Review

# FOLFOX *Versus* FOLFIRI: A Comparison of Regimens in the Treatment of Colorectal Cancer Metastases

LARA MARIA PASETTO, ANTONIO JIRILLO, GIROLAMA IADICICCO, ELENA ROSSI, MYRIAM KATJA PARIS and SILVIO MONFARDINI

UO of Medical Oncology, Via Gattamelata 64 (Azienda Ospedaliera - Università), 35128 Padova, Italy

**Abstract.** Colorectal adenocarcinoma ranks second as a cause of death due to cancer in the Western world. Already at the time of the primary tumor, 15-25% of the patients present with liver metastases while another 20% will develop metastasis following treatment of the colorectal primary. Without any treatment the median survival after the detection of metastases is approximately 9 months, depending on the extent of the disease at the time of diagnosis. Clinical trials with the "FOLFOX and FOLFIRI families" of drugs, designed for the treatment of metastatic colorectal cancer, their results and the costs of each therapy are examined. For each drug, the cost/mg, the cost/mg/m² and the cost/therapy (according to its duration) are evaluated according to the prices reported in the Italian Directory of Medicines and Manufacturers, 63rd Edition, November 2003.

Hepatic metastases are the major cause of morbidity and mortality in patients with gastrointestinal carcinomas (1). At the present time, resection is the only therapeutic option; after a curative resection, median survival time (MST) is roughly 30 months and disease-free survival (DFS) at 5 years is 34%. Longer survival is observed in cases with fewer than 4 lesions, lesions smaller than 4 cm, absence of extrahepatic disease, presence of lesions appearing more than 2 years after the resection of a stage I or II colorectal cancer and presence of normal CEA level (2).

When radical surgery resection of metastases is not possible (80-90% of cases), chemotherapy has to be considered as purely palliative; in this case MST does not exceed 19-20 months (3).

Correspondence to: Lara Maria Pasetto, Divisione di Oncologia Medica - Direzione, Via Gattamelata 64, - Azienda Ospedale – Università, 35128 Padova, Italy. Tel: +39 049-8215931, Fax: +39-049-8215932, e-mail: laramary@libero.it

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### Systemic chemotherapy

In patients with a potentially curative resection of metastases (4, 5), there are as yet only two published randomized trials of systemic chemotherapy alone *versus* observation (6, 7). In the first one (6), the trend in 4-year DFS (45% *versus* 35%) and overall survival (OS) (57% *versus* 47%) does not establish a role for 5-fluorouracil and leucovorin (5FU/LV) combination. On the contrary, in the second one (7) a good advantage for the chemotherapy arm (5FU and folinic acid - FA -) in terms of DFS (33% *versus* 24%), but not of OS (51% *versus* 44%), is shown. Other studies to verify the role of chemotherapy after radical surgery of metastasis are ongoing.

In 80-90% of cases, radical surgery of metastases is not possible. In these cases, chemotherapy has to be considered as purely palliative. For 40 years, 5FU has been studied more than other drugs because it represented the only efficacious treatment for advanced colorectal cancer. With the introduction of irinotecan (CPT11), a topoisomerase I inhibitor, and oxaliplatin, a DNA cross-linking agent, improved success in the treatment of pre-treated or chemonaive patients has been shown (8).

In this paper, the results of each trial with these drugs and the costs of the combination therapy expressed in Euro (round brackets), according to the prices reported in the Italian Directory of Medicines and Manufacturers, are analyzed.

#### CPT11

Studies of second-line CPT11 monochemotherapy are usually associated with 14-22% response rate (RR) (T I). The response rate is durable and similar to that achieved with 5FU/FA as first-line treatment in metastatic disease. The median duration of response is 6-8 months. Diarrhea grades 3-4 and leucopoenia represent two of the major

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Table I. Systemic CPT11 monochemotherapy.

Authors	Drugs N°		MST (months)
Second-line t	herapy		
Fuchs (10)	CPT11 125mg/m²/wk for 4wks q6 vs CPT11 300-350mg/m² q3wks	291	9.9 vs 9.9 (n.s.)
Cunningham (11)	CPT11 350mg/m <sup>2</sup> q3wks + BSC vs BSC alone	279	9.2 vs 6.5
Rougier (13)	CPT11 350mg/m <sup>2</sup> q3wks vs De Gramont	267	10.8 vs 8.5
First-line the	rapy		
Shimada (14)	CPT11 100mg/m²/wk or 150mg/m² q2wks, or 350mg/m² q 3 wks	307 2	nr nr
Firvida (15)	CPT11 350mg/m <sup>2</sup> q3wks	65 2	19.9

d = day; q = every; wks = weeks; nr = not reported; pts = patients; RR = response rate; MST = median survival time; n.s. = not significant

toxicities, especially after a weekly schedule (the three-weekly schedule has the same activity as the weekly-schedule, but is better tolerated) (9, 10).

The first two randomized studies demonstrating CPT11 efficacy after 5FU failure were European (11, 12). In the first one (11), CPT11 plus best supportive care (BSC) was compared to BSC alone. OS was significantly better in the first group (p<0.0001) with a 1-year survival of 36.2% and 13.8%, respectively. In the second (12), CPT11 plus BSC was compared to infusional 5FU. One-year survival was 45% and 32%, respectively. The CPT11 regimen was associated with a longer survival, fewer tumor-related symptoms and a better quality of life (QOL) than that observed with 5FU bolus or with the literature data on BSC alone. Progression-free survival (PFS) was also improved in the CPT11-containing arm.

In another multicenter phase III trial (13), the survival and clinical benefit of irinotecan was compared with second-line 5FU by continuous infusion (c.i.). Two hundred and seventy-seven patients who had failed to respond to first-line 5FU, or whose disease had progressed after treatment with first-line 5FU, were randomly allocated irinotecan 300-350 mg/m² infused once every 3 weeks or 5FU by c.i.. One-year survival was 45% and 32%, respectively (p=0.03). Median PFS was longer with irinotecan (4.2 versus 2.9 months for

irinotecan *versus* fluorouracil, respectively; p=0.030). The median DFS was 10.3 months and 8.5 months (p=0.06) for irinotecan and fluorouracil, respectively. Both treatments were equally well tolerated. Even in this case, the MST was longer in the first group of patients.

