Original article

Annals of Oncology 16: 878–886, 2005
doi:10.1093/annonc/mdi185
Published online 18 April 2005

Oxaliplatin plus high-dose folinic acid and 5-fluorouracil i.v. bolus (OXAFAFU) versus irinotecan plus high-dose folinic acid and 5-fluorouracil i.v. bolus (IRIFAFU) in patients with metastatic colorectal carcinoma: a Southern Italy Cooperative Oncology Group phase III trial†

P. Comella[1]*, B. Massidda[2], G. Filippelli[3], S. Palmeri[4], D. Natale[5], A. Farris[6], F. De Vita[7], F. Buzzi[8], S. Tafuto[9], L. Maiorino[10], S. Mancarella[11], S. Leo[12], V. Lorusso[13], L. De Lucia[14] & M. Roselli[15]

[1]Department of Medical Oncology, National Tumour Institute, Naples; [2]Chair of Medical Oncology, University Medical School, Cagliary; [3]Medical Oncology, City Hospital, Paola; [4]Chair of Medical Oncology, University Medical School, Palermo; [5]Medical Oncology, City Hospital, Penne; [6]Chair of Medical Oncology, University Medical School, Sassari; [7]Chair of Medical Oncology, Second University Medical School, Naples; [8]Medical Oncology, City Hospital, Terni; [9]Medical Oncology, City Hospital, Pozzuoli; [10]Medical Oncology, San Gennaro Hospital, Naples; [11]Medical Oncology, City Hospital, Campi Salentina; [12]Medical Oncology, IRCCS, Castellana Grotte; [13]Department of Medical Oncology, National Tumour Institute, Bari; [14]Medical Oncology, City Hospital, Caserta; [15]Department of Surgical Oncology, Tor Vergata University Medical School, Rome, Italy

Received 22 December 2004; revised 11 January 2005; accepted 12 January 2005

Purpose: The primary end point of this phase III trial was to compare the response rate (RR) of oxaliplatin (OXA) plus levo-folinic acid (*l*-FA) and 5-fluorouracil (5-FU) bolus with that of irinotecan (IRI) plus *l*-FA and 5-FU bolus in advanced colorectal carcinoma.

Patients and methods: Patients with measurable metastatic colorectal carcinoma were randomly allocated to receive: IRI 200 mg/m^2 on day 1, *l*-FA 250 mg/m^2 intravenously plus 5-FU 850 mg/m^2 on day 2 (IRIFAFU); or OXA 100 mg/m^2 on day 1, *l*-FA 250 mg/m^2 plus 5-FU 1050 mg/m^2 on day 2 [OXAFAFU high dose (hd)]. Cycles were given every 2 weeks. After a planned interim analysis, OXA was reduced to 85 mg/m^2 and 5-FU to 850 mg/m^2 [OXAFAFU low dose (ld)].

Results: Two hundred and seventy-four patients (IRIFAFU, 135; OXAFAFUhd, 71; OXAFAFUld, 68) were treated. Forty-two confirmed responses were achieved with IRIFAFU, 29 with OXAFAFUhd and 32 with OXAFAFUld. The response rate with OXAFAFU [44%; 95% confidence interval (CI) 35% to 52%] was significantly higher ($P = 0.029$) than that of IRIFAFU (31%; 95% CI 23% to 40%). Occurrence of grade ≥3 neutropenia with OXAFAFUld was similar to that for IRIFAFU (29% versus 31%), while severe diarrhoea was significantly lower (12% versus 24%). Median failure-free survival (7 versus 5.8 months; $P = 0.046$) and overall survival of patients (18.9 versus 15.6 months; $P = 0.032$) were significantly prolonged with OXAFAFU.

Conclusions: OXAFAFU was more active and less toxic than IRIFAFU, and it should be preferred in the first-line treatment of advanced colorectal cancer patients.

Key words: 5-fluorouracil, irinotecan, metastatic colorectal carcinoma, oxaliplatin, randomized trial.

Introduction

For decades, 5-fluorouracil (5-FU) has been the only available drug for the treatment of metastatic colorectal carcinoma. 5-FU has usually been administered as an intravenous (i.v.) bolus and/or infusion, concurrently with folinic acid (FA), methotrexate (MTX) or both, in order to achieve greater activity than 5-FU alone [1–4]. This approach has recently been demonstrated to minimally prolong the survival of

†Other Southern Italy Cooperative Oncology Group (SICOG) investigators and institutions taking part in this trial are listed in the Acknowledgements.

**Correspondence to:* Dr P. Comella, Division of Medical Oncology A, Department of Medical Oncology, National Tumour Institute, Via M. Semmola, 80 131 Naples, Italy. Tel. +39-081-5903-227; Fax: +39-081-5903821; E-mail: pasqualecomella@libero.it

© 2005 European Society for Medical Oncology

Downloaded from http://annonc.oxfordjournals.org/ at Biblioteca Area Biomedica on December 11, 2011

patients in comparison with 5-FU alone [5]. In contrast, despite different toxicity profiles, a similar survival was seen whichever schedule was used, i.e. weekly, biweekly or monthly [6, 7].

