 180 mg/m^2 90-min intravenously (i.v.) and l-LV 200 mg/m^2 2-h i.v. on day 1, followed by 5-FU 400 mg/m^2 i.v. bolus and 5-FU 2400–3000 mg/m^2 48-h i.v. continuous infusion, repeated every 2 weeks] followed by FOLFOX-6 (oxaliplatin 100 mg/m^2 2-h i.v. on day 1 and l-LV 200 mg/m^2 2-h i.v. on day 1, followed by 5-FU 400 mg/m^2 i.v. bolus and 5-FU 2400–3000 mg/m^2 48-h i.v. continuous infusion, repeated every 2 weeks) at progression (arm A), or the reverse (arm B). Both sequences achieved similar activity and efficacy, and, of interest, median survival was 21.5 months in arm A and 20.6 months in arm B, which are the highest survival times reported up to now in any randomized study of metastatic colorectal cancer. This study suggests that the exposure of metastatic colorectal cancer patients to all three most active agents, 5-FU/LV, irinotecan and oxaliplatin, is associated with promising survival. In addition, the recent study by Goldberg et al. [17], which demonstrates the superiority of the FOLFOX-4 regimen to IFL, suggests the importance of the exposure to all these three agents to achieve prolonged survival, because in the IFL arm only 24% of patients could receive oxaliplatin as second-line treatment, while in the FOLFOX-4 arm 60% of patients were able to receive salvage treatment with irinotecan. Furthermore, in a sequential strategy, not all patients who progress after first-line chemotherapy are able to receive second-line treatment, and therefore not all are exposed to these three active agents. In fact, clinical trials suggest that approximately 20% to 40% of patients, mainly because of deterioration of their performance status and liver function, will not be fit enough to undergo further chemotherapy and will receive only supportive care [9, 10, 12, 17, 18]. Moreover, a recent pooled analysis of seven phase III trials in metastatic colorectal cancer demonstrates that survival is correlated with the proportion of patients who received all the three active drugs in the course of their disease, but not with the proportion of patients who received any second-line therapy [18]. Therefore, if feasible and tolerable, the best way to expose 100% of patients to all these three active agents might be to administer them upfront. However, it has yet to be determined whether a combination of these three agents is better than giving them sequentially as two lines, and whether a regimen combining these three agents allows their administration at optimal doses. In addition, no data so far support the hypothesis that patients progressing rapidly on a two-drug combination (FOLFIRI, FOLFOX) will respond to a triple combination (FOLFOXIRI) or to any currently available chemotherapy.

On the basis of these considerations, we attempted to develop a new and potentially more active and efficacious chemotherapy regimen combining irinotecan, oxaliplatin and 5-FU/LV in the first-line treatment of metastatic colorectal cancer. We conducted a phase I–II study in 42 metastatic colorectal cancer patients [19], who received irinotecan 125–175 mg/m^2 1-h i.v. infusion on day 1, oxaliplatin 100 mg/m^2 2-h i.v. infusion on day 1, l-LV 200 mg/m^2 2-h i.v. infusion on day 1 and 5-FU 3800 mg/m^2 as a 48-h i.v. chronomodulated continuous infusion starting on day 1, repeated every 2 weeks (FOLFOXIRI), demonstrating a high antitumor activity (overall response rate 71.4%) and a promising efficacy (median progression-free survival 10.4 months, median overall survival 26.5 months) of this new combination. However, this regimen required a chronomodulated infusion of 5-FU, and because of neutropenia, the main toxicity observed, 32% of cycles required granulocyte colony-stimulating factor (G-CSF) support in order to be able to recycle within 2 weeks. Furthermore, 35% of cycles required dose reductions of at least one drug and 16% of cycles were delayed by at least 1 week because of toxicity. Hence, the delivered dose intensity was only $\sim$78% of planned. Therefore, we conducted the present phase II study to evaluate the safety and the activity of a simplified biweekly FOLFOXIRI regimen with slightly reduced doses of irinotecan and oxaliplatin and a continuous, rather than chronomodulated, infusion of 5-FU. This was in the attempt to develop a new three-drug combination that is less myelotoxic and more easily administered in a multicenter setting in comparison with the initial FOLFOXIRI regimen, while maintaining its promising activity and efficacy.