According to these results, the efficacy of first-line CPT11 monotherapy was assessed in two phase II clinical studies (14, 15) conducted in Japan, Europe and U.S. Toxicity was the same as observed in second-line therapy but RR and MST were better (22% and 19.9 months, respectively).

#### **CPT11** and 5-Fluorouracil

Second-line chemotherapy. With the first studies of the combination, CPT11 and the de Gramont ("folfiri") regimen were administered as second-line chemotherapy (16). The results were associated with 6% partial remission (PR) and 61% stable disease (SD). MST was of 10.7 months. Douillard's randomized study (17) comparing the "folfiri" regimen (1,228.6 Euro - according to the Author's evaluation -) to 5FU/LV alone confirmed these good results with a RR of 40.8% (p<0.001), a time to progression (TTP) of 6.7 months (versus 4.4, p<0.001), a MST of 17.4 months (p=0.03), and a 1-year survival of 69% (versus 59%, p=0.03) in the first arm (T II-III). Although the use of combination therapy increased the likelihood of neutropenia, the incidence of febrile neutropenia and infection remained low. Other toxic effects were manageable, non-cumulative and reversible.

In Mabro's study (18), a new regimen ("folfiri" 2 – 1,228.6 Euro -) was analyzed. Seventeen percent objective responses were observed with a median PFS of 4.1 months and a MST of 9.7 months. Grades 3-4 toxicities were nausea 17%, diarrhea 31%, mucositis 14%, neutropenia 52%, and febrile neutropenia 14%. "Folfiri" 2 achieved a good rate of response and stabilization (52%) in heavily pretreated patients despite significant toxicity.

Maindrault-Goebel's trial (19) evidenced a PR in 20% of cases and a SD in 55% of patients with a different "folfiri" regimen ("folfiri" 3 – 1,332.4 Euro -) in 22 patients resistant to 5FU and oxaliplatin ("folfox" regimen). The regimen was based on the synergism between CPT11 given before or after 5FU. The good RR translated into a prolonged PFS (6.7 months). The GERCOR group confirmed these results in a prospective phase II study on 57 patients with the same characteristics as the previous trial (20). A RR of 20.5% and a PFS of 5.9 months were obtained. RR and PFS were better than those observed after the simplified or chronomodulated "folfiri" regimens in "folfox" pretreated patients (16, 21). From an economic point of view, it was 13.7% more expensive than the first regimen (1,106.6-1,150.0 Euro) but 54% cheaper than the second one (2,909.17 Euro).

First-line chemotherapy. Because of the CPT11 second-line promising results in metastatic colorectal cancer unresponsive to TS inhibitors, in the United States, where 5FU/LV bolus was used almost exclusively, bolus 5FU/LV as part of the Mayo Clinic regimen (5FU 425mg/m² + LV 20mg/m² day 1 to 5 every 4 weeks) was used in conjunction with CPT11 (22). Van Cutsem et al. (23) administered CPT11 plus the Mayo Clinic regimen to 33 chemonaive patients. A SD in 49% of cases and a RR in 30%, was reported. One-year survival was 58%; median PFS was 7.2 months and MST was 16 months. Grades 3-4 diarrhea and neutropenia were the most frequent severe toxic events, seen in 24% and 64% of patients, respectively. The regimen was well tolerated and promising with regard to that expected with either single agent.

According to these good results, in Saltz's three-arm randomized trial (24), CPT11 and 5FU/LV bolus (IFL) (1,338.14 Euro) in different combinations (arm 1), were compared to the Mayo Clinic regimen alone (arm 2), and to CPT11 monochemotherapy (arm 3). PFS (p=0.004), RR (p<0.001) and OS (p=0.04) were significantly improved in the first group of patients. The results for the third group of patients were similar to the second one. Diarrhea grade 3 was more common in the first arm, while mucositis grades 3-4 or neutropenia grade 4 were less frequent than in the other two groups of patients. Over half of the patients in the group treated with 5FU/LV received CPT11 as second-line treatment. First-line administration of CPT11/5FU/LV was superior to the sequential administration 5FU/LV - CPT11. The results helped to improve local tumor control and to prolong survival, so these two prospective randomized trials became the basis for the U.S. (24) and European (25) approval of CPT11/5FU/LV as a first-line treatment.

In a randomized study on an intent to treat analysis (26), CPT11 alternated with the Mayo Clinic regimen (arm 1) was compared to the Mayo Clinic regimen alone (arm 2). PFS (p=0.897) and MST (p=0.99) were similar in both arms but the study was closed prematurely because most of the investigators, due to the then current results (24, 25), no longer considered the Mayo Clinic arm as the standard regimen.

In Europe, where infusional 5FU/LV is predominantly used, in a multicenter randomized trial (25, 27) AIO (once weekly) (2,328.6-2,341.2 Euro) or the de Gramont regimens (every 2 weeks) combined with CPT11 were compared to 5FU/LV or de Gramont alone. RR was significantly better in the first arm (49% versus 31%, p<0.001) with a longer TTP (median 6.7 vs 4.4 months, p<0.001) and OS (median 17.4 vs 14.1 months, p=0.031), with reversible, noncumulative and manageable toxicity grades 3-4 and with a better QOL than in the Mayo's arm. In the analysis, it was determined that CPT11 treatment for colorectal cancer was

cost-effective. A major factor favouring the cost effectiveness of the CPT11-treated group was the lower cumulative patients' costs associated with the treatment of medical side-effects.

Saltz and Douillard's studies (24, 25) demonstrated that CPT11 with 5FU/FA provided unprecedented response and survival benefits with a strong safety profile and an improved QOL for a large population of patients receiving this regimen.

In a multicenter phase II trial, the good results of CPT11 and 5FU/FA (bolus) association (1,183.82 Euro) were confirmed by Glimelius *et al.* (28). The overall RR was of 43% with a 10-month median duration of response. The estimated median TTP and MST were 6.4 months and 15.6 months, respectively, in the intention-to-treat population. Grades 3-4 neutropenia were of 6%, whilst grades 3-4 nonhematological toxicities were infrequent. The low incidence of grades 3-4 toxicities, the high objective RR and good tumor control with a strong safety profile and low costs (11.5% cheaper than IFL regimen) justified the further evaluation of this combination in the context of randomized clinical trials and provided a good alternative to Saltz's bolus regimen (24) for patients who could not receive infusional 5FU.