During the last decade, new drugs have shown activity in this disease. First, irinotecan (IRI) has been proven to prolong survival and improve quality of life of 5-FU-refractory patients [8], and to have an activity comparable to FA/5-FU in the first-line setting [9]. These findings suggested the lack of cross-resistance between IRI and FA/5-FU, supporting the commencement of trials testing their combination in front-line treatment. Saltz et al. [9] reported on IRI plus FA/5-FU bolus given for four consecutive weeks every 6 weeks (IFL regimen). The response rate (RR) was significantly greater (39% versus 21%), and progression-free survival (PFS) (median 7 versus 4.3 months) and overall survival (OS) (median 14.8 versus 12.6 months) were significantly longer with the IFL in comparison with those obtained with the Mayo Clinic regimen. Douillard et al. [10] administered the AIO or LV5FU2 regimen recycled either weekly or biweekly, alone or combined with IRI. RR (35% versus 22%), PFS (median 6.7 versus 4.4 months) and OS (median 17.4 versus 14.1 months) favoured the IRI-including treatment. In the Southern Italy Cooperative Oncology Group (SICOG) trial 9801, IRI was given biweekly on day 1, followed by levo-FA (*l*-FA) and 5-FU bolus on day 2. This IRIFAFU regimen produced a significantly greater RR (36% versus 20%) and longer PFS (median 7.2 versus 4.8 months) in comparison with a double modulation of 5-FU by means of MTX and *l*-FA [11]. However, OS for the two arms was similar (14.7 versus 14.8 months, respectively).

Oxaliplatin (OXA) has shown activity *in vitro* against 5-FU-resistant colon cancer cell lines [12], and it is effective in both chemonaïve and 5-FU-pretreated patients [13–15]. Interestingly, preclinical studies have shown the greatest cell kill when OXA was followed by a short rather than prolonged 5-FU exposure [16]. However, in early clinical trials OXA was usually combined with chronomodulated or flat infusional 5-FU [17–20]. In front-line, the FOLFOX4 regimen obtained a significantly greater RR (51% versus 23%) and longer PFS (median 9 versus 6.2 months) in comparison with LV5FU2. OS was also longer (median 16.2 versus 14.7 months) [20]. Conversely, there are still few clinical data about efficacy of OXA and FA/5-FU given as bolus. Some investigators have explored the addition of OXA to FA/5-FU delivered daily for 5 days (i.e. Machover or Mayo Clinic regimen). Activity was reported in 40% to 45% of patients [21, 22], but toxicity was substantial. More recently, Hochster et al. [23] administered OXA 85 mg/m^2 on day 1 and 15, and FA 20 mg/m^2 plus 5-FU 500 mg/m^2 on days 1, 8 and 15, recycling every 28 days, achieving a 63% RR and a 15.9 month median OS in 41 patients. The Nordic Group explored the addition of OXA 85 mg/m^2 to a combination of FA 60 mg/m^2 and 5-FU 500 mg/m^2 given for two consecutive days, administered biweekly, obtaining a 62% RR and a median OS of 16.1 months [24].

Therefore, the combination of OXA and FA/5-FU bolus showed promising activity in metastatic patients. For these reasons, we carried out a phase I study to find the recommended doses for an OXA plus FA/5-FU bolus biweekly regimen (OXAFAFU). Although the maximum tolerated doses were not reached up to 130 mg/m^2 for OXA and 1050 mg/m^2 for 5-FU, some concern about the occurrence of cumulative neurotoxicity suggested OXA 100 mg/m^2 was not exceeded in further evaluation. Therefore, we set up a multicentre randomised phase III trial to assess the activity and toxicity of OXAFAFU, and to compare this new regimen with the IRIFAFU in metastatic colorectal cancer patients [25].

Patients and methods

Patient selection

Main inclusion criteria were: histologically proven diagnosis of adenocarcinoma of the colon or rectum; age ≥18 years and life expectancy >3 months; Eastern Cooperative Oncology Group performance status (PS) ≤2; metastatic unresectable disease; at least one bidimensionally measurable lesion; neutrophils count ≥2000/mm^3, platelet count ≥100 000/mm^3, bilirubin ≤1.25× upper normal limit (UNL), alanine aminotransferase and aspartate aminotransferase ≤5× UNL; and normal renal function (calculated creatinine clearance ≥60 ml/min). Patients previously exposed to palliative chemotherapy as well as those who had received adjuvant treatment within the last 6 months were excluded. Other main exclusion criteria were: inflammatory bowel diseases or significant diarrhoea during the last week, previous total colectomy or ileostomy, bowel obstruction; uncontrolled metabolic disorders or active infections; severe cardiac arrhythmia, or acute myocardial infarction in the last 6 months; symptomatic cerebral metastasis; concomitant or previous malignant tumour. This protocol was approved by the Independent Ethics Committee of the National Tumour Institute of Naples, and written informed consent was required from each patient.

Patients evaluation

Medical history and physical examination were taken at study entry. Biochemistry profile, blood cell count with white cell count and differential, and carcinoembryonic antigen (CEA) serum level assessment, were routinely performed. Target lesions were measured by computed tomography (CT) or magnetic resonance imaging (MRI) scans no more than 4 weeks before initial therapy. During treatment, white cell count with differential was performed weekly. Biochemistry, symptoms, body weight and non-haematological toxicity were checked before each cycle. Toxicity was scored according to WHO criteria [26]. Neuropathy was defined according to the Lévi scale [27]. For the study purpose, the worst toxicity suffered by each patient during the whole treatment was recorded.

CT or MRI scans were repeated after every four cycles, and at the end of treatment. Response was defined according to WHO criteria [26]. Responses were reassessed 8 weeks after their first documentation, and only confirmed responses were computed in the activity analysis. Duration of response was calculated from initial therapy up to documented progression of disease (PD), or last follow-up. Failure-free survival (FFS) was calculated from registration to the time of treatment discontinuation for any reason (occurrence of progression or unacceptable toxicity, because of patient's refusal or when it was deemed in the patient' best interest by the attending physician). OS was calculated from registration to death for any cause, or patient's last follow-up.

