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Phase III Randomized Trial of FOLFIRI Versus FOLFOX4 in the Treatment of Advanced Colorectal Cancer: A Multicenter Study of the Gruppo Oncologico Dell'Italia Meridionale

Giuseppe Colucci, Vittorio Gebbia, Giancarlo Paoletti, Francesco Giuliani, Michele Caruso, Nicola Gebbia, Giacomo Cartenì, Biagio Agostara, Giuseppe Pezzella, Luigi Manzione, Nicola Borsellino, Andrea Misino, Sante Romito, Ernesto Durini, Stefano Cordio, Marisa Di Seri, Massimo Lopez, and Evaristo Maiello

From the Oncology Institute, Bari; University; La Maddalena Hospital; M. Ascoli Hospital, Palermo; Regina Elena Institute; La Sapienza University, Rome; Centro Oncologico; S. Luigi Hospital, Catania; Cardarelli Hospital, Naples; Ospedale Nord, Taranto; S. Carlo Hospital, Potenza; Cardarelli Hospital, Campobasso; G. Panico Hospital, Tricase, Italy.

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Giuseppe Colucci, MD, Medical and Experimental Oncology Unit, Oncology Institute, Via Amendola 209, 70126 Bari, Italy; e-mail: colucci@goim.it.

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ABSTRACT

Purpose

We performed this phase III study to compare the irinotecan, leucovorin (LV), and fluorouracil (FU) regimen (FOLFIRI) versus the oxaliplatin, LV, and FU regimen (FOLFOX4) in previously untreated patients with advanced colorectal cancer.

Patients and Methods

A total of 360 chemotherapy-naive patients were randomly assigned to receive, every 2 weeks, either arm A (FOLFIRI: irinotecan 180 mg/m^2 on day 1 with LV 100 mg/m^2 administered as a 2-hour infusion before FU 400 mg/m^2 administered as an intravenous bolus injection, and FU 600 mg/m^2 as a 22-hour infusion immediately after FU bolus injection on days 1 and 2 [LV5FU2]) or arm B (FOLFOX4: oxaliplatin 85 mg/m^2 on day 1 with LV5FU2 regimen).

Results

One hundred sixty-four and 172 patients were assessable in arm A and B, respectively. Overall response rates (ORR) were 31% in arm A (95% CI, 24.6% to 38.3%) and 34% in arm B (95% CI, 27.2% to 41.5%; $P = .60$). In both arms A and B, median time to progression (TTP; 7 *v* 7 months, respectively), duration of response (9 *v* 10 months, respectively), and overall survival (OS; 14 *v* 15 months, respectively) were similar, without any statistically significant difference. Toxicity was mild in both groups: alopecia and gastrointestinal disturbances were the most common toxicities in arm A; thrombocytopenia and neurosensorial were the most common toxicities in arm B. Grade 3 to 4 toxicities were uncommon in both arms, and no statistical significant difference was observed.

Conclusion

There is no difference in ORR, TTP, and OS for patients treated with the FOLFIRI or FOLFOX4 regimen. Both therapies seemed effective as first-line treatment in these patients. The difference between these two combination therapies is mainly in the toxicity profile.

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INTRODUCTION

The availability of new active drugs in the clinical practice of the treatment of advanced colorectal cancer (CRC) patients has deeply changed the prognosis of these patients. In the past, the standard treatment for patients with advanced CRC was fluorouracil (FU) biochemically modulated by leucovorin (LV), which globally demonstrated a response rate of 23%,[1] with a median survival time that rarely exceeded 10 to 12

months. Therefore, the results of systemic treatment were disappointing, and patient prognosis remained poor.

New approaches were clearly needed to improve clinical results. A bimonthly schedule of FU, administered as a bolus and continuous infusion, combined with high-dose LV (LV5FU2) was randomly compared with the monthly North Central Cancer Treatment Group–Mayo Clinic regimen (FU bolus and low-dose LV). In the patients with measurable disease, the bimonthly schedule obtained significantly better results in terms of response rate and median progression-free survival and resulted in fewer grade 3 and 4 toxicities (granulocytopenia, diarrhea, and mucositis) than the monthly schedule.[2] Therefore, this regimen became the new standard option for advanced CRC patients in some European countries.

In recent years, a number of new treatment options have become available. In particular, two new cytotoxic agents, irinotecan (CPT-11) and oxaliplatin (OHP), have been proven to have efficacy in the treatment of CRC. After encouraging observations of substained activity in colon cancer cell lines,[3] CPT-11, a specific inhibitor of topoisomerase I, demonstrated, in several clinical studies, significant single-agent activity against CRC resistant to FU-based first-line therapy in phase II[4-6] and phase III studies,[7,8] with significant improvement in results when CPT-11 was compared with best supportive care alone or with FU by continuous infusion. Therefore, because of these results, CPT-11 was considered the reference treatment for patients with FU-refractory advanced CRC. Furthermore, two first-line phase III trials[9,10] showed a significant improvement in results with the addition of CPT-11 to FU-LV combination therapy (FOLFIRI). In particular, in the European study,[9] the FOLFIRI regimen, compared with LV5FU2 (AIO regimen), obtained a significant difference in terms of overall survival (OS; 17.4 *v* 14.1 months, respectively; $P = .031$), response rate (35% *v* 22%, respectively; $P = .005$), and time to progression (TTP; 6.7 *v* 4.4 months, respectively; $P < .001$). The overall response rate (ORR) of the FOLFIRI arm in this study was similar to that observed in our previous randomized phase II trial[11] comparing FOLFIRI with LV5FU2 (40% *v* 18%, respectively). In addition, in an American trial,[10] the addition of CPT-11 to an FU bolus administration (IFL) obtained significantly better results than CPT-11 alone or FU-LV alone, and therefore, this regimen represented the standard treatment for patients with advanced CRC in the United States.