#### **Oxaliplatin**

Oxaliplatin is a novel platinum analogue, which has a wide spectrum of anticancer activity in in vitro system. It has biochemical, pharmacological and cytotoxic properties different to those of cisplatin and carboplatin. If compared to them, it is a better DNA synthesis inhibitor, it gives lower resistance, and has a better synergism with 5FU. Doselimiting toxicity (DLT) is neurotoxicity. Acute neurotoxicity manifests one hour after the infusion and ends two or three days later; chronic toxicity is dose-cumulative related and ranges from 12% at 900 mg/m² to 75% at 1500 mg/m². It is reversible 5-6 months after the end of the treatment.

In second-line option, RR is about 10% after 5FU administration. In first-line trials, oxaliplatin as 130 mg/m<sup>2</sup> over 2 hours every 3 weeks exhibited results at least as good as 5FU or CPT11 with RR of 24.3% and SD of 40.5%; TTP was 6-7.2 months with MST of 13.2-14.5 months (29).

#### Oxaliplatin and 5-Fluorouracil

Oxaliplatin is more effective when combined with 5FU/LV as first or second-line option, because of the synergism between the two drugs giving double the response (RR of 54% as first-line therapy) than 5FU/LV alone (RR of 23-29%) (30). Even median PFS is of 45% (12.1 weeks), longer in the combination arm than in the other (8 *versus* 6.2 months), whilst MST is not significantly different in both

Table II. Common schema of systemic chemotherapy with CPT11 and 5FU.

Schema	Authors	Drugs	Dose (mg/m <sup>2</sup> )	Administration	Day
"FOLFIRI"	Douillard	CPT11	180	30-90'	1
(q2wks)	(17)	FA	200	2 hours	1 and 2
(1)	` '	5FU	400	bolus	1 and 2
		5FU	600	22 hours <i>c.i.</i>	1 and 2
Simplified	Maindrault-	CPT11	180	30-90'	1
"FOLFIRI"	Goebel	FA	200	2 hours	1
(q2wks)	(27)	5FU	400	bolus	1
,	, ,	5FU	2400-3000	46 hours <i>c.i.</i>	1
"FOLFIRI" 2	Mabro	CPT11	180	30-90'	3
(q2wks)	(18)	LV	400	2 hours	1
,		5FU	2000	46 hours <i>c.i.</i>	1
		Hydroxyurea	1500		0-2
"FOLFIRI" 3	Mabro	CPT11	100	30-90'	1 and 3
(q2wks)	(20)	LV	400	2 hours	1
	, ,	5FU	2000	46 hours <i>c.i.</i>	1
AIO	Douillard	CPT11	80	30-90'	1
(weeklyx	(25)	FA	500	2 hours	1
6wksq8)	, ,	5FU	2000-2300	24 hours <i>c.i.</i>	1
IFL	Saltz	CPT11	125	30-90'	1
(weeklyx4	(24)	FA	20	bolus	1
wksq6)	, ,	5FU	500	bolus	1
NORDIC	Glimelius	CPT11	210	30-90'	1
schedule	(28)	FA	60	bolus	1 and 2
(q2wks)	, ,	5FU	500	bolus	1 and 2
IRIFAFU	Comella	CPT11	200	30-90'	1
(q2wks)	(55)	FA	250	2 hours	2
,	, ,	5FU	850	bolus	2
CHRONO-	Garufi	CPT11	325	30-90'	1
MODULATED	(21)	FA	175	chronomodulated	1-5
(q3wks)	` /	5FU	700	chronomodulated	1-5

groups of patients (10-17 months with only 1.5 months longer in the first group than in the second one). This is probably due to 30-45% of responses to a second-line combination therapy with oxaliplatin  $\pm$  5FU/LV after a first-line 5FU/LV failure (T IV-V).

Second-line chemotherapy. de Gramont (31, 32) was the first Author to compare, in a non-randomized study, three 5FU-oxaliplatin ("folfox") regimens. After the "folfox" 2 regimen (1,998.60-2,042.60 Euro), the study reported a RR (46%) superior to "folfox" 1 (2,373.96 Euro) or 3 (1,795.22-1,809.22 Euro). From the start of "folfox" 2, median PFS was 7 months and MST 17 months. Grade 3-4 toxicities per patient was: peripheral neuropathy 9%, nausea 4%,

diarrhea 9%, mucositis 13%, neutropenia 39%, thrombocytopenia 11%, alopecia 9%, and allergy 2%. Overall, 21 patients (46%) experienced grade 3-4 toxicity. A toxicity grade 3 was experienced by 54% of patients with the "folfox" 1 regimen, 45% with "folfox" 2 and 40% with "folfox" 3. Similar toxicities with a neuropathy of grades 3-4 of 90% were confirmed by the Andre's study with the "folfox" 3 regimen (33).

In another non-randomized study between "folfox" 3 and 4 (1,386.78 Euro) (34), RR was superior with "folfox" 4 (18.4% versus 23.5%), but median duration of response (7.5 months), PFS (4.6 versus 5.1 months) and MST (10.6 versus 11.1 months) were similar in both regimens; costs were 33.7% superior with the first regimen. The overall

Table IIa. Common schema of chemotherapy with CPT11 and 5FU costs.