Downloaded from http://annonc.oxfordjournals.org/ at Biblioteca Area Biomedica on December 11, 2011

Treatment

Patients were stratified according to centre, previous adjuvant chemotherapy and PS, and randomly allocated to receive: IRI 200 mg/m^2 i.v. (90 min) on day 1, *l*-FA 250 mg/m^2 i.v (2 h), 5-FU 850 mg/m^2 i.v. bolus on day 2 (IRIFAFU regimen); or OXA 100 mg/m^2 i.v. (2 h) on day 1, *l*-FA 250 mg/m^2 i.v. (2 h), 5-FU 1 050 mg/m^2 i.v. bolus on day 2 [OXAFAFU high dose (hd)]. In both arms, cycles were repeated every 2 weeks. A planned interim analysis on toxicity was carried out when half of the target population had been treated, to assess whether frequency of febrile neutropenia exceeded 10% of patients, which was the predefined restraint for dosage amendment. At that time the actual occurrence of febrile neutropenia among patients treated with OXAFAFUhd was 13%, and therefore the study regimen was amended: OXA and 5-FU were reduced to 85 mg/m^2 and 850 mg/m^2, respectively [OXAFAFU low dose, (ld)] for the subsequent patients.

Cytotoxic drugs in each doublet were reduced by 25% after occurrence of grade 4 haematological toxicity, or grade 3 non-haematological toxicity, on previous cycle. Chemotherapy was administered until the confirmed achievement of a complete response (CR) (minimum of eight cycles), or up to 12 cycles. Treatment was discontinued earlier in the case of documented PD, unacceptable toxicity, patient's refusal or when it was believed in the best patient's interest by the attending physician. After PD, a cross-over policy, i.e. IRIFAFU in second-line after OXAFAFU in first-line and *vice versa*, was advised but not mandatory.

Statistical considerations

We assumed that the OXAFAFU regimen might increase by 50% (from 5 to 7.5 months) the median FFS in comparison with the IRIFAFU regimen. With 257 events on the whole series of patients there is an 80% power to demonstrate this difference with a 0.05 alpha error [28]. Therefore, a recruitment of 280 patients has been planned for the comparative analysis. This number of patients may also give an 80% power to detect a 15% difference in RR between the OXAFAFU and IRIFAFU [29].

The occurrence of responses and toxicities was compared using the χ^2-test or Fisher's exact test where appropriate [30], and a P value <0.05 was considered significant. Univariate and multivariate analyses were performed for identifying factors associated with RR. Actuarial median [with 95% confidence interval (CI)] of FFS and OS times were obtained using the Kaplan–Meier method [31], and compared using the log-rank test [32].

Results

Patient characteristics

From January 2001 to June 2003, 288 patients were registered onto this study. However, 12 (4%) patients did not meet the inclusion criteria, and were excluded, leaving 276 patients for randomisation. Before amendment (June 2002), 74 patients were randomly allocated to receive IRIFAFU, and 71 patients to receive OXAFAFUhd. Thereafter, 62 patients were assigned to IRIFAFU, and 69 patients to OXAFAFUld. Patients' results were well-balanced with respect to stratification factors and other baseline characteristics (Table 1).

Delivered treatments

Two patients (one allocated to receive IRIFAFU, and another to receive OXAFAFUld) refused the assigned regimen. Patients treated with IRIFAFU received a median number of eight (range one to 16) cycles, and stayed on study for a median of 16 weeks (range 2–44). Median number of cycles was eight (range one to 12) for both OXAFAFUhd and OXAFAFUld patients. These patients received the allocated treatment for a median of 18 weeks (range 2–40) and 22 weeks (range 2–39), respectively. A slightly higher proportion of patients treated with IRIFAFU (19%) dropped out for refusal or toxicity compared with those treated with OXAFAFUhd (11%) or OXAFAFUld (12%) (Table 2).

Dose intensity and OXA cumulative dosage

Among patients treated with IRIFAFU, dose intensity (DI) slightly decreased over time: median DI over the first four cycles (DI_4) was 88 mg/m^2/week for IRI and 372 mg/m^2/week for 5-FU; corresponding values were 82 mg/m^2/week and 343 mg/m^2/week over eight cycles (DI_8), and 76 mg/m^2/week and 346 mg/m^2/week over 12 cycles (DI_{12}).

A similar trend was seen for OXAFAFUhd: DI_4 was 41 mg/m^2/week for OXA, and 426 mg/m^2/week for 5-FU, while DI_8 was 37 mg/m^2/week and 374 mg/m^2/week, and DI_{12} was 39 mg/m^2/week and 354 mg/m^2/week, respectively. DI was quite similar for OXAFAFUld: DI_4 was 39 mg/m^2/week for OXA and 417 mg/m^2/week for 5-FU; DI_8 was 34 mg/m^2/week and 344 mg/m^2/week, and DI_{12} was 35 mg/m^2/week and 327 mg/m^2/week, respectively. Cumulative OXA dosage was 705 mg/m^2 (range 100–1200) with OXAFAFUhd, and 780 mg/m^2 (range 82–1114) with OXAFAFUld.

Activity

There were 42 confirmed responses (16 CRs and 26 PRs) among patients treated with IRIFAFU, 29 (seven CRs and 22 PRs) among patients treated with OXAFAFUhd and 32 (13 CRs and 19 PRs) among patients treated with OXAFAFUld. CRs were usually achieved in patients with a limited spread of disease. In detail, 12 of 16 CRs in IRIFAFU group were achieved in patients with only one involved organ (which was the liver in eight cases); in OXAFAFUhd group, six of seven CRs had only one site of disease (liver in four cases), while in OXAFAFUld group, eight of 13 CRs had a single metastatic site (liver in five cases).

In all, OXAFAFU yielded a significantly higher RR (44%; 95% CI 35% to 52%) than IRIFAFU (31%; 95% CI 23% to 40%) ($P = 0.029$). The proportion of patients achieving a PR was also greater among patients treated with OXAFAFU (29% versus 19%; $P = 0.002$), while no difference was seen in occurrence of CRs (14% versus 12%), although a non-significant trend towards a higher achievement of CRs was observed among patients treated with OXAFAFUld. The difference in RR between IRIFAFU and OXAFAFUld was also significant ($P = 0.032$). Moreover, the rate of disease control (response or stabilisation) was greater with OXA (66%) than with IRI (58%) (Table 3).