OHP, a new cytotoxic agent from the diaminocyclohexane platinum family, has a mechanism of action similar to the other platinum derivates, with a different spectrum of antitumor activity against some tumor models; in particular, activity against colon cell lines and synergistic activity of OHP and FU in experimental models have been demonstrated.[12,13] Activity of OHP as a single agent in previously treated patients with CRC was demonstrated in phase II trials, with a response rate of approximately 10%.[14] However, OHP in combination with FU and LV (mainly high-dose LV and FU in infusional administration) resulted in objective response rates from 18% to 46%, with median survival time ranging from 10 to 17 months.[15-18] In first-line therapy, a European randomized phase III trial[19] demonstrated significant superiority of the combination regimen of OHP, LV, and bolus plus infusional FU (FOLFOX4) over the Mayo Clinic regimen in terms of response rate (50% *v* 22%, respectively; $P = .0001$) and progression-free survival (8.2 *v* 6.0 months, respectively; $P = .0003$), with no statistical difference in median OS time (16.2 *v* 14.7 months, respectively; $P = .12$).

After the results of the two large previously mentioned randomized French studies,[9,19] the FOLFOX4 and the CTP-11 plus LV5FU2 combination regimens represented the reference first-line treatments for patients with advanced CRC in many European countries. Subsequently, the CTP-11 plus LV5FU2 regimen was slightly modified to become the FOLFIRI regimen.

Taking into account these studies, in 1999, the Gruppo Oncologico dell'Italia Meridionale (GOIM) started a randomized trial (GOIM protocol No. 9901) to compare the FOLFIRI regimen used in the study by Douillard et al[9] with the FOLFOX4 combination therapy reported by de Gramont et al[19] in patients with advanced CRC. The primary end point of our study was response rate, and the secondary end points were TTP, OS, and toxicity profile.

PATIENTS AND METHODS

Patient Selection

The elegibility criteria included the following: age ≥ 18 and ≤ 75 years, histologically confirmed locally advanced and/or metastatic CRC with bidimensionally measurable disease, anticipated life expectancy of at least 3 months, Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate bone marrow (platelet count $\geq$ 100,000/L, WBC count $\geq$ 4,000/L, granulocyte count of $\geq 1500/\mu L$, and a hemoglobin level of $\geq$ 10.0 mg/dL), renal (serum creatinine concentration $\leq$ 2.0 mg/dL), and hepatic functions (serum bilirubin level $\leq$ 2.0 mg/dL and AST $< 3\times$ the institutional normal level in the absence of liver involvement with cancer or up to $5\times$ the institutional normal level when cancer was present in the liver).

Patients had to be previously untreated for advanced disease, except for those patients in whom this therapy had been performed in the adjuvant phase at least 6 months before enrollment. No concurrent uncontrolled medical illness was allowed.

Patients were excluded if any of these criteria were not met and if they had any active or uncontrolled infections; known brain metastases or carcinomatous meningitis; interstitial pneumonia or interstitial fibrosis; history of myocardial infarction within the previous 6 months or current clinical evidence of congestive heart failure (patients taking medication for congestive heart failure and showing no clinical signs or symptoms were eligible); symptoms of coronary artery disease; history of thromboembolic disease; history in the past 5 years of a prior malignancy, except for adequately treated basal cell or squamous cell skin cancer or in situ

cervical cancer; and any psychiatric or psychological disorders that interfere with consent and precluded treatment or adequate follow-up. Pregnant or lactating women and patients with peripheral neuropathy were also excluded. Radiotherapy was allowed only in sites other than those measurable for response evaluation.

Pretreatment evaluation included a complete medical and clinical-physical examination, performance status evaluation, baseline measurement of tumor size based on scans, x-ray examination or other radiographic means (comprising full assessment of all known metastatic disease), chest x-ray, ECG, CBC count with leukocyte differential, platelet count, and serum chemistries and electrolytes and tumor markers. Patients were required to agree to and sign a statement of informed consent before entry onto the study. Informed consent was previously approved by the Scientific Committee of the GOIM and the ethics committees of each individual participating institution.

Treatment Plan

Randomization to either the FOLFIRI regimen (arm A) or FOLFOX4 regimen (arm B) was performed centrally at the GOIM headquarters in Bari, Italy. The random ratio between the two arms (A *v* B) was 1:1.

According to our previous experiences,[11,20] the size and site of disease were considered prognostic variables for the stratification of patients, and therefore, patients were stratified according to presence or absence of hepatic disease and by total tumor burden, which was defined as limited or extensive disease using 10 cm^2 as the cutoff value. This cutoff value was arbitrarily chosen. The estimation of tumor size ($>$ or $<$ 10 cm^2) was determined according to the sum of the products of the largest perpendicular diameters of all measurable lesions for site of the disease. It was found that this stratification method could be easily reproduced in the various centers participating in the study and did not seem to be subject to investigator bias. Thus, the stratification factors were as follows: (1) size of disease (limited or extensive disease; $<$ or $>$ 10 cm^2, respectively) and (2) liver involvement (with or without liver involvement; H+ and H−, respectively). The following four patient categories were obtained: group 1, H+ and tumor more than 10 cm^2; group 2, H+ and tumor less than 10 cm^2; group 3, H− and tumor more than 10 cm^2; and group 4, H− and tumor less than 10 cm^2.

Patients were randomly assigned to receive either arm A or arm B (Fig 1). Arm A (FOLFIRI regimen) consisted of CPT-11 180 mg/m^2 (150 mg/m^2 for patients age $\geq$ 70 and $<$ 75 years) only on day 1, with LV 100 mg/m^2 (L-isomer form) administered as a 2-hour infusion before FU 400 mg/m^2 administered as an intravenous bolus injection; FU 600 mg/m^2 was administered as a 22-hour infusion immediately after FU bolus injection. LV and FU were repeated on days 1 and 2 according to a previously reported schedule.[9] Arm B (FOLFOX4) consisted of OHP 85 mg/m^2 only on day 1, with LV 100 mg/m^2 (L-isomer form) administered as a 2-hour infusion before FU 400 mg/m^2 administered as an intravenous bolus injection; FU 600 mg/m^2 was administered as a 22-hour infusion immediately after FU bolus injection. LV and FU were repeated on days 1 and 2 according to a previously reported schedule.[19] Both regimens were administered at 2-week intervals.