Schema	Drugs	Dose (mg/m <sup>2</sup> )	Day	Cost/mg	Cost/mg/m <sup>2</sup>	Cost/cycle (€)
"FOLFIRI"	CPT11	180	1	2.595	467.10	467.10
(q2wks)	FA	200	1 and 2	0.3287	66.60	133.20
(17)	5FU	400	1 and 2	0.007	2.80	5.60
· ,	5FU	600	1 and 2	0.007	4.20	8.40
						614.3x2=1,228.6
Simplified	CPT11	180	1	2.595	467.10	467.10
'FOLFIRI"	FA	200	1	0.3287	66.60	66.60
(q2wks)	5FU	400	1	0.007	2.80	2.80
(27)	5FU	2400-3000	1	0.007	16.8-21	16.8-21
(= / )	51.0	2.00 2000	-	0.007	10.0 21	553.3-557.5x2=
						1,106.6-1,115.0
'FOLFIRI" 2	CPT11	180	3	2.595	467.10	467.10
(q2wks)	LV	400	1	0.3287	133.20	133.20
(18)	5FU	2000	1	0.007	14	14
(=0)	Hydroxyurea	1500	0-2	?	?	614.3x2 = 1,228.6
"FOLFIRI" 3	CPT11	100	1 and 3	2.595	259.50	519
(q2wks)	LV	400	1	0.3287	133.20	133.20
(20)	5FU	2000	1	0.007	14	14
						666.2x2=1,332.4
AIO	CPT11	80	1	2.595	207.60	207.60
(weeklyx6wksq8)	FA	500	1	0.3287	166.50	166.50
(25)	5FU	2000-2300	1	0.007	14-16.1	14-16.1
						388.1-390.2x6
						=2,328.6-2,341.2
IFL	CPT11	125	1	2.595	324.375	324.375
(weeklyx4wksq6)	FA	20	1	0.3287	6.66	6.66
(24)	5FU	500	1	0.007	3.50	3.50
						334.535x4 =
						1,338.14
NORDIC schedule	CPT11	210	1	2.595	544.95	544.95
(q2wks)	FA	60	1 and 2	0.3287	19.98	39.96
(28)	5FU	500	1 and 2	0.007	3.50	7
,						591.91x2 =
						1,183.82
IRIFAFU	CPT11	200	1	2.595	519	519
(q2wks)	FA	250	2	0.3287	83.25	83.25
(55)	5FU	850	2	0.007	5.95	5.95
,		*	•			608.2x2=
						1,216.4
CHRONO-	CPT11	325	1	2.595	843.375	843.375
MODULATED	FA	175	1-5	0.3287	58.275	116.55
(q3wks)	5FU	700	1-5	0.007	4.90	9.80
(21)	2.0	, 50	1.0	0.507		969.725x3=
` /						2,909.175

incidence of neutropenia grades 3-4 was worse in the second arm (15% versus 36.9%) in which DLT was a cumulative sensory neurotoxicity imposing therapy interruption in patients still responding.

Maindrault-Goebel *et al.* (35) treated 60 patients with the "folfox" 6 regimen (1,893.52-1,910.32 Euro) and compared it with "folfox" 2. RR (PR in 27% of cases and SD in 45%) and costs were 5.3% lower than those obtained with the

Table III. Activity of more common schema of systemic chemotherapy with CPT11 and 5FU.

Authors	Drugs	N° PTS	S RR (%)	MST (months)
Second-lin	ne trials			
Andre (16)	Simplified "FOLFIRI" with LV 400mg/m <sup>2</sup>	33	6	10.7
Douillard (17)	"FOLFIRI"	113	40.8	17.4
Mabro (18)	"FOLFIRI" 2	29	17	9.7
Mabro (20)	"FOLFIRI" 3	57	20.5	nr
First-line	randomised trials			
Saltz (24)	IFL (with 5FU/LV bolus) vs Mayo Clinic vs CPT11 125mg/m²/wk x4wks q6wks	683	39 vs 21 vs 21 (p=0.001)	14.8 vs 12.6 vs 12.0 (p=0.04)
Douillard (25)	AIO or "FOLFIRI" (with infusional 5FU/LV) vs 5FU 2600mg/m² 24hour c.i.+ LV 500mg/m² weekly or de Gramont regimen		49 vs 31 (p<0.001)	17.4 vs 14.1 (p=0.031)
Pozzo (26)	CPT11 350mg/m <sup>2</sup> alternated to Mayo Clinic vs Mayo Clinic	156	25.8 vs 14	17.1 and 14.5 (p=0.99)

d=day; q=every; wks=weeks; c.i.=continuous infusion; nr=not reported; pts=patients; RR=response rate; MST=median survival time; LV=levamisol

"folfox" 2 regimen, while MST was similar (10.8 months). Median PFS was of 5.3 months. Overall grades 3-4 toxicity were 46% (peripheral neuropathy 16%, nausea 7%, diarrhea 7%, mucositis 5%, neutropenia 24%, thrombocytopenia 2%).

A GERCOR (36) and GISCAD's (37) studies compared "folfox" 4 and 2. Median TTP (6 months *versus* 5 months) and OS (7 months *versus* 9 months) were similar. Treatment was active in patients with hepatic disease only; tumor growth control was comparable with results reported in the literature for second-line standard treatment (RR of 18%-21%). Both schedules exhibited an acceptable toxicity; "folfox" 4 appeared 32% less expensive than "folfox" 2.

In a recent study (38), the "folfox" 7 regimen (a simplified de Gramont regimen with high-dose oxaliplatin) (2,235.48 Euro) gave a RR similar to that achieved with the "folfox" 2 regimen. Median PFS was 6 months, costs were 9% superior

but overall toxicity grades 3-4 were lower (38%) than those reached with "folfox" 2.

When the same regimen was compared with "folfox" 4 (39), RR were 64% and 58%, respectively (p=n.s.). The time to disease control was 12.3 and 10.3 months with a similar toxicity. According to the results of the two studies, "folfox" 7 was considered to be one of the more active, convenient and well tolerated second-line regimens (even if 38% more expensive than "folfox" 4) (40).

A more robust study (41) comparing de Gramont regimen to oxaliplatin monochemotherapy and to "folfox" 4 resulted in the approval of oxaliplatin in combination with 5FU/LV as a second-line therapy for patients with metastatic colorectal cancer by the Food and Drug Administration (FDA). A total of 459 out of 821 enrolled patients were evaluable at the time of the planned interim analyses. The "folfox" 4 regimen was superior to the de Gramont control arm and also to the single-agent oxaliplatin. The objective RR and the TTP of 4.6 months for "folfox" 4 were superior to the RR and TTP of 1.6 months for single-agent oxaliplatin and also to the RR and TTP of 2.7 months for the de Gramont regimen.