Patients and methods

Patient selection

Main eligibility criteria included: histologically confirmed diagnosis of colorectal adenocarcinoma with unresectable metastatic disease, age <75 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, measurable disease, leukocyte count ≥3500/mm^3, neutrophil count >1500/mm^3, platelet count ≥100 000/mm^3, serum creatinine ≤1.3 mg/dl, serum bilirubin <1.5 mg/dl, and aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase ≤2.5× normal values (<5× normal values if liver metastases were present). Previous adjuvant or palliative

chemotherapy with fluoropyrimidines or raltitrexed was allowed. Exclusion criteria included: previous chemotherapy including irinotecan or oxaliplatin, symptomatic cardiac disease, myocardial infarction in the last 24 months, uncontrolled arrhythmia, active infection, inflammatory bowel disease and total colectomy. The study was conducted in accordance to the Declaration of Helsinki and to the Good Clinical Practice guidelines. Patients were informed of the investigational nature of the study and provided their written informed consent before registration onto the study.

Treatment

The treatment planned consisted of: irinotecan 165 mg/m^2 in 250 ml of NaCl 0.9% over 1 h, followed immediately by oxaliplatin 85 mg/m^2 in 250 ml dextrose 5% and l-LV 200 mg/m^2 in 250 ml dextrose 5%, infused concomitantly over 2 h via a Y-connector, followed immediately by 5-FU 3200 mg/m^2 infused as a 48-h continuous infusion. Administration of the regimen required the implant of a central venous catheter and the use of an external volumetric programmable pump (Deltec CADD-1; Deltec Inc., St Paul, MN, USA) or of a portable elastomeric infusion system (Baxter INFUSOR LV; Baxter Healthcare Corporation, Deerfield, IL, USA). Treatment was repeated every 2 weeks (Figure 1). Treatment was administered biweekly until evidence of progression, unacceptable toxicity, patient refusal or for a maximum of 12 cycles. Treatment was delayed when, on the planned day of treatment, neutrophils <1000 mm^3, platelets <100 000 mm^3 or persistent diarrhea or stomatitis grade >1 were present. In the case of peripheral neurotoxicity grade >2 [National Cancer Institute Common Toxicity Criteria (NCI CTC)], oxaliplatin was interrupted. In the case of previous dose-limiting toxic effects, treatment was continued after resolution with doses of irinotecan, oxaliplatin and 5-FU reduced by 25%, except in the case of grade 3–4 diarrhea, when only irinotecan and 5-FU doses were reduced by 25%. In the case of life-threatening toxic effects, treatment was definitively interrupted or continued at doses reduced by 50%.

To prevent nausea and vomiting 5-HT$_3$ antagonists i.v. + dexamethasone 16 mg i.v. were administered before chemotherapy, and 5-HT$_3$ antagonists were given orally at standard doses in the 2 days following chemotherapy. Atropine 0.25 mg subcutaneously was given in case of cholinergic syndrome, and was given prophylactically in the following cycles. Loperamide 2 mg orally every 2 h and oral rehydration were prescribed in case of delayed diarrhea. No prophylactic treatment with cytokines for neutropenia was recommended.

Assessability, toxicity and response criteria

Pretreatment evaluation included history and physical examination, performance status assessment, complete blood cell with differential and platelet counts, complete blood profile, carcinoembryonic antigen, urine analysis, electrocardiogram, chest X-ray or computed tomography (CT) scan, abdominal CT scan and/or sonogram, and any other appropriate diagnostic procedure to evaluate metastatic sites. During treatment, a physical examination was performed every 2 weeks, a complete blood cell count every week, and blood profile and urine analysis every 2 weeks. Sites of metastatic disease were re-evaluated every 8 weeks. For the evaluation of liver or abdominal metastases an abdominal CT scan or MRI was required. A chest X-ray and/or an abdominal sonogram or CT scan were repeated at least every 6 months if there was no evidence of lung or abdominal disease, respectively. Toxic effects were monitored weekly and were scored according to standard NCI CTC criteria. Responses were evaluated every 8 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria [20]. Tumor measurements were reviewed by an independent radiologist. Duration of response was calculated from the first day of treatment to the date of first observation of progressive disease or last examination.

Drug	*Day 1*	*Day 2*	*Day 3*
CPT-11	**165** mg/m^2 IV 1-h		
LOHP	**85** mg/m^2 IV 2-h		
l-LV	**200** mg/m^2 IV 2-h		
5-FU	**3,200** mg/m^2 IV 48-h continuous infusion		
Repeated every 2 weeks			

Figure 1. Treatment schedule. CPT-11, irinotecan; LOHP, oxaliplatin; l-LV, leucovorin; 5-FU, 5-fluorouracil; IV, intravenous.