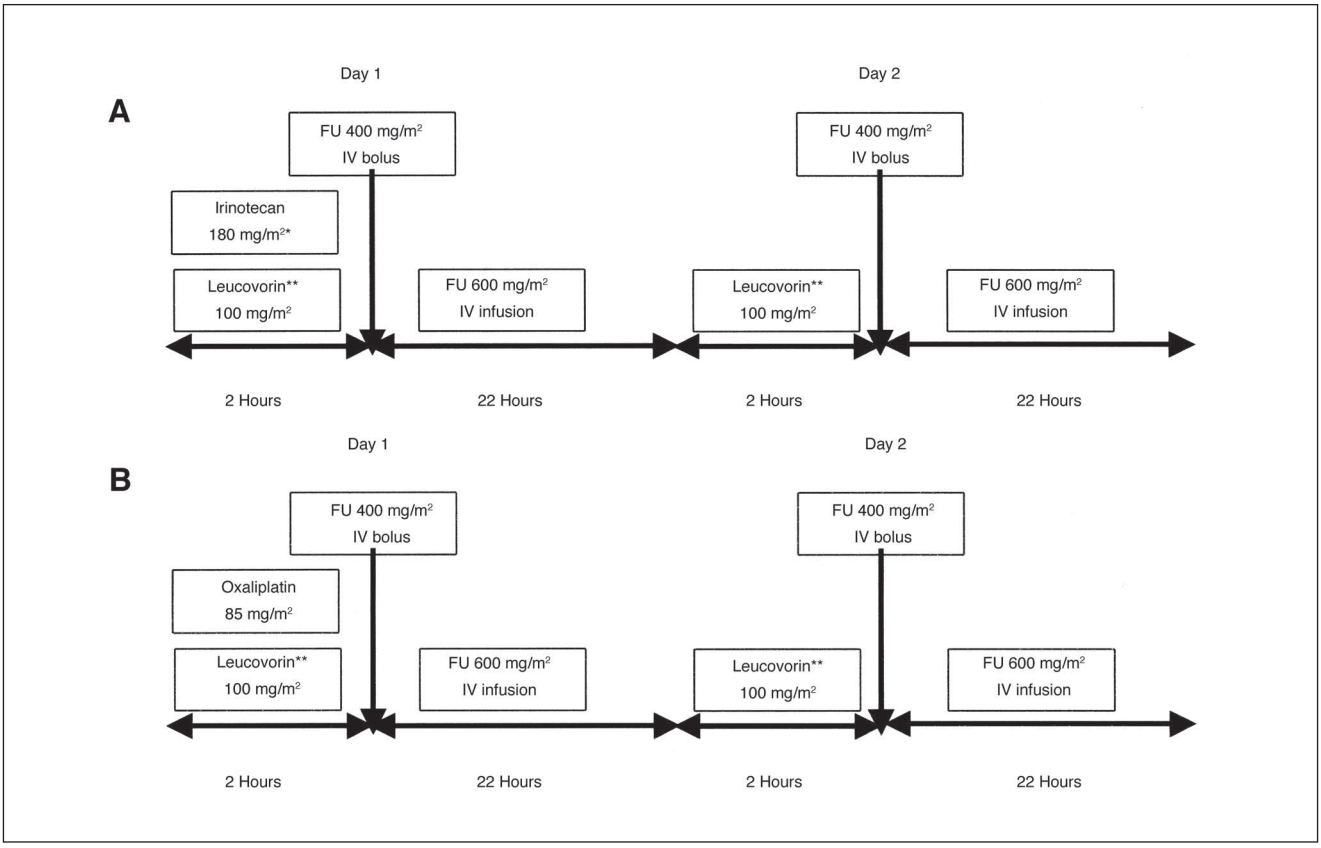

Fig 1. Chemotherapy regimens. FU, fluorouracil; IV, intravenous; FOLFIRI, irinotecan, leucovorin, and fluorouracil regimen; FOLFOX4, oxaliplatin, leucovorin, and fluorouracil regimen. (*) Patients between 70 and 75 years old: 150 mg/m^2; (**) L-isomer form.

Evaluation of Response and Toxicity

Survival, response duration, and TTP were determined from the date of first treatment until death or last follow-up and progression. Objective response was first evaluated after four cycles of treatment and then every 2 months, according to a slight modification of WHO criteria.[21] Briefly, a complete response (CR) was considered the complete disappearance of all evident tumor signs as estimated by two observations not less than 4 weeks apart. Partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the largest perpendicular diameters of all measurable disease lasting at least 4 weeks, without occurrence of new lesions. Stable disease (SD) was defined as a change of less than 50% in the size of disease, and progressive disease was defined as an increase of greater than 25% in the area of the measurable tumoral deposits or the appearance of new lesions. The sum of CRs and PRs was reported as ORR. Response rates were provided for all patients (ie, intent-to-treat analysis [ITT]) and for assessable patients.

All toxicities, other than peripheral neuropathy, were graded according to the National Cancer Institute Common Toxicity Criteria. Peripheral neuropathy was graded according to the specific grading system of Levì et al.[22]

Prophylactic antiemetics were routinely administered before each administration of the two regimens. Diarrhea or abdominal cramping or important symptoms of a cholinergic syndrome that occurred during or within 1 hour after receiving CPT-11 were treated with atropine (0.25 mg subcutaneously). Routine use of a granulocyte colony-stimulating factor was not used in this trial. For symptoms of diarrhea and/or abdominal cramping that occurred more than 12 hours after receiving treatment, patients were instructed to begin taking loperamide as soon as the first liquid stool occurred (2 mg orally every 2 hours for at least 12 hours and up to 12 hours after the last liquid stool, without exceeding a total treatment duration of 48 hours). Oral rehydration with large volumes of water and electrolytes was prescribed during the whole diarrhea episode. If diarrhea persisted for more than 24 hours despite the recommended loperamide treatment, a 7-day, prophylactic, oral, broad spectrum antibiotic therapy with fluoroquinolone was initiated.