First-line chemotherapy. Levi et al. (42) tested the effect as first-line therapy of oxaliplatin combined with 5FU/LV chronomodulated infusion (coinciding with relevant circadian rhythms) (2,025.54 Euro) or constant-rate infusion. RR (p=0.003) and median TTP (p=0.006) were significantly better in the first group of patients than in the second. MST was similar in both groups and 3-year survival was 22% versus 21%. Chronotherapy reduced 5-fold the rate of several mucosal toxicities (14% versus 76%, p<0.0001) and halved that of functional impairment from peripheral sensitive neuropathy (16% versus 31%, p<0.01). Chronotherapy appeared less toxic and more effective than constant-rate infusion.

In a phase III randomized study, Giacchetti et al. (43) treated 200 patients with chronomodulated 5FU/LV infusion for 5 days without oxaliplatin (arm 1) or with (arm 2) (42, 44). PFS was of 6.1 months versus 8.7 months, respectively (p=0.048). For the first arm, MST (19.4 months) exceeded by nearly 6 months that commonly achieved in the literature and OS was longer than that observed with conventional 5FU/LV (42, 45, 46). In the second arm, the survival rate was comparable to that previously achieved in first-line treatment. Oxaliplatin increased the activity of chronomodulated 5FU/LV with acceptable toxicity (mucosal toxicity and sensitive neuropathy). Fifty-seven patients in the control group received oxaliplatin as second-line treatment after 5FU/LV failure. The results confirmed that a second-line treatment prolongs survival in metastatic colorectal cancer.

A study by de Gramont et al. (47) randomized 420 patients to receive either "folfox" 4 or the de Gramont regimen alone. The first arm resulted in higher RR (50.7% versus 22.3%; p=0.0001) and improved median PFS (9 months versus 6.2 months, p=0.0001) than the second one. Overall survival was not statistically different despite a numerical advantage for the group receiving oxaliplatin (median, 16.2 versus 14.7 months, p=0.12). "Folfox" 4 regimen gave higher frequencies of grades 3-4 neutropenia (41.7% versus 5.3%), grades 3-4 diarrhea (11.9% versus 5.3%), and grade 3 neurosensory toxicity (18.2% versus 0%), but this did not result in impairment of QOL. Survival without disease progression or deterioration in global health status was longer in patients allocated to oxaliplatin treatment (p=0.004). The lack of statistically significant survival benefit favouring the addition of oxaliplatin to 5FU/LV in these two studies delayed the FDA approval of oxaliplatin in first-line therapy in the United States.

Subsequent phase II studies in first-line therapy with the "folfox" 4 regimen alone (48) reported 6.2% complete remissions (CR), 28% PR, and 25% SD. Median duration of response was 5 months and 1-year survival 72%. Neutropenia grades 3-4 occurred in 50% of patients. The treatment was well tolerated and effective.

The efficacy of the combination of oxaliplatin plus 5FU/FA compared with bolus 5FU/FA (as the standard Mayo Clinic regimen) has been shown by a more recent phase III clinical trial (49). RR was 51.4% versus 21.5% (p=n.s.); PFS was 8 months versus 5.6 months (p=0.0001), respectively.

Oxaliplatin administered with 5FU/LV, according to the typical US schedule (weekly bolus of 5FU and low-dose of LV) (2,252.092 Euro), has given a RR in 74% of cases with 26% SD (50). Median TTP was 8.5 months. This study is ongoing, however, the 95% confidence interval for response and TTP overlap those values reported in the studies using 5FU *c.i.*/LV and oxaliplatin according to the de Gramont regimen with less costs (47). These data suggest the efficacy of this new schedule and the necessity to study it better.

## **CPT11 + 5-Fluorouracil** *versus* **Oxaliplatin + 5-Fluorouracil**

First-line chemotherapy. A phase III study, in which both CPT11 and oxaliplatin were paired with a similar infusion schedule of 5FU/LV, was performed (51) (T VI). A crossover design was mandatory for both groups to have similar exposure to both treatment arms as first and second-line therapies. Patients were randomized to receive either "folfiri" up to progression followed by "folfox" 6 as second-line therapy or the alternative sequence of "folfox" 6 up to progression followed by "folfiri". The RR to first-line therapy were similar (56% for the "folfiri" arm and 54% for

the "folfox" 6 arm) with a second surgery performed to remove metastases in 9% (7% of which had radical resection - R0 -) and in 22% of patients (13% of which had R0, p=0.26), respectively, and with a PFS of 8.5 versus 8 months (p=0.26). In addition to grade 3 sensory neurotoxicity, grades 3-4 neutropenia and thrombocytopenia were significantly more frequent with "folfox" 6 than with "folfiri". Grades 3-4 febrile neutropenia, nausea/vomiting, mucositis and fatigue were significantly more frequent with "folfiri" than with "folfox" 6. More grade 2 alopecia was observed with "folfiri". Overall, more patients experienced grades 3-4 toxicities with "folfox" 6 than "folfiri" (74% versus 53%, p=0.001), but more patients had serious adverse events with "folfiri" than with "folfox" 6 (14% versus 5%, p=0.03). The second-line therapy with "folfox" 6 resulted in higher activity than that with "folfiri" (15% versus 4%) with a PFS of 4.2 versus 2.5 months. The toxicity profile in each regimen showed minor differences compared with first-line therapy. Grades 3-4 neutropenia and thrombocytopenia and neurotoxicity were less frequent with "folfox" 6, while gastrointestinal toxicity were less frequent with "folfiri". Overall, 49% of the patients experienced grades 3-4 toxicities with "folfox" 6 second-line versus 44% with "folfiri" (p=n.s.). Serious related adverse events occurred in 6% of the patients with "folfiri" and in 4% of patients with "folfox" 6. This trial suggested that CPT11 or oxaliplatin in combination with prolonged 5FU/LV infusion have similar efficacy results in the management of metastatic colorectal cancer. In first-line therapy, grades 3-4 mucositis, nausea/vomiting and grade 2 alopecia were more frequent with "folfiri", and grades 3-4 neutropenia and neurosensory toxicity were more frequent with "folfox" 6. Therefore, the sequence of administration should be determined by reasons other than efficacy or toxicity (i.e. convenience or comorbidities).