Statistical analysis

The minimax two-stage sequential design described by Simon [21] was used to determine the number of patients to be included. Because responses with standard reference combinations of irinotecan + 5-FU/LV or oxaliplatin + 5-FU/LV are observed in ~40% of patients, a response rate of ≥60% for a new regimen that has acceptable toxic effects would be considered promising. Therefore, the design parameters p0 (response rate in null hypothesis) and p1 (response rate in alternative hypothesis) selected were 0.40 and 0.60, respectively. Considering in addition an α and β error probability of 0.10 and 0.20, the first stage of the study required 16 patients, and if at least six objective responses were observed, the second stage required a total of 28 patients. If at least 14 patients responded after the second accrual stage, treatment was considered promising unless other considerations indicated otherwise. The distribution of time to progression and time to death were calculated from the date of treatment start using the Kaplan–Meier method.

Results

Patients and study treatment

A total of 32 patients with unresectable metastatic colorectal carcinoma entered the study. Median age was 63 years (range 43–74), ECOG performance status was 1–2 in 14 (44%) patients, 28 (88%) had liver metastases, and among these, eight (29%) had liver involvement >50% (evaluated at CT scan), 17 (53%) had multiple metastatic sites, and nine (28%) had received previous adjuvant (eight patients) or palliative (one) chemotherapy with 5-FU/LV or raltitrexed (Table 1). Among all the 32 patients entered into the study, a total of 336 cycles of chemotherapy were administered with a median of 12 cycles per patient (range three to 14).

Toxicity and dose intensity

All patients were assessable for safety. The most common toxic effects were neutropenia, diarrhea, nausea and vomiting, stomatitis, peripheral neurotoxicity, alopecia, and thrombocytopenia. However, grade 3–4 toxic effects were uncommon except for neutropenia. In particular, 4% of cycles were associated with grade 4 neutropenia, although only 1% were complicated by fever, 1% with grade 3 diarrhea and 1% with grade 3 stomatitis (Table 2). Among all 32 patients,

Table 1. Patients' characteristics

Characteristic	No. of patients (%)
Patients	32
Age (years) [median (range)]	63 (43–74)
Sex	
Male	26 (81)
Female	6 (9)
ECOG performance status	
0	18 (56)
1–2	14 (44)
Primary	
Colon	21 (66)
Rectum	11 (34)
Previous surgery on primary tumor	30 (94)
Number of metastatic sites	
Single	15 (47)
Multiple	17 (53)
Metastases	
Synchronous	21 (56)
Metachronous	11 (44)
Site of disease	
Liver	28 (88)
Lung	9 (28)
Abdomen	15 (47)
Other	2 (6)
Liver involvement	
<25%	8 (25)
25–50%	12 (38)
>50%	8 (25)
Previous chemotherapy	9 (28)
Adjuvant	8 (25)
Palliative	1 (3)
Previous radiotherapy	2 (6)
Baseline LDH	
Normal	19 (59)
Above upper normal limit	13 (41)
Baseline CEA	
Normal	11 (34)
>10 ng/ml	21 (66)

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen.

five (16%) had at least one episode of grade 3 diarrhea, two (6%) of grade 3 stomatitis and 12 (37%) developed a grade 2–3 peripheral neurotoxicity (Table 3). Eleven (34%) patients experienced at least one episode of grade 4 neutropenia and four (12%) had an episode of febrile neutropenia. Because three out four episodes of febrile neutropenia were short-lasting and managed rapidly with outpatient therapy, only one resulted in hospitalization requiring parenteral antibiotics. Moreover, there were no episodes of documented infections and no toxic deaths occurred. In eight patients (25%), oxaliplatin was permanently discontinued because of neurotoxicity. Seven (22%) patients and 54 (16%) cycles required dose reductions of at least one drug; 54 (16%) cycles were delayed >1 week because of neutropenia (9%), other toxic effects (5%) or for non-treatment-related reasons (2%). The median dose intensities of irinotecan, oxaliplatin and 5-FU calculated during the entire treatment period among the 32 patients treated were 71 mg/m^2/week (86% of planned), 38 mg/m^2/week (89% of planned) and 1443 mg/m^2/week (90% of planned), respectively. Although the use of G-CSF was not planned, it was used in 76 (23%) cycles, mainly to maintain the planned biweekly schedule, because persistent neutropenia on the day of recycle was not permitted.

Table 2. Maximum toxicity per cycle (336 cycles)

Adverse event	NCI CTC grade (%)			
	1	2	3	4
Nausea/vomiting	34	11	–	–
Diarrhea	29	9	1	–
Stomatitis	20	4	1	–
Thrombocytopenia	4	1	–	–
Neutropenia[a]	17	18	9	4

[a]Febrile neutropenia: 1%.
NCI CTC, National Cancer Institute Common Toxicity Criteria.