If multiple toxicities were observed, the dose administered was based on the most severe toxicity experienced. The dose adjustment schedule was evaluated at the beginning of a new course (based on laboratory analyses on the scheduled day of treatment and on maximum toxicity encountered during the previous course). Dose reductions or treatment delays were calculated according to the nonhematologic toxicity or myelosuppression recorded at the time of the planned recycling (day 14). The drug dose level was reduced in the case of severe or persistent toxicity; the LV dose remained fixed (100 mg/m^2), whereas CPT-11 was reduced to 150 mg/m^2 (125 mg/m^2 for patients with between the ages of 70 and 75 years), FU bolus was reduced to 300 mg/m^2, and FU continuous infusion was reduced to 500 mg/m^2. In the case of persistent grade 3 toxicity or whenever grade 4 toxicity was recorded, chemotherapy was definitively stopped. In the presence of grade 2 to 3 hematologic toxicity, treatment was delayed for 1 week or until hematologic recovery. If recovery was not reached, the dose level was reduced. For grade 0 to 2 gastrointestinal toxicity, dose administration was 100%, and for grade 3 toxicity, after a 1-week delay, the dose level was reduced. For neurosensory toxicity, recommended dose modifications are listed in Table 1.

Statistical Analysis

Evaluation of objective response was the primary end point in this trial. Objective responses were reported as relative rates with their 95% CIs. Secondary end points were TTP, OS, and toxicity.

As derived from published data[9,19] at the time when the study was started, the expected response rates were 35% and 50% for the FOLFIRI and the FOLFOX4 regimens, respectively. Therefore, the study was designed to have the power to detect a 15% difference in objective response rate between the two arms, using a two-sided log-rank test with an α risk of .05 and a β risk of .20. The number of patients to be included in each arm was calculated to be 176.

All of the randomly assigned patients were included in the survival analysis. To compare the difference between treatment groups for the proportion of patients with objective response, the z test of normal distribution and 95% CIs for proportions were used. The Wilcoxon rank sum test was used to evaluate the difference in the response duration between the treatment groups.[23]

A univariate analysis of survival according to the product-limit (Kaplan-Meier) estimate was performed.[24] Comparisons between survival distributions were made by the log-rank test. In multivariate analyses, the Cox proportional hazards model was used to study the effects of different variables on survival.[25]

Statistical significance was defined as $P \leq .05$ for univariate and multivariate analyses. All P values were based on two-sided testing.

RESULTS

Patient and Clinical Characteristics

Between March 1999 and November 2002, 360 consecutive patients were admitted onto the trial from the participating centers. Of these patients, 178 were assigned to the FOLFIRI regimen (arm A), and 182 were assigned to the FOLFOX4 regimen (arm B). The arms were well balanced with respect to stratification factors and other baseline

Table 1. Recommended Dose Modifications

Type of Toxicity	Duration of Toxicity		
	≤ 7 Days	> 7 Days, ≤ 14 Days	Persistent Between Courses
Cold-related dysesthesia	None	None	None
Paresthesia without pain	None	None	Stop until recovery; then restart at 75 mg/m^2
Paresthesia associated with pain	None	Reduction: 75 mg/m^2*	Stop
Paresthesia with functional impairment	None	Reduction: 75 mg/m^2*	Stop

*If complete recovery and no neurologic symptoms at time of visit. In case of unbearable symptoms during the course, even if fully recovered at time of visit, oxaliplatin administration was delayed until the next cycle and reintroduced at the dosage of 75 mg/m^2.

characteristics (Table 2). The median age in both groups was 62 years. In arms A and B, 55 and 52 patients previously received adjuvant therapy, respectively. The majority of patients had a primary colon cancer (66% and 68% in arms A and B, respectively) and liver metastases (72% in arm A and 73% in arm B). Slightly more patients assigned to the FOLFIRI regimen had metachronous metastatic disease, whereas, in the FOLFOX4 arm, more patients had lymph node involvement. About half of the patients had multiple sites of disease in both arms (FOLFIRI, 44%; FOLFOX4, 46%). Moreover, 31% of patients in arm A and 32% of patients in arm B had previously received LV plus FU–based adjuvant chemotherapy.

Table 2. Patient Characteristics

Characteristic	FOLFIRI (n = 178)		FOLFOX4 (n = 182)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	93	52	109	60
Female	85	48	73	40
Age, years				
Median	62		62	
Range	32-75		31-75	
Performance status, ECOG				
Median	0		0	
0	108	60	106	58
1	67	38	68	38
2	3	2	8	4
Previous adjuvant therapy				
Yes	55	31	52	29
No	123	69	130	71
Primary tumor				
Colon	118	66	123	68
Rectum	60	34	59	32
Metastatic disease				
Synchronous	104	58	114	63
Metachronous	74	42	68	37
Stratification groups				
H+, tumor > 10 cm^2	96	54	100	55
H+, tumor < 10 cm^2	32	18	33	18
H−, tumor > 10 cm^2	28	16	28	15
H−, tumor < 10 cm^2	22	12	21	12
Site of disease				
Liver	128	72	133	73
Lung	49	28	45	25
Pelvis	15	8	13	7
Peritoneum	12	7	11	6
Lymph node	25	14	34	19
Primary tumor	22	12	21	12
Liver only	64	50	68	51
Liver + other sites	64	50	65	49
No. of sites				
1	100	56	99	54
≥ 2	78	44	83	46

Abbreviations: FOLFIRI, irinotecan, fluorouracil, and leucovorin; FOLFOX4, oxaliplatin, leucovorin, and bolus plus infusional fluorouracil; ECOG, Eastern Cooperative Oncology Group; H+, with liver involvement; H−, without liver involvement.