Another trial comparing oxaliplatin or CPT11 in association with a similar schedule of 5FU/LV, and the Mayo Clinic regimen (52), resulted too toxic (4 treatment-related deaths occurred on oxaliplatin and 5FU/LV and 6 treatment-related deaths occurred on CPT11 and 5FU/LV) and stopped two of three experimental arms. Nine percent of the patients experienced grades 3-4 fatigue with both regimens, 9% experienced grades 3-4 vomiting with oxaliplatin regimen versus 19% with CPT11, 20% versus 25% reported diarrhea, 39% versus 37% febrile neutropenia, 2% versus 16% neutropenia and 13% versus 11% infection. It also terminated the control arm (Mayo Clinic) which was no longer the relevant control arm due to the registration of the IFL regimen (Saltz's schedule). The trial was revised with IFL becoming the new control arm (24, 53).

According to Saltz's results (24, 53), Goldberg *et al.* (54, 55) compared IFL, "folfox" 4, and the combination of oxaliplatin and CPT11 (Wasserman's schedule). This

Table IV. Common schema of systemic chemotherapy with Oxaliplatin and 5FU.

Shema	Authors	Drugs	Dose (mg/m <sup>2</sup> )	Administration	Day
'FOLFOX" 1	de Gramont	OXA	130	2 hours	1
q2wks)	(31)	FA	500	2 hours	1 and 2
		5FU	1500-2000	22 hours <i>c.i.</i>	1 and 2
FOLFOX" 2	de Gramont	OXA	100	2 hours	1
q2wks)	(32)	FA	500	2 hours	1 and 2
,	, ,	5FU	1500-2000	22 hours <i>c.i.</i>	1 and 2
FOLFOX" 3	Andre	OXA	85	2 hours	1
q2wks)	(33)	FA	500	2 hours	1 and 2
4)	()	5FU	1500-2000	22 hours <i>c.i.</i>	1 and 2
FOLFOX" 4	Andre	OXA	85	2 hours	1
q2wks)	(34)	FA	200	2 hours	1 and 2
1/	()	5FU	400	bolus	1 and 2
		5FU	600	22 hours <i>c.i.</i>	1 and 2
FOLFOX" 5	(not yet	OXA	100	2 hours	1
q2wks)	experimented)	FA	200	2 hours	1 and 2
1)		5FU	400	bolus	1 and 2
		5FU	600	22 hours <i>c.i</i> .	1 and 2
FOLFOX" 6	Maindrault-	OXA	100	2 hours	1
q2wks)	Goebel	FA	400	2 hours	1 and 2
1)	(35)	5FU	400	bolus	1 and 2
	()	5FU	2400-3000	46 hours <i>c.i.</i>	1 and 2
FOLFOX" 7	Maindrault-	OXA	130	2 hours	1
q2wks)	Goebel	FA	400	2 hours	1 and 2
1)	(38)	5FU	2400	46 hours <i>c.i.</i>	1
OXA-FU c.i.	Chau	OXA	100	2 hours	1
q2wks)	(40)	5FU	300	2-week <i>c.i.</i>	1-15
CHRONO-	Levi	OXA	125	6 hours	1
MODULATED	(44)	FA	300	chronomodulated	1-5
q3wks)	Giacchetti	5FU	700	chronomodulated	1-5
qo wasy	(45)	51 0	, 00		
OXAFUFA	Hochster	OXA	85	2 hours	1 and 15
q4wks)	(50)	FA	20	bolus	1, 8 and 15
1)	(00)	5FU	500	bolus	1, 8 and 15
OXAFAFU	Comella	OXA	100	2 hours	1
q2wks)	(57)	FA	250	bolus	2
7)	(57)	5FU	1050	bolus	2

trial was initially designed to have six-arms and was eventually reduced to a three-arm trial. Because of early deaths, CPT11 dosage was reduced from 125 to 100 mg/m²/day and 5FU dosage from 500 to 400 mg/m²/day. The toxicity profile of the "folfox" 4 arm appeared to be more favourable than that observed in the other arms with lower rates of severe nausea, vomiting, diarrhea, febrile neutropenia, and dehydration (but

higher rates of paresthesias and neutropenia). The costs (5.2% cheaper than the other regimen), median TTP of 8.7 months *versus* 6.9 months, RR of 45% *versus* 31%, MST of 19.5 months *versus* 15 months and overall survival of 18.6 months *versus* 14.1 months favoured "folfox" 4 over IFL. While increased efficacy with oxaliplatin may be the variable responsible for this statistically significant improvement in survival, the difference in the infusion of

Table IVa. Common schema of chemotherapy with Oxaliplatin and 5FU costs.