Table 3. Maximum toxicity per patient (32 patients)

Adverse event	NCI CTC grade (%)			
	1	2	3	4
Nausea/vomiting	56	44	–	–
Diarrhea	47	34	16	–
Stomatitis	44	22	6	–
Alopecia	52	40	–	–
Neurotoxicity	41	34	3	–
Cutaneous	9	–	–	–
Thrombocytopenia	22	6	3	–
Neutropenia[a]	9	25	25	34

[a]Febrile neutropenia: 12%.
NCI CTC, National Cancer Institute Common Toxicity Criteria.

Antitumor activity and survival

With respect to the evaluation of antitumor activity of treatment and the intention-to-treat analysis, all 32 patients were considered assessable. Four (13%) patients with liver (two), lung (one) and liver + lymph node (one) metastases obtained a complete response and 19 (59%) a partial response, for an objective response rate of 72% (95% confidence interval 53% to 86%). Responses lasted a median of 11.1+ months (range 8.3–22.1+). In the remaining nine patients, seven

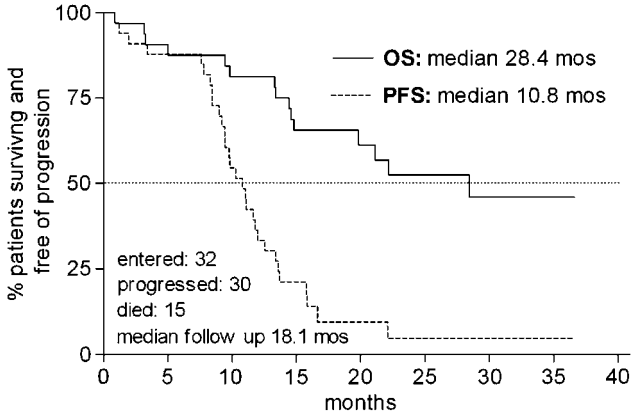

Figure 2. Actuarial progression-free (PFS) and overall survival (OS) curves.

(22%) disease stabilizations and two (6%) progressions were observed. The response rate among the nine patients who had received previous adjuvant or palliative chemotherapy was 78%, and among the 23 patients who were chemotherapy-naive was 70%. Surgical removal of residual disease was considered after chemotherapy in 15 (47%) patients and a radical (R0) resection was performed in eight (25%) (six patients with liver involvement only, one with liver and lymph node metastases, and one with liver and lung metastases). After a median follow-up of 18.1 months, the median progression-free and overall survivals were 10.8 and 28.4 months, respectively, and curves, estimated by the Kaplan–Meier method from the first day of treatment, are reported in Figure 2.

Discussion

Over the past years, improvements in chemotherapy for metastatic colorectal cancer have resulted in significant benefits in terms of antitumor activity and efficacy [22]. Several data have suggested that the best results are achieved in patients who are exposed to all three of the main active agents (5-FU, irinotecan and oxaliplatin), but that in a sequential strategy only 60% to 80% of patients are able to receive second-line treatments and therefore to be exposed to all these three agents. These considerations support the strategy to develop potentially more active first-line regimens combining 5-FU with both irinotecan and oxaliplatin. For this purpose, we studied a three-drug combination of irinotecan, oxaliplatin and 5-FU/LV (FOLFOXIRI) using the treatment sequence irinotecan → oxaliplatin → 5-FU, because an *in vitro* study on two human colon cancer cell lines showed that synergy occurs only when irinotecan precedes oxaliplatin/5-FU exposure [23]. A biweekly schedule was also chosen because previous studies had demonstrated that for the agents we used, this schedule has a favorable toxicity profile, which allows the delivery of significant dose intensities, is active and is convenient in an outpatient setting. We administered 5-FU as a 48-h continuous infusion without any bolus to reduce the related toxic effects, thus favoring its combination with optimal doses of irinotecan and oxaliplatin.

In our initial phase I–II study [19] we demonstrated that biweekly irinotecan, oxaliplatin and infusional 5-FU modulated by LV could be combined at significant doses of each single agent with acceptable toxic effects. Of interest, this combination was associated with a high degree of antitumor activity, with a response rate of 71.4% and a complete response rate of 11.9%. This allowed the performance of radical surgery on residual metastases in 11 patients (26%) who were initially unresectable. Median progression-free and overall survival (10.4 and 26.5 months, respectively) were also very promising.