Therapeutic Outcome

A total of 336 patients were deemed assessable for response (164 in arm A, 92%; and 172 in arm B, 95%). Overall, 24 patients (14 in arm A and 10 in arm B) were considered nonassessable for the following reasons. In arm A, four patients were not assessable because of noneligibility or protocol violation, six patients refused to continue the treatment despite low toxicity, three patients were not assessable because of toxicity, and one patient was not assessable because of early death unrelated to chemotherapy. In arm B, four patients were not assessable because of noneligibility or protocol violation, five patients refused to continue treatment (not for toxicity), and one patient was not assessable because of toxicity.

Among the patients excluded for toxicity in arm A, one patient had a cardiac ischemic episode after the second cycle of treatment, and two patients died for hematologic reasons (one severe treatment-related febrile neutropenia and one disseminated intravascular coagulation); whereas in arm B, one patient stopped the treatment because of grade 3 hepatic toxicity (transaminase) after the first cycle of therapy.

A total of 1,264 cycles of the FOLFIRI regimen were administered during the study, with a median of eight cycles per patient (range, one to 22 cycles). A total of 1,321 cycles of the FOLFOX4 combination therapy were administered, with a median of eight cycles per patient (range, one to 15 cycles). The average number of cycles (ITT analysis) was 7.14 and 7.26 cycles in arms A and B, respectively. More than 12 cycles were administered to four patients in arm A and two patients in arm B.

The response rates for the two treatment arms are listed in Table 3. Response rates between the FOLFIRI arm and the FOLFOX4 arm did not statistically differ, whether evaluated as ITT analysis ($P = .60$) or as assessable patients only ($P = .71$). The ORR in the assessable patients was 34% in arm A (95% CI, 26.9% to 41.4%) and 36% in arm B (95% CI, 28.9% to 43.2%). When ITT analysis was performed, ORR was 31% in arm A (95% CI, 24.6% to 38.3%) and 34% in arm B (95% CI, 27.2% to 41.5%). When also considering SD, the overall tumor growth control rate (CR + PR + SD) was 76% and 74% in arms A and B, respectively (70% in both arms in ITT analysis).

The median duration of response was 9 months in arm A and 10 months in arm B ($P = .06$), whereas the median TTP according to ITT analysis was 7 months in both arms (Fig 2). According to the ITT analysis, the median OS (Fig 3) was 14 and 15 months for patients in arms A and B, respectively ($P = .28$). The median follow-up time of the study was 31 months (range, 11 to 56 months), and the 1-year survival rate was 55% and 62% ($P = .16$) in arms A and B, respectively.

Table 3. Response Rates for the Treatment Arms

Response	FOLFIRI	FOLFOX4	*P*
No. of patients entered	178	182	
No. of patients assessable	164	172	
Response			
CR			
No.	8	9	
%	4.8	5.2	
PR			
No.	48	53	
%	29.2	30.8	
SD			
No.	68	66	
%	41.6	38.3	
PD			
No.	40	44	
%	24.4	25.7	
CR + PR, No.	56	62	
Response rate			
Assessable population			
%	34	36	.71
95% CI	26.9 to 41.4	28.9 to 43.2	
Intent-to-treat population			
%	31	34	.60
95% CI	24.6 to 38.3	27.2 to 41.5	
Duration, months			
Response			
Median	9	10	.06
Range	4-47	5-27	
TTP			
Median	7	7	.64
Range	1-47	1-32	
Survival			
Median	14	15	.28
Range	1-48	1-43	

Abbreviations: FOLFIRI, irinotecan, fluorouracil, and leucovorin; FOLFOX4, oxaliplatin, leucovorin, and bolus plus infusional fluorouracil; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTP, time to progression.

Second-line therapy (mainly consisting of OHP regimens after CPT-11 and CPT-regimens after OHP) was administered to 61% of patients previously treated with FOLFIRI and to 58% of patients previously treated with FOLFOX4. Overall, patients receiving second-line therapy had a median OS of 17 months, whereas patients who did not receive a second-line therapy had a median OS of 10 months.

According to the obtained objective response, the median OS in arms A and B were as follows: patients with CR + PR, 18 *v* 20 months, respectively; patients with SD, 15 *v* 15 months, respectively; and patients with progressive disease, 8 *v* 9 months, respectively. In the group of patients with hepatic metastatic disease, no difference was found between the arms A and B in response rate (33% and 34%, respectively, with ITT analysis; $P = .86$), whereas patients with lung metastases obtained better but not statistically

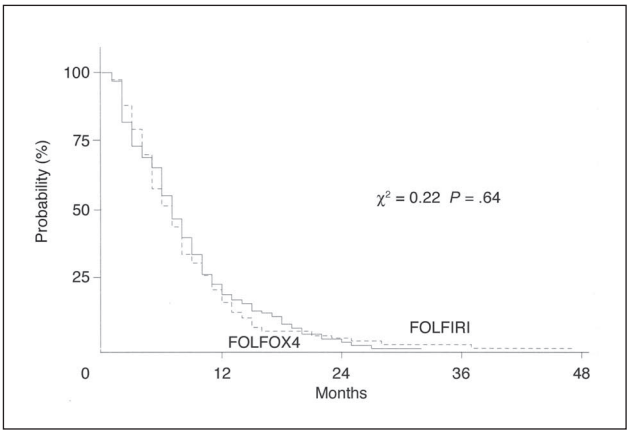

Fig 2. Time to progression. FOLFIRI, irinotecan, leucovorin, and fluorouracil regimen; FOLFOX4, oxaliplatin, leucovorin, and fluorouracil regimen.

significant results with the FOLFOX4 regimen (25% and 40% for arms A and B, respectively, with ITT analysis; $P = .11$).