Schema	Drugs	Dose (mg/m <sup>2</sup> )	Day	Cost/mg	Cost/mg/m <sup>2</sup>	Cost/cycle (€)
"FOLFOX" 1	OXA	130	1	6.446	837.98	837.98
(q2wks)	FA	500	1 and 2	0.3287	164.35	328.70
(31)	5FU	1500-2000	1 and 2	0.007	10.5-14	21-28
						1,186.98x2=2,373.96
"FOLFOX" 2	OXA	100	1	6.446	644.6	644.60
(q2wks)	FA	500	1 and 2	0.3287	164.35	328.70
(32)	5FU	1500-2000	1 and 2	0.007	10.5-14	21-28
						994.3x2=1,998.60 1,021.3x2=2,042.60
'FOLFOX" 3	OXA	85	1	6.446	547.91	547.91
(q2wks)	FA	500	1 and 2	0.3287	164.35	328.70
(33)	5FU	1500-2000	1 and 2	0.007	10.5-14	21-28
						897.61x2=1,795.22
						904.22x2=1,809.22
"FOLFOX" 4	OXA	85	1	6.446	547.91	547.91
(q2wks)	FA	200	1 and 2	0.3287	65.74	131.48
(34)	5FU	400	1 and 2	0.007	2.80	5.60
	5FU	600	1 and 2	0.007	4.20	8.40
						693.39x2 = 1,386.78
"FOLFOX" 5	OXA	100	1	6.446	644.60	644.60
(q2wks)	FA	200	1 and 2	0.3287	65.74	131.48
	5FU	400	1 and 2	0.007	2.80	5.60
	5FU	600	1 and 2	0.007	4.20	8.40
						790.08x2=1,580.16
"FOLFOX" 6	OXA	100	1	6.446	644.60	644.60
(q2wks)	FA	400	1 and 2	0.3287	131.48	262.96
(35)	5FU	400	1 and 2	0.007	2.80	5.60
	5FU	2400-3000	1 and 2	0.007	16.8-21	33.6-42
						646.76x2=1,893.52 955.16x2=1,910.32
"FOLFOX" 7	OXA	130	1	6.446	837.98	837.98
(q2wks)	FA	400	1 and 2	0.3287	131.48	262.96
(38)	5FU	2400	1	0.007	16.80	16.80
						1,117.74x2=2,235.48
OXA-FU c.i.	OXA	100	1	6.446	644.60	644.60
(q2wks)	5FU	300	1-15	0.007	2.10	4.20
(40)						648.80x2=1,297.60
CHRONO-	OXA	125	1	6.446	805.75	805.75
MODULATED	FA	300	1-5	0.3287	98.61	197.22
(q3wks)	5FU	700	1-5	0.007	4.90	9.80
(45)						1,012.77x2=2,025.74
OXAFUFA	OXA	85	1 and 15	6.446	547.91	1,095.82
(q4wks)	FA	20	1, 8 and 15	0.3287	6.574	19.722
(50)	5FU	500	1, 8 and 15	0.007	3.50	10.50
						1,126.042x2 = 2,252.092
OXAFAFU	OXA	100	1	6.446	644.60	644.60
(q2wks)	FA	250	2	0.3287	82.175	82.175
(58)	5FU	1050	2	0.007	7.35	7.35
						734.125x2=1,468.25

Table V. Activity of more common schema of systemic chemotherapy with oxaliplatin and 5FU.

Authors	Drugs	N° PTS	RR (%)	MST (months)
Second-lin	ne therapy			
de Gramont (31)	"FOLFOX" 1 vs "FOLFOX" 2 vs "FOLFOX" 3	113	29.2 (41.7 for "FOLFOX" 4)	11 (13 for "FOLFOX" 4)
de Gramont (32)	"FOLFOX" 2	44	46	17
Andre (33)	"FOLFOX" 3	30	20	14.5
Andre (34)	"FOLFOX" 3 vs "FOLFOX" 4	97	18.4 vs 23.5	10.6 vs 11.1
Maind-rault -Goebel (35)	"FOLFOX" 6	60	27	10.8
Mosconi (37)	"FOLFOX" 2 vs "FOLFOX" 4	76	21.8 vs 18.2	9 vs 7
Maind- rault -Goebel (38)	"FOLFOX" 7	48	42	16.1
Andre (39)	"FOLFOX" 7 vs "FOLFOX" 4	625	64 vs 58	not yet reached
Chau (40)	OXA+5FU c.i.	38	28.9	9.1
Rothenberg (41)	"FOLFOX" 4 vs de Gramont vs OXA 85 mg/m <sup>2</sup> q2wks	459	9.9 vs 0 vs 1.3	not yet reached

d = day; q = every; chr = chronomodulated; wks = weeks; c.i. = continuous infusion; n.s. = not significant; cy = cycle; pts = patients; RR = response rate; MST = median survival time; LV = levamisol; OXA = oxaliplatin

5FU (bolus infusion in the IFL regimen and prolonged infusion in "folfox" 4) and the imbalance in second-line therapy (a high percentage of patients received second-line CPT11 chemotherapy in the "folfox" 4 arm while few patients in the IFL arm received second-line oxaliplatin) perhaps is the alternative explanation for the better efficacy results favouring "folfox" 4 over IFL in this randomised phase III trial (TTP of 8.8 months and 6.9 months, respectively).

Table V. Activity of more common schema of systemic chemotherapy with oxaliplatin and 5FU.

Authors	Drugs	N° PTS	RR (%)	MST (months)
First-line	therapy			
Levi (42)	Chronomodulated regimen vs OXA + Mayo Clinic	186	51 vs 29 (p=0.003)	15.9 vs 16.9 (p=n.s.)
Giac- chetti (43)	Chronomodulated regimen (with 5FU/LV chronomodulated regimen without C	ono) vs	53 vs 16 (p<0.001)	19.4 vs 19.9 (p=n.s.)
de Gramont (47)	"FOLFOX" 4 (with 5FU/LV infusion) vs de Gramont	420	50.7 vs 22.3 (p=0.0001)	16.2 vs 14.7
Kour- oussis (48)	"FOLFOX" 4	32	34.2	not yet reached
Grothey (49)	OXA 50 mg/m²/wl + FA 500 mg/m²/wl + 5FU 2000 mg/m 24h c.i. x 4wksq6 (with 5FU/LV bold Mayo Clinic	vk <sub>1</sub> 2	51.4 vs 21.5 (p=n.s.)	not reported
Hochster (50)	OXAFUFA	23	74	not yet reached

d = day; q = every; chr = chronomodulated; wks = weeks; c.i. = continuous infusion; n.s. = not significant; cy = cycle; pts = patients; RR = response rate; MST = median survival time; LV = levamisol; OXA = oxaliplatin; FUFA = 5FU and FA

Four multicenter-randomized trials evaluating the efficacy of OC *versus* FC (5FU and CPT11), or FC-FO (5FU and CPT11-5FU and oxaliplatin) *versus* FC, or FC *versus* FO are ongoing (56-60). No study has yet reported a significant difference of RR and MST between two drugs in first or second-line treatments of colorectal liver metastases.

#### Conclusion

Patients with isolated, potentially resectable, colorectal cancer metastases should be treated surgically to give them more hope for long-term survival, but only 10-15% of them usually have a limited and resectable disease. In the other cases,

Table VI. Randomised trials between CPT11 and oxaliplatin regimens.