Downloaded from http://annonc.oxfordjournals.org/ at Biblioteca Area Biomedica on December 11, 2011

Table 1. Characteristics of eligible patients according to treatment

Characteristics	IRIFAFU		OXAFAFUhd		OXAFAFUld		OXAFAFU	
	n	%	*n*	%	*n*	%	*n*	%
Eligible patients	136	100	71	100	69	100	140	100
Males	72	53	46	65	35	51	81	58
Females	64	47	25	35	34	49	59	42
Median age, years (range)	62 (38–80)		62 (41–79)		63 (37–76)		62 (37–79)	
Aged ≥70 years	22	16	16	22	12	17	28	20
Primary								
Colon	97	71	51	72	50	72	101	72
Rectum	39	29	20	28	19	28	39	28
Previous surgery	111	82	49	69	55	80	104	74
Previous adjuvant chemotherapy	34	25	19	27	15	22	34	24
ECOG PS								
0	82	60	33	47	42	61	75	54
1	50	36	35	49	26	38	61	44
2	4	4	3	4	1	1	4	3
No. of metastatic sites								
1	73	54	31	44	38	55	69	49
2	49	36	32	45	23	33	55	39
3+	14	10	8	11	8	12	16	11
Liver involvement	99	73	56	79	52	75	108	77
Synchronous metastasis	82	60	43	61	46	67	89	64
Weigh loss ≥5% during last 6 months	45	33	20	28	26	38	46	33
Symptoms of disease	50	37	31	44	28	41	59	42
CEA value >5 ng/ml	91	67	48	68	50	72	98	70
CEA value >100 ng/ml	35	26	25	35	14	20	39	28

IRIFAFU, biweekly bolus FA/5-FU + irinotecan; OXAFAFUhd, biweekly bolus FA/5-FU + oxaliplatin, high doses; OXAFAFUld, biweekly bolus FA/5-FU + oxaliplatin, low doses; FA, folinic acid; 5-FU, 5-fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen.

Regardless of treatment, RR was adversely affected by several baseline characteristics: PS ≥1, presence of symptoms of disease, loss of body weight, CEA baseline value >100 ng/ml, no primary surgery and two or more disease sites. Including these factors together with the type of treatment in the multivariate analysis, only a good PS ($P = 0.000$), the OXAFAFU regimen ($P = 0.011$) and a low CEA baseline value ($P = 0.035$) showed a significant correlation with RR.

Time to response achievement was 2.9 months (range 1.6–9) for IRIFAFU, and 3.2 months (range 1.7–9.3) for OXAFAFU. Median duration of CRs was 5.2 months (range 2–19) in the IRIFAFU group, 17.2 months (range 2.4–25.3) in the OXAFAFUhd group and 8.5 months (range 2–16.4) in the OXAFAFUld group. Median duration of all responses was 7.9 months (range 1.9–20.8) for patients treated with IRI, and 8.5 months (range 1.5–22.1) for patients treated with oxaliplatin (OXAFAFUhd, 10.5 months; OXAFAFUld, 7.9 months).

Table 2. Summary of administered treatments

Treatment	IRIFAFU (*n* = 135)	OXAFAFUhd (*n* = 71)	OXAFAFUld (*n* = 68)
Total number of cycles	1022	549	572
Median cycles/patient (range)	8 (1–16)	8 (1–12)	8 (1–12)
No. of patients (%) receiving			
≥4 cycles	117 (87)	63 (89)	61 (90)
≥8 cycles	77 (57)	40 (56)	46 (68)
≥12 cycles	41 (30)	18 (25)	23 (34)
No. of patients (%) off treatment			
As per protocol	96 (71)	54 (76)	50 (74)
Refusal	15 (11)	6 (8)	6 (9)
Toxicity	11 (8)	2 (3)	2 (3)
Disease complication	3 (2)	5 (7)	5 (7)
Physician's decision	10 (7)	4 (6)	5 (7)

IRIFAFU, biweekly bolus FA/5-FU + irinotecan; OXAFAFUhd, biweekly bolus FA/5-FU + oxaliplatin, high doses; OXAFAFUld, biweekly bolus FA/5-FU + oxaliplatin, low doses; FA, folinic acid; 5-FU, 5-fluorouracil.

Downloaded from http://annonc.oxfordjournals.org/ at Biblioteca Area Biomedica on December 11, 2011

Table 3. Activity reported according to treatment

Responses	IRIFAFU		OXAAFUhd		OXAFAFUld		OXAFAFU	
	n	%	*n*	%	*n*	%	*n*	%
Complete response	16	12	7	10	13	19	20	14
Partial response	26	19	22	31	19	28	41	29
Stable disease	36	27	15	21	15	22	30	22
Progressive disease	38	28	19	27	14	21	33	24
Not assessed	19	14	8	11	7	10	15	11
Treated patients	135	100	71	100	68	100	139	100

IRIFAFU, biweekly bolus FA/5-FU + irinotecan; OXAFAFUhd, biweekly bolus FA/5-FU + oxaliplatin, high doses; OXAFAFUld, biweekly bolus FA/5-FU + oxaliplatin, low doses; FA, folinic acid; 5-FU, 5-fluorouracil.

Off-study treatments

Soon after the discontinuation of front-line treatment, nine patients with PR (three in the IRIFAFU group and six in the OXAFAFU group) were rendered disease-free by surgical resection of liver metastases.

At progression after first-line IRIFAFU, 77 (57%) patients received second-line treatments. Among these, 62 patients received OXA associated with 5-FU or capecitabine. Local treatment of liver metastases (radiofrequency ablation or intra-arterial chemotherapy) was performed in five patients. Eighteen (13%) patients received a third-line treatment (oral fluoropyrimidines). Among patients receiving OXAFAFU in front-line, salvage treatments were delivered in 78 (56%) patients: IRI, alone or combined with 5-FU or mitomycin C, was administered in 52 patients. Six patients underwent local management for liver metastases. Twenty (14%) patients received third-line treatment with oral fluoropyrimidines.