When objective response rates were analyzed according to the primary site of tumor, in arm A and B patients with rectal and colon cancer, we observed (ITT analysis) response rates of 30% (18 of 60 patients) versus 37% (22 of 59 patients) and 32% (38 of 118 patients) versus 33% (40 of 123 patients), respectively. In the 64 patients in arm A in whom liver represented the only metastatic disease site, we obtained 26 objective responses (41%), whereas in arm B, 24 (35%) of 68 patients obtained an objective response. Furthermore, in patients with liver plus other disease sites, we observed 15 objective responses in arm A (15 of 64 patients; 23%) and 21 objective responses in arm B (21 of 65 patients; 32%). Secondary surgery to remove liver metastases was performed in nine patients in the FOLFIRI arm (5.1%) versus eight patients in the FOLFOX4 arm (4.4%).

Considering the four stratification groups, the response rates in arms A and B were as follows (ITT analysis): H+ and tumor more than 10 cm^2, 30% *v* 37%, respectively ($P = .31$); H+ and tumor less than 10 cm^2, 37.5% *v* 24%,

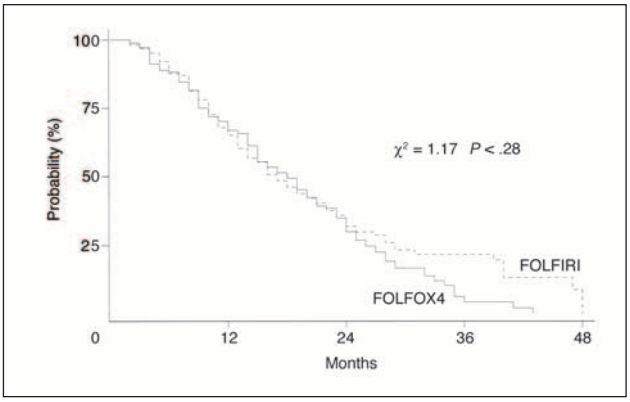

Fig 3. Overall survival. FOLFIRI, irinotecan, leucovorin, and fluorouracil regimen; FOLFOX4, oxaliplatin, leucovorin, and fluorouracil regimen.

respectively ($P = .25$); H− and tumor more than 10 cm^2, 25% *v* 29%, respectively ($P = .76$); and H− and tumor less than 10 cm^2, 36% *v* 43%, respectively ($P = .66$). In the patients with only a single site of disease, we observed a 38% ORR in arm A and a 34% ORR in arm B ($P = .60$), whereas in patients with multiple sites of disease, the ORRs were 23% and 34% in arms A and B, respectively ($P = .13$).

Multivariate analysis of prognostic factors related to response rate did not show any statistical difference. In Table 4, multivariate analysis of prognostic factors related to OS is reported. The only factor predictive of improved OS was the number of metastatic sites, and in the four stratification groups, only patients with the absence of metastatic liver disease less than 10 cm^2 had statistically better survival than patients with liver metastases more than 10 cm^2.

Toxicity

All patients were assessable for toxicity. In arm A, there were two therapy-related deaths as a result of hematologic toxicity (febrile neutropenia); another patient died of a disseminated intravascular coagulation (not related to the treatment) because of concomitant progressive disease. There were no treatment-related deaths in arm B.

The observed toxicities, according to the National Cancer Institute Common Toxicity Criteria, are listed in Table 5. Overall, toxicity was mild in both patient groups; grade 3 to 4 toxicities were uncommon in both arms, with no statistical difference. When all grades of toxicities were analyzed, significant statistical differences between the two arms (A *v* B) were found for thrombocytopenia (15% *v* 43%, respectively; $P < .0001$), nausea and vomiting (72% *v* 59%, respectively; $P = .009$), diarrhea (63.5% *v* 46%, respectively; $P = .0007$), loss of hair (42% *v* 19%, respectively; $P < .0001$), and neurologic toxicity (5% *v* 45%, respectively; $P < .0001$).

The most frequent toxicity in FOLFIRI arm was gastrointestinal; as expected, in this arm, more alopecia and gastrointestinal toxicities (mainly grade 1 to 2) were observed. Symptoms related to a cholinergic syndrome occurred in 18 patients treated with CPT-11 (10%). All these events were manageable.

In arm B, more grade 1 to 2 thrombocytopenia was observed; furthermore, as expected, neurologic toxicity was more frequent. In the case of neurologic toxicity, we observed mainly cold-sensitive dysesthesias or paresthesias, which occurred at low total cumulative doses and which were reversible and did not require discontinuation of treatment. Only eight patients developed grade 3 neuropathy (4%), and reversibility of this sensory neurotoxicity was observed in all patients.

Hypersensitivity reactions were observed only in the FOLFOX4 arm and occurred mainly as grade 1 to 2 toxicity after five to six cycles of treatment; premedication with dexamethasone and antihistamine drugs in subsequent cycles enabled these patients to continue therapy with full-dose treatment. In the two patients with grade 3 to 4 hypersensitive toxicity, treatment continued without OHP.

The death rates within the first 60 days of treatment were 2.8% for patients receiving FOLFIRI and 1.1% for patients receiving FOLFOX4 ($P = .24$). In the FOLFIRI arm, one patient died of disseminated intravascular coagulation, two patients died of therapy-related febrile neutropenia, and two patients died of progressive disease. In the FOLFOX4 arm, two patients died of progressive disease. No chemotherapy-related deaths were observed in the FOLFOX4 arm.