On the basis of these results, we designed this study in the attempt to develop a simplified and better-tolerated FOLFOXIRI regimen that could be administered more easily in clinical practice as well as in multicenter settings. To obtain this we planned the administration of slightly reduced doses of irinotecan, oxaliplatin and 5-FU, and the delivery of 5-FU by a continuous, rather than chronomodulated, 48-h infusion. This simplified regimen produced a lower incidence of both hematological and non-hematological toxic effects. In particular, the incidences of grade 3 diarrhea and grade 3 stomatitis were reduced from 21% to 16% and from 10% to 6% of patients, respectively. Grade 4 neutropenia was observed in 34% of patients and in 4% of cycles, compared with 55% and 7%, respectively, in the previous study. Also, the use of G-CSF was reduced by about one-third (23% of cycles compared with 32%). The median delivered dose intensity was increased from 78% up to 88% of that planned. Of interest, results in terms of antitumor activity (overall response rate of 72% and a post-chemotherapy R0 surgical resection rate of 25%) and efficacy (median progression-free survival 10.8 months, median survival of 28.4 months) were similar to those previously reported, and remained very promising.

Other groups have evaluated similar three-drug combinations in colorectal and non-colorectal cancer patients, associating irinotecan and oxaliplatin with different schedules of 5-FU/LV. All these studies have confirmed the feasibility of these combinations, with neutropenia and diarrhea being the dose-limiting toxic effects, and showed a promising antitumor activity in metastatic colorectal cancer patients. In particular, Souglakos et al. [24] treated 31 metastatic colorectal cancer patients with first-line irinotecan 150 mg/m^2 on day 1, oxaliplatin 65 mg/m^2 on day 2, followed by standard de Gramont schedule LV-modulated bolus plus infusional 5-FU on days 2 and 3, repeated every 2 weeks, and achieved an overall response rate of 58%, and reported grade 3–4 diarrhea and neutropenia in 32% and 45% of patients, respectively. Ychou et al. [25] associated escalating doses of irinotecan and oxaliplatin given at day 1 with the standard de Gramont regimen (LV5FU2) or with the simplified LV5FU schedule given at days 1 and 2, repeated every 2 weeks, in patients with advanced solid tumors. The recommend doses of irinotecan and oxaliplatin are 180 mg/m^2 and 85 mg/m^2, respectively; grade 3–4 diarrhea affected 27% of patients, 78% of whom had grade 3–4 neutropenia. Calvo et al. [26] reported a 69% response rate on 26 patients treated with irinotecan 250 mg/m^2

on day 1, oxaliplatin 120 mg/m^2 on day 1 and LV 500 mg/m^2 plus 5-FU 2600 mg/m^2 over 24 h on days 1 and 15, repeated every 4 weeks. The authors observed grade 3–4 diarrhea in 34% and grade 3–4 neutropenia in 38% of patients. Moreover, Garufi et al. [27] demonstrated the feasibility of this triple-drug combination using a chronomodulated infusion of 5-FU and oxaliplatin, and Comella et al. [28] and Goetz et al. [29] using bolus 5-FU.

Compared with these previously reported regimens, our schedule seems to be particularly convenient for the patient and for the health-care facility, requiring only one or two admissions to the outpatient facility every 2 weeks. Moreover, in our regimen we omit the administration of 5-FU by i.v. bolus and are able to deliver elevated dose intensities of irinotecan, oxaliplatin and 5-FU continuous infusion (approaching their recommended doses when used as single agent), producing a high response rate and promising progression-free and overall survival, coupled with a relatively low occurrence of non-hematological toxic effects (the incidence of grade 3–4 diarrhea being the lowest reported with this combination). Finally, neutropenia, which is still relatively frequent, is usually short lasting and rarely complicated. Therefore, prophylactic therapy with G-CSF does not seem to be justified in all patients. However, prophylactic G-CSF should be considered in patients with a previous episode of grade 4 neutropenia or with persistent neutropenia on the day of recycle.

In conclusion, this simplified FOLFOXIRI combination has manageable toxic effects and very promising antitumor activity. While the safety profile seems to be improved in comparison with our previous FOLFOXIRI regimen, the antitumor activity and efficacy seem to be maintained. Therefore, this simplified FOLFOXIRI regimen represents the experimental arm in the randomized multicenter study currently being conducted by the Gruppo Oncologico Nord Ovest (GONO) in Italy, comparing a standard irinotecan + 5-FU/LV combination (FOLFIRI) with FOLFOXIRI.

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