Toxicity

At interim analysis, neutropenia was more pronounced with OXAFAFUhd than with IRIFAFU (grade ≥3, 55% versus 39%; $P = 0.029$), and febrile neutropenia was more frequent (19% versus 9%; $P = 0.041$) After dosage amendment, despite a greater occurrence of thrombocytopenia of any grade with OXAFAFUld, no difference in severe haematological toxicity was seen between this regimen and the reference treatment (Table 4). As for non-haematological toxicity, occurrence of diarrhoea was significantly lower among patients treated with OXAFAFUld, and grade ≥3 was less frequent (12% versus 28%; $P = 0.005$). The proportion of patients complaining of severe emesis was more than halved (4% versus 10%; $P = 0.113$). Hair loss was also less pronounced with OXA-based treatment. Grade 3 neuropathy was recorded in 14% of patients treated with OXAFAFUhd, and in 3% of patients treated with OXAFAFUld, despite similar OXA cumulative

Table 4. Frequency of toxicity according to treatment (underlined percentages reported with OXAFAFU regimens are significantly different from those reported with IRIFAFU regimen)

Toxicity	IRIFAFU (*n* = 135)		OXAFAFUhd (*n* = 71)		OXAFAFUld (*n* = 68)		OXAFAFU (*n* = 139)	
Grade	Any	≥3	Any	≥3	Any	≥3	Any	≥3
Neutropenia	59	31	*78*	*55*	49	29	65	40
Febrile neutropenia/infections	9	7	*19*	13	3	3	11	7
Anaemia	33	1	35	2	35	1	35	3
Thrombocytopenia	10	1	*32*	4	*29*	3	32	4
Emesis	62	10	54	4	53	4	54	6
Diarrhoea	66	28	*44*	*13*	*32*	*12*	39	11
Stomatitis	23	3	*35*	6	15	4	26	4
Fatigue	5	2	6	4	7	3	6	3
Neuropathy	5	1	*48*	*14*	*47*	3	48	7
Cholinergic	10	2	0	0	0	0	0	0
Hair loss	49	23	*23*	*1*	*9*	*2*	16	1
Allergic	1	0	4	1	7	1	5	1
Treatment-related death	–	2	–	1	–	1	-	1

IRIFAFU, biweekly bolus FA/5-FU + irinotecan; OXAFAFUhd, biweekly bolus FA/5-FU + oxaliplatin, high doses; OXAFAFUld, biweekly bolus FA/5-FU + oxaliplatin, low doses; FA, folinic acid; 5-FU, 5-fluorouracil.

Downloaded from http://annonc.oxfordjournals.org/ at Biblioteca Area Biomedica on December 11, 2011

dosages. This finding might be explained by the reduced amount of OXA, and consequently by its decrease serum peak concentration after each administration. Overall, 44% of patients treated with OXAFAFUld and 53% treated with IRIFAFU suffered from at least one episode of grade ≥3 toxicity (except for alopecia). Early deaths (within 60 days from initial therapy) were 4% in both the IRIFAFU and OXAFAFU groups. Five patients died because of severe adverse events possibly or probably related to the received treatment: three patients (two in the IRIFAFU group and one in the OXAFAFUhd group) died as a consequence of severe diarrhoea; one patient died of myocardial infarction after the first course of IRIFAFU, and another patient had a gastric haemorrhage after the first course of OXAFAFUld.

FFS and OS

After a median follow-up of 24 months (range 10–36), 252 (91%) patients had an induction failure, and 150 (54%) patients died. According to treatment, median FFS was 5.8 months (95% CI 4.4–7.2) for patients treated with IRIFAFU, 6 months (95% CI 4.4–7.6) for patients treated with OXAFAFUhd and 7.6 months (95% CI 5.9–9.3) for patients treated with OXAFAFUld. Median OS was 15.6 months (95% CI 13.5–17.9) for IRIFAFU and 18.9 months (95% CI 15.3–22.5) for OXAFAFU. In detail, median OS was 17.6 months (95% CI 13.1 to 22.1) for patients treated with OXAFAFUhd, while it exceeded 23 months for patients treated with OXAFAFUld.

PS was the baseline clinical feature mostly affecting the outcome of patients. Indeed, FFS was 8.3 months and OS 20.5 months, for patients with PS 0, as opposed to 3.4 months and 11.1 months, respectively, for patients with PS ≥1. The difference of FFS for patients treated with IRI and those treated with OXA was statistically significant ($P = 0.046$) when adjusted for PS (Figure 1). Comparison of OS between IRI- and OXA-treated patients, which was of borderline significance ($P = 0.058$), reached a significant level ($P = 0.032$) when adjusted for PS. It is noteworthy that OS curves of the two

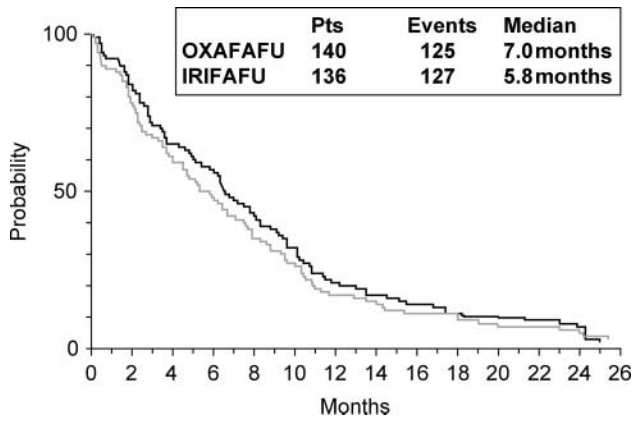

Figure 1. Failure-free survival curves according to treatment (black line, OXAFAFU; grey line, IRIFAFU). OXAFAFU, oxaliplatin plus high-dose folinic acid and 5-fluorouracil i.v. bolus; IRIFAFU, irinotecan plus high-dose folinic acid and 5-fluorouracil i.v. bolus.