DISCUSSION

Our study is the first randomized trial of a head-to-head comparison between the FOLFIRI and FOLFOX4 regimens

Table 4. Multivariate Analysis of Prognostic Factors

Variable	HR	SE	*P*	95% CI for HR
Treatment	1.044	0.143	.752	0.798 to 1.366
Age	1.009	0.007	.255	0.993 to 1.024
Sex	0.946	0.129	.686	0.723 to 1.237
Adjuvant therapy	1.204	0.203	.269	0.865 to 1.676
Synchronous/metachronous metastases	1.055	0.175	.746	0.761 to 1.463
Single/multiple sites	1.348	0.188	.033	1.024 to 1.774
PS ECOG, 0 *v* 1	1.088	0.158	.562	0.817 to 1.449
PS ECOG, 0 *v* 2	1.648	0.165	.813	0.813 to 3.341
H−, tumor < 10 cm^2 *v* H−, tumor > 10 cm^2	1.201	0.338	.515	0.691 to 2.088
H−, tumor < 10 cm^2 *v* H+, tumor < 10 cm^2	1.082	0.311	.782	0.616 to 1.901
H−, tumor < 10 cm^2 *v* H+, tumor > 10 cm^2	1.688	0.418	.034	1.039 to 2.743

Abbreviations: HR, hazard ratio; PS, performance status; ECOG, Eastern Cooperative Oncology Group; H−, without liver involvement; H+, with liver involvement.

Table 5. Observed Toxicities for Both Treatment Arms

Toxicity	FOLFIRI				FOLFOX4			
	Grade 1 to 2		Grade 3 to 4		Grade 1 to 2		Grade 3 to 4	
	No.	%	No.	%	No.	%	No.	%
Anemia	67	38	1	1	60	33	3	2
Leukopenia	65	37	5	3	70	38	5	3
Neutropenia	63	35	17	10	58	32	18	10
Thrombocytopenia	26	15	1	1	76	42	3	3
Nausea/vomiting	120	67	8	4	102	56	5	3
Diarrhea	95	53	18	10	74	41	9	5
Mucositis	61	34	2	1	52	29	2	1
Loss of hair	75	42	—	—	35	19	—	—
Cholinergic syndrome	18	10	—	—	—	—	—	—
Neurologic*	9	5	—	—	74	41	8	4
Fever	26	15	2	1	37	20	—	—
Asthenia	28	16	—	—	24	13	—	—
Cardiac	2	1	1	1	3	2	2	1
Skin	6	3	—	—	7	4	—	—
Hypersensitivity	—	—	—	—	4	2	2	1

Abbreviations: FOLFIRI, irinotecan, fluorouracil, and leucovorin; FOLFOX4, oxaliplatin, leucovorin, and bolus plus infusional fluorouracil.
*Peripheral neuropathy was graded according to the specific grading system of Levì et al.[22]

in the treatment of advanced CRC. For the last few decades, FU-based chemotherapy remained the mainstay of treatment of CRC patients, and its biomodulation with LV obtained better response rates than FU alone, but meta-analysis data failed to demonstrate a survival benefit compared with FU alone.[1] Prolonged infusion of FU showed better results in terms of response rate and OS than FU alone,[26] and a hybrid regimen of FU (LV5FU2) with a bolus and an infusional administration of FU obtained significant improvements in response rate and TTP compared with the standard low-dose LV-FU bolus schedule of the North Central Cancer Treatment Group regimen.[2] Furthermore, the addition to LV5FU2 of CPT-11 or OHP showed better results than LV5FU2 alone in two large studies,[9,19] and therefore, these regimens were commonly used in European countries as first-line therapy in advanced CRC patients.

To verify and compare the activity of these two regimens, the GOIM, in 1999, started protocol No. 9901. Three hundred sixty consecutive, nonseletected patients were entered onto this trial and randomly assigned to receive either the FOLFIRI regimen according to Douillard et al[9] or the FOLFOX4 regimen according to de Gramont et al.[19]

Our results showed that no difference in terms of tumor regression rate was observed in the two arms, with objective responses observed in 31% of patients in the FOLFIRI arm and 34% of patients in the FOLFOX4 arm ($P = .60$). The characteristics of patients were well balanced in the two arms, and the patients were representative of candidates for first-line chemotherapy in clinical practice, with an elevated number of patients with unfavorable prognostic factors in both arms, such as multiple liver disease, tumor burden, and previous adjuvant chemotherapy. These considerations might explain the relatively lower response rates observed in our study compared with the response rates of previous studies.[9,19]

In particular, when we considered the FOLFIRI arm, the characteristics of patients entered onto our study seemed similar to the characteristics of patients in the study by Douillard et al[9]; in addition, the objective response rate reported in our study according to an ITT analysis (31%) was similar that reported in the study by Douillard et al[9] (32%). In the Douillard study, it was not possible to know the number of patients with a single site of metastatic disease, and a slightly smaller percentage of patients than in our trial had previously received adjuvant chemotherapy (26% *v* 31%, respectively). In the study by Tournigand et al,[27] the objective response rate obtained with the FOLFIRI first-line treatment was 56%, but in this trial, there were fewer patients with multiple sites of disease (41%) and with previously adjuvant therapy (17%) than in our study. These findings were reported as negative prognostic factors in the analysis of previous experiences.[10,19] The FOLFOX4 regimen obtained a 34% response rate in our study. With the same regimen, de Gramont et al[19] observed an ITT response rate of 50%. In this latter study, some characteristics of enrolled patients appeared prognostically more favorable than in our study (20% had received adjuvant therapy and 33% had metachronous metastases *v* 29% and 37%, respectively, in our study). Tournigand et al,[27] with a slightly different schedule and a higher OHP dose (FOLFOX6 regimen), observed tumor regression in 54% of patients; again,

in this study, 21% of patients had received adjuvant therapy, and 41% had multiple sites of disease.

However, apart from considering the demographic characteristics of the entered patients, the patients entered onto the present trial were representative of candidates for first-line chemotherapy in clinical practice. Most patients had unfavorable prognostic factors such as high liver involvement (> 25%).