Authors	Drugs	N° PTS	Observations
First-line the	гару		
Tournigand (51)	Simplified "FOLFIRI" vs "FOLFOX" 6	215	RR 54% vs 51%. II line with "folfox" 6 gave RR > than "folfiri" (15% vs 4%, p=0.05)
Morton (52)	CPT11 275mg/m <sup>2</sup> d1 + LV 20mg/m <sup>2</sup> d2-5 + 5FU 400mg/m <sup>2</sup> d2-5 vs OXA 130mg/m <sup>2</sup> + LV 20mg/m <sup>2</sup> d1-5 + 5FU 320mg/m <sup>2</sup> d1-5 vs Mayo Clinic	169	Mayo Clinic arm closed due to the superiority of Saltz regimen (IFL) over 5FU/LV. OXA and CPT11 arms also closed because of regimen toxicity
Goldberg (55)	IFL vs "FOLFOX" 4 vs OXA 85mg/m <sup>2</sup> d1 + CPT11 200mg/m <sup>2</sup> d1 q3wks (Wasserman regimen – OC -)	813	The toxicity profile ad OS of "folfox" 4 was the most favorable of 3 regimens
Schalhorn (56)	AIO vs CPT11 80mg/m²/wk + OXA 85mg/m² d1,15,29 x6wk	159	Acceptable toxicity n.s. differences in the interim analysis
Souglakos (57)	CPT11 150mg/m <sup>2</sup> d1 + OXA 65mg/m <sup>2</sup> d2 + de Gr vs "FOLFIRI"	120	RR 57% vs 38% MST has not yet been achieved
Comella (58)	IRIFAFU vs OXAFAFU	48	RR 33% vs 45.8%
Falcone (59)	CPT11 165mg/m <sup>2</sup> d1 + OXA 85mg/m <sup>2</sup> d1 + LV 200mg/m <sup>2</sup> d1 + 5FU 3200mg/m <sup>2</sup> 48hc.i. vs "FOLFIRI"	70	Acceptable toxicity: similar g.i. toxicity; ↑ neutropenia in the I arm
Salgado (60)	CPT11 180mg/m <sup>2</sup> + LV 400mg/m <sup>2</sup> + 5FU 400mg/m <sup>2</sup> + 5FU 2400mg/m <sup>2</sup> 46hc.i. vs OXA 85mg/m <sup>2</sup> + LV 400mg/m <sup>2</sup> + 5FU 4400mg/m <sup>2</sup> + 5FU 2400mg/m <sup>2</sup> 46h c.i.	113	RR 50% vs 67% (p=n.s.)

d = day; q = every; wks = weeks; c.i. = continuous infusion; h = hours; n.s. = not significant; cy = cycle; pts = patients; RR = response rate; MST = median survival time; OXA = oxaliplatin; de Gr = de Gramont; g.i. = gastrointestinal

systemic chemotherapy may prolong survival, decrease tumor-related symptoms, improve general well being or maintain it at a high level for a longer period of time (11). Although the impact on overall survival is modest, treatment is recommended. Infusional regimen with modulated 5FU gives an objective RR of up to 30% to 40%. The addition of CPT11 or oxaliplatin to 5FU improves RR, TTP and OS (61-64).

Randomised trials comparing CPT11 and 5FU bolus to the Mayo Clinic regimen alone and to CPT11 monochemotherapy reported PFS (p=0.004), RR (39%, p<0.001) and MST (14.8 months, p=0.04) significantly improved in the first group of patients (24). Even in Europe, AIO (more expensive) or de Gramont regimens with infusional 5FU/LV combined with CPT11 (cheaper) and compared to 5FU/LV or de Gramont alone (25, 27) gave a RR (49%, p<0.001), TTP (p<0.001) and MST (17.4 months, p=0.031) significantly better in the combined arm than in the other.

On the other hand, similar studies with oxaliplatin and bolus 5FU/FA compared with the Mayo Clinic regimen, reported RR of 51.4% and PFS of 8 months (p=0.0001) after polichemotherapy (49). Moreover, in a trial comparing oxaliplatin and infusional 5FU/LV with the de Gramont regimen alone, a higher RR (50.7%, p=0.0001) and improved median PFS (9 months, p=0.0001) resulted in the "folfox" arm (47).

These data showed that CPT11 and oxaliplatin combined with bolus 5FU/LV (1,183.82-1,338.14 Euro *versus* 1,468.25-2,252.092 Euro - with oxaliplatin-regimen 19.4-49.4% more expensive than the CPT11-regimen -) or infusional (1,106.60-2,341.20 Euro *versus* 1,297.60-2,373.96 Euro - with oxaliplatin-regimen 1.4-14% more expensive than the CPT11-regimen) gave better results than the Mayo Clinic (bolus) or the de Gramont (infusional 5FU/LV) monochemotherapy in terms of RR (40-50% *versus* 20-22%) but not of MST (14-16 months).

Other studies comparing the "folfox" 4 versus "folfiri" regimens reported a more favorable "folfox" arm in term of overall survival (18.6 months versus 14.1) and costs (1,267.65 versus 1,338.14 - 5% -) over IFL. While increased efficacy (patients who were initially unresectable were more often able to undergo hepatic resection with "folfox") coupled with a favorable toxicity profile with oxaliplatin could be the variable responsible for this statistically significant improvement in survival, the difference in the infusion of 5FU (bolus infusion in the IFL regimen and prolonged infusion in "folfox" 4) could be the alternative explanation for the better results in efficacy favouring "folfox" 4 over IFL. A phase III study in which simplified "folfiri" and "folfox" 6 were paired with a similar infusion schedule of 5FU/LV (51), the RR was similar (54% versus 51%); the first regimen was 37.1% cheaper than the other (1,115.00 Euro versus 1,893.521,910.32 Euro) but grades 3-4 mucositis, nausea and vomiting and grade 2 alopecia were more common than with oxaliplatin. The second-line therapy with "folfox" 6 resulted in higher activity than with "folfiri" (15% versus 4%). This trial suggested that CPT11 or oxaliplatin in combination with prolonged 5FU/LV had similar results in efficacy but different toxicities in the management of metastatic colorectal cancer. Confirmatory studies with larger accrual goals are currently underway.

In this paper, the Authors examined clinical trials with the "FOLFOX and FOLFIRI families