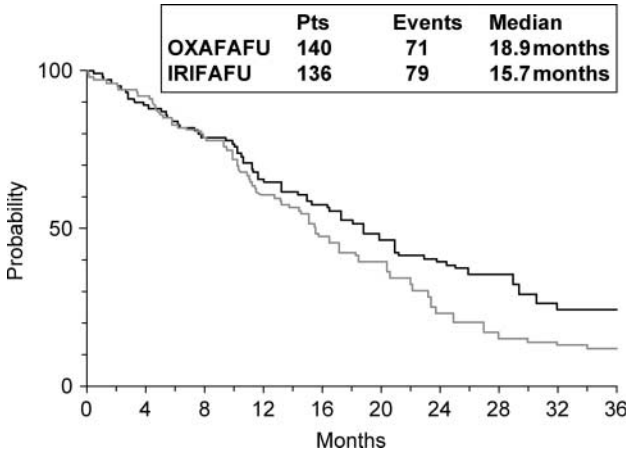

Figure 2. Overall survival curves according to treatment (black line, OXAFAFU; grey line, IRIFAFU). OXAFAFU, oxaliplatin plus high-dose folinic acid and 5-fluorouracil i.v. bolus; IRIFAFU, irinotecan plus high-dose folinic acid and 5-fluorouracil i.v. bolus.

groups of patients progressively diverged after the first year of follow-up: indeed, survival probability was 60% versus 65% at 12 months, 42% versus 52% at 18 months, and 23% versus 39% at 24 months, respectively (Figure 2). Moreover, we noted that OS of patients sequentially treated with all three active drugs, i.e. 5-FU, IRI and OXA, was significantly longer in comparison with that of patients not receiving all three drugs (median 16.6 versus 13 months, respectively) ($P = 0.009$).

Discussion

First of all, we wish to remark that the activity of the IRIFAFU regimen in this and in our previous study [11] was comparable. This observation supports the reproducible efficacy of IRIFAFU in metastatic colorectal cancer. Moreover, activity and toxicity of IRIFAFU appeared quite similar to those reported with IFL [9].

With these premises in mind, we believe that the present trial provided evidence that OXAFAFU is more active than IRIFAFU. Indeed, the greater RR was obtained using stringent criteria (i.e. including only confirmed responses). Moreover, this greater activity was independent of PS and CEA baseline value, which were the only pretreatment variables affecting RR in the multivariate analysis, and it was obtained despite the dose reduction implemented after the interim analysis on toxicity. Therefore, RR of OXAFAFU was not related to the dosage, provided that a similar number of cycles, duration of treatment and DI were administered in the two groups of patients treated with this regimen.

The higher RR was obtained at the price of similar occurrence of haematological toxicity (with amended dosages), and lower non-haematological toxicity in comparison with IRIFAFU. The better tolerability was also confirmed by a longer FFS time. Since FFS is also affected by factors other than PD, we believe it provided a clinically important measurement of the treatment on study in comparison with the reference

Downloaded from http://annonc.oxfordjournals.org/ at Biblioteca Area Biomedica on December 11, 2011

Table 5. Efficacy and toxicity of 5-FU and FA with either oxaliplatin or irinotecan in advanced colorectal carcinoma (randomised trials)

Study, author	Arm	Patients	ACT (%)	PS 0–1 (%)	Liver+ (%)	RR (%)	PFS (months)	MST (months)	60-day mortality (%)	Neutropenia (%)	Diarrhoea (%)	Neuropathy (%)	
GERCOR, Tournigand [33]	FOLFOX6	111	21	94	80	54	8.0	20.6	3	44	11	34	
										$P = 0.003$			
	FOLFIRI	109	17	83	87	56	8.5	21.5	4	24	14	0	
N9741, Goldberg [34]	FOLFOX4	267	16	93	NA	45	8.7	19.5	2.6	50	12	18	
						$P = 0.002$	$P = 0.0014$	$P = 0.0001$		$P = 0.04$	$P = 0.001$	$P = 0.001$	
	IFL	264	15	93	NA	31	6.9	15.0	4.5	40	28	3	
SICOG 0103, present study	OXAFAFU	140	24	97	78	44	8.2	18.9	4	29	12	3	
						$P = 0.029$		$P = 0.032$					$P = 0.005$
	IRIFAFU	136	25	97	73	31	7.5	15.6	4	31	28	1	

ACT, adjuvant chemotherapy; PS, performance status; RR, response rate; PFS, progression-free survival; MST, median survival time; FOLFOX, biweekly infusional plus bolus FA/5-FU + oxaliplatin; FOLFIRI, biweekly infusional plus bolus FA/5-FU + irinotecan; IFL, weekly bolus FA/5-FU + irinotecan; OXAFAFU, biweekly bolus FA/5-FU + oxaliplatin; IRIFAFU, biweekly bolus FA/5-FU + irinotecan; 5-FU, 5-fluorouracil; FA, folinic acid.

regimen. Patients compliance was favoured by our policy of delivering a maximum of 12 cycles, so that chronic toxicities, namely OXA-induced peripheral neuropathy, rarely occurred. This is in contrast with other trials, in which neuropathy with functional impairment was reported in higher proportions of patients [20, 21, 33, 34].

Recently, two trials randomly compared OXA and IRI associated with FA/5-FU in advanced colorectal cancer patients (Table 5). In the GERCOR study, patients were treated biweekly with *l*-FA 200 mg/m^2 infusion, plus 5-FU 400 mg/m^2 bolus and 2400–3000 mg/m^2 infusional over 46 h, preceded by either OXA 100 mg/m^2 (FOLFOX6) or IRI 180 mg/m^2 (FOLFIRI) [33]. After PD, patients received the alternative regimen in a cross-over design. In this study, no differences in RR, PFS or OS were observed. The conclusions were that the two regimens used sequentially provided an outstanding long survival, and that any efforts should be made in the future for increasing the proportion of patients who will receive both treatments.

Goldberg et al. [34] reported comparative results of three regimens: IFL, FOLFOX4, and IROX (a combination of IRI and OXA). In this study, all the efficacy parameters (RR, 45% versus 31%; PFS, 8.7 versus 6.9 months; OS, 19.5 versus 15 months), as well as the acute toxicity profile, favoured the FOLFOX4 in comparison with the IFL. These investigators concluded that FOLFOX4 should be considered as first-line standard of care for metastatic colorectal cancer [34]. However, because of different doses and schedules of 5-FU, these results could not isolate, at least in terms of activity, the relative independent contribution of OXA versus IRI, and of infused versus bolus 5-FU. Furthermore, as recently pointed out [35], this trial had the drawback of an imbalanced proportion of patients receiving second-line treatments.

Therefore, our study was the first one directly comparing OXA and IRI, both associated with FA/5-FU i.v. bolus. The results of this trial demonstrated that OXAFAFU was more active than IRIFAFU. Moreover, patients treated with OXAFAFU had a significantly longer FFS and OS. At this point, it is important to remember that our trial was not powered to reach a level of significance with an actual 3-month difference in median OS. However, it has recently been stressed that the lack of a statistically significant survival prolongation in trials assessing combination regimens in metastatic colorectal cancer patients should not be interpreted as an evidence of no survival benefit at all [36].

Our findings were obtained despite the fact that similar proportions of patients in both arms were given second- and third-line treatment, and received sequentially all three active drugs. It may be extrapolated from the GERCOR trial that FOLFOX6 was more active after failure of FOLFIRI regimen than *vice versa* (RR 15% versus 4%, and PFS 4.2 versus 2.5 months, respectively). If we apply this observation to our patients, we could argue that an OXA-based regimen in second-line, although more active, did not compensate for a less active IRI-based treatment in first-line. In fact, we observed that median OS for patients sequentially receiving all three cytotoxic agents differed according to front-line treatment: it was 18.6 months for patients in OXAFAFU arm, and 15.9 months for patients in IRIFAFU arm. For these reasons, we believe that OXAFAFU should be used first in the treatment of metastatic colorectal cancer patients. Moreover, it should be taken into account that not all patients will receive second-line treatment. In our experience, the proportion of these patients is progressively increasing, from ~40% of our previous study to >50% in the present one. However, many patients still do not receive salvage treatment for several reasons. For these patients, survival expectancy is affected only by the front-line treatment. Therefore, it is crucial for them to receive the most tolerable and effective regimen,

Downloaded from http://annonc.oxfordjournals.org/ at Biblioteca Area Biomedica on December 11, 2011

because a significant correlation between RR and survival has already been established for these patients [37].

In conclusion, the OXAFAFU regimen showed activity and toxicity comparable with those reported with the FOLFOX4. In our opinion, the OXAFAFU is preferable because it does not require central venous catheter and infusional devices, being more comfortable for outpatient treatment and less costly. For these reasons, the OXAFAFU regimen is from now on the reference regimen for SICOG investigators, to be challenged in future trials.

Acknowledgements

We acknowledge the contribution of Dr Anna Crispo, and Dr Maurizio Montella for the statistical analysis. We also wish to thank Dr Marina Lincenziato for her excellent data management, and Ms Liliana Gallifuoco for her invaluable secretarial assistance. This work was supported by Aventis Pharma, Milan and Sanofi Synthelabo, Milan, Italy.

Other SICOG investigators (and Institutions) taking part in this trial were: Rossana Casaretti, Antonio Avallone (National Tumour Institute, Naples); Maria Teresa Ionta (University Medical School, Cagliari); Antonio Gambardella (Second University Medical School, Naples); Giuseppe De Cataldis (Da Procida Hospital, Salerno); Anna Russo (University Medical School, Palermo); Salvatore Del Prete (City Hospital, Frattamaggiore); Annunziato Iannelli (City Hospital, Siderno); Maria di Grazia (City Hospital, Caserta); Teresa Bellelli (Clinic Malzoni, Agropoli); Enrico Barbato (City Hospital Aversa); Maddalena Bianco (City Hospital, Castellammare); Liberato Di Lullo (City Hospital, Isernia); Ettore Greco (City Hospital, Lametia); Filomena Del Gaizo (City Hospital, Avellino); and Sergio Catanzani (City Hospital, Terni, Italy).

References

1. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 1992; 10: 896–903.
2. Advanced Colorectal Cancer Meta-Analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. J Clin Oncol 1994; 12: 960–969.
3. Abad A, Garcia P, Gravalos C et al. Sequential methotrexate, 5-fluorouracil (5FU), and high dose leucovorin versus 5-FU and high dose leucovorin versus 5-FU alone for advanced colorectal cancer. Cancer 1995; 75: 1238–1244.
4. Glimelius B. Biochemical modulation of 5-fluorouracil: A randomized comparison of sequential methotrexate, 5-fluorouracil and leucovorin versus sequential 5-fluorouracil and leucovorin in patients with advanced symptomatic colorectal cancer. Ann Oncol 1993; 4: 235–250.
5. Meta-Analysis Group in Cancer. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: An updated meta-analysis. J Clin Oncol 2004; 22: 3766–3775.
6. de Gramont A, Bosset JF, Milan C et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French Intergroup study. J Clin Oncol 1997; 15: 808–815.
7. Köhne C-H, Wils J, Lorenz M et al. Randomized phase III study of high-dose fluorouracil given as a weekly 24-hour infusion with or without leucovorin versus bolus fluorouracil plus leucovorin in advanced colorectal cancer. European Organization of Research and Treatment of Cancer Gastrointestinal Group study 40952. J Clin Oncol 2003; 21: 3721–3728.
8. Rougier P, Van Cutsem E, Bajetta E et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998; 352: 1407–1412.
9. Saltz LB, Cox JV, Blanke C et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 2000; 343: 905–914.
10. Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. Lancet 2000; 355: 1041–1047.
11. Comella P, Crucitta E, De Vita F et al. Addition of either irinotecan or methotrexate to bolus fluorouracil and high-dose leucovorin every two weeks in advanced colorectal carcinoma: A randomized study of the Southern Italy Cooperative Oncology Group. Ann Oncol 2002; 13: 866–873.
12. Raymond E, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: A review of preclinical and clinical studies. Ann Oncol 1998; 9: 1053–1071.
13. Becouarn Y, Ychou M, Ducreux M et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. J Clin Oncol 1998; 16: 2739–2744.
14. Díaz-Rubio E, Sastre J, Zaniboni A et al. Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: A phase II multicentric study. Ann Oncol 1998; 9: 105–108.
15. Machover D, Díaz-Rubio E, De Gramont A et al. Two consecutive phase II study of oxaliplatin (L-OHP) for the treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines. Ann Oncol 1996; 7: 95–98.
16. Fischel J-L, Etienne M-C, Formento P, Milano G. Search for the optimal schedule for the oxaliplatin/5-fluorouracil association modulated or not by folinic acid: Preclinical data. Clin Cancer Res 1998; 4: 2529–2535.
17. Brienza S, Besmaine MA, Soulie P et al. Oxaliplatin added to 5-fluorouracil-based therapy (5-FU +/− FA) in the treatment of 5-FU pretreated patients with advanced colorectal cancer (ACRC): Results from the European compassionate use program. Ann Oncol 1999; 10: 1311–1316.
18. Rothenberg ML, Oza AM, Bigelow RH et al. Superiority of oxaliplatin and fluorouracil–leucovorin compared with either therapy alone in patients progressive colorectal cancer after irinotecan and fluorouracil–leucovorin: Interim results of a phase III trials. J Clin Oncol 2003; 21: 2059–2069.
19. Giacchetti S, Perpoint B, Zidani R et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil–leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2000; 18: 136–147.
20. de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000; 18: 2938–2947.
21. Ravaioli A, Marangolo M, Pasquini E et al. Bolus fluorouracil and leucovorin with oxaliplatin as first-line treatment in metastatic colorectal cancer. J Clin Oncol 2002; 20: 2545–2550.
22. Zori Comba A, Blajman C, Richardet E et al. A randomized phase II study of oxaliplatin alone versus oxaliplatin combined with

Downloaded from http://annonc.oxfordjournals.org/ at Biblioteca Area Biomedica on December 11, 2011

5-fluorouracil and folinic acid (Mayo Clinic regimen) in previously untreated metastatic colorectal cancer patients. Eur J Cancer 2001; 37: 1006–1013.
23. Hochster HS, Chachoua A, Speyer J et al. Oxaliplatin with weekly bolus fluorouracil and low-dose leucovorin as first line therapy for patients with advanced colorectal cancer. J Clin Oncol 2003; 21: 2703–2707.
24. Sørbye H, Glimelius B, Berglund A et al. Multicenter phase II study of Nordic fluorouracil and folinic acid bolus schedule combined with oxaliplatin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2004; 22: 31–38.
25. Comella P. Randomized trial comparing the addition of either oxaliplatin or irinotecan to high-dose folinic acid and 5-fluorouracil i.v. bolus every two weeks in metastatic colorectal carcinoma: A Southern Italy Cooperative Oncology Group study (SICOG 0103). Clin Colorectal Cancer 2003; 3: 186–189.
26. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207–214.
27. Lévi F, Misset JL, Brienza S et al. A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid, and oxaliplatin using ambulatory multichannel programmable pump. High antitumor effectiveness against metastatic colorectal cancer. Cancer 1992; 69: 893–900.
28. Simon R. Design and conduct of clinical trials. In De Vita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology, 4th edition. Philadelphia, PA: JB Lippincott Co. 1993; 418–440.
29. Thall PF, Simon R, Ellenberg SS. A two-stage design for choosing among experimental treatments and a control in clinical trials. Biometrics 1989; 45: 537–547.
30. Cochran WG. Some methods for strengthening the common chi-square test. Biometrics 1954; 10: 417–451.
31. Kaplan ES, Meier P. Non parametric estimation for incomplete observations. J Am Stat Assoc 1958; 53: 557–580.
32. Mantel N. Evaluation of survival data and two new ranks of order statistics arising in its considerations. Cancer Chemother Rep 1966; 50: 163–170.
33. Tournigand C, André T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 2004; 22: 229–237.
34. Goldberg RM, Sargent DJ, Morton RF et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004; 22: 23–30.
35. Punt CJA. New options and old dilemmas in the treatment of patients with advanced colorectal cancer. Ann Oncol 2004; 15: 1453–1459.
36. Di Leo A, Buyse M, Bleiberg H. Is overall survival a realistic primary end point in advanced colorectal cancer studies? A critical assessment based on four clinical trials comparing fluorouracil plus leucovorin plus the same treatment combined with either oxaliplatin or CPT-11. Ann Oncol 2004; 15: 545–549.
37. Buyse M, Thirion P, Carlson RW et al. Relation between tumor response to first-line chemotherapy and survival in advanced colorecal cancer: A meta-analysis. Lancet 2000; 356: 373–378.

Downloaded from http://annonc.oxfordjournals.org/ at Biblioteca Area Biomedica on December 11, 2011