Previous studies have shown that, in first-line therapy, the addition of CPT-11 or OHP to the LV5FU2 regimen or to bolus FU has an impact on survival of patients with metastatic CRC,[9,10,19] and the median OS observed in these trials was between 15 and 17 months. No difference in OS was observed between the FOLFIRI and FOLFOX4 arms in our study (14 *v* 15 months, respectively; $P = .28$). These results are somewhat lower than those reported by other authors with the same or similar regimens.[9,19,27,28] This difference may be a result of the patient characteristics selected in our trial, as commented on earlier.

As previously reported in other trials, in addition to the presence of negative prognostic factors, second-line therapies have also shown an impact on survival. In our study, second-line therapy was administered to 61% of the FOLFIRI arm and to 58% of the FOLFOX4 arm. In the Tournigand et al[27] study, 74% and 62% of patients received second-line chemotherapy in the FOLFIRI and the FOLFOX arms, respectively. In the three-arm study (IFL, FOLFOX4, and irinotecan plus oxaliplatin [IROX]) reported by Goldberg et al,[2] second-line therapy was administered to 67%, 75%, and 70% of patients, respectively. Second-line chemotherapy could have contributed to OS in this trial; in fact, because OHP was not readily available in North America, only 24% of patients received this drug after discontinuing the IFL arm, whereas CPT-11 was administered to 60% of patients after discontinuing the FOLFOX4 regimen. This difference could have contributed to the statistically significant improvement in OS in the FOLFOX4 arm compared with the IFL arm (19.5 *v* 15 months, respectively; $P = .0001$), but the exact role of second-line chemotherapy in determining results remains unclear.

When the three main effective drugs (FU, OHP, and CPT-11) were used in a higher percentage of patients, better results were observed in terms of OS. In the Tournigand et al[27] study, 82% and 74% of patients received second-line treatment after the FOLFIRI and FOLFOX6 first-line regimens, respectively, and OS was greater than 20 months in both groups. In our study, the median OS time of patients treated with the three main drugs was 18 months.

As expected, the toxicity profile of both regimens showed some differences. Also, for the safety evaluation, our study is the first study with a head-to-head comparison between FOLFIRI and FOLFOX4. The adverse event profile was favorable overall for both regimens, and grade 3 to 4 toxicities were uncommon in both arms, with no statistical difference. In the FOLFIRI arm, the most frequent toxicity was gastrointestinal (mainly grade 1 to 2 diarrhea and nausea and vomiting), and the rates of toxic effects were similar overall to those observed in the study by Douillard et al.[9]

More grade 1 to 2 thrombocytopenia and, as expected, sensory neuropathy (mainly cold-sensitive dysesthesias or paresthesias) occurred in our study in the FOLFOX4 arm compared with the FOLFIRI arm. Only eight patients experienced grade 3 neuropathy, which was reversible in all patients and did not require discontinuation of treatment. The median number of FOLFOX4 cycles administered in this study was eight, and this justifies the observed low rate of neurosensory toxicity. With the same regimen in the de Gramont et al[19] study, 18% of patients experienced grade 3 neurologic toxicity, and the frequency of this adverse event was clearly related to the exposure to OHP; 10% of patients had grade 2 to 3 neuropathy after three and nine cycles of FOLFOX4, 25% had grade 2 to 3 neuropathy after eight and 12 cycles, and 50% had grade 2 to 3 neuropathy after 10 and 14 cycles. Furthermore, with an enhanced dose of OHP and with a higher median number of cycles,[12] severe neurologic toxicity occurred in 34% of patients treated with the FOLFOX6 regimen,[28] and 19% of patients had grade 3 neuropathy at the beginning of FOLFIRI second-line therapy.

In conclusion, this study has demonstrated that there is no difference in response rate, TTP, and OS for patients treated with the FOLFIRI or FOLFOX4 regimens, and both combination therapies seemed effective as first-line treatment in advanced CRC patients. Our results confirm the efficacy of the addition of OHP or CTP-11 to the LV5FU2 schedule and the mild toxicity of both regimens. Furthermore, FU still remains the basic component of the most efficacious regimens, and infusional FU is the best partner in combination with OHP or CTP-11.[29] The difference between these two combination therapies is mainly the toxicity profile; more gastrointestinal side effects and alopecia were observed in the FOLFIRI arm, and more thrombocytopenia, neurotoxicity, and hypersensitivity reactions were observed in the FOLFOX4 arm. Therefore, in clinical practice, the treatment choice must be individually tailored on these bases.

Improvement of the results obtained with these two combination treatments should be possible with the addition of new drugs. In particular, targeted therapies, such as two monoclonal antibodies directed against epidermal growth factor receptors or vascular endothelial growth factor (cetuximab and bevacizumab, respectively), showed antitumor activity alone and in combination with chemotherapy in advanced CRC.[30,31] Phase II and III trials are ongoing in the United States and Europe.

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Appendix

The following investigators are members of the Southern Italy Oncology Group (GOIM) and are coauthors of the article: Oncology Institute, Bari: Severino Montemurro, Antonio Cramarossa, Vito Lorusso, Maurizio Di Bisceglie; Centro Catanese di Oncologia, Catania: Maurizio Chiarenza; University, Palermo: Maria Rosaria Valerio; Cardarelli Hospital, Naples: Teresa Guida; M. Ascoli Hospital, Palermo: Vita Leonardi; Ospedale Nord, Taranto: Salvatore Pisconti; S. Carlo Hospital, Potenza: Gerardo Rosati; Cardarelli Hospital, Campobasso: Francesco Carrozza; Miulli Hospital, Acquaviva delle Fonti: Giuseppe Nettis; Buccheri La Ferla Hospital, Palermo: Matteo Valdesi; Hospital, Paola: Gianfranco Filippelli; Analysis Center, Catania: Santo Fortunato; Hospital, Campi Salentina: Sergio Mancarella; and Hospital, Manduria: Cosimo Brunetti.

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The authors indicated no potential conflicts of interest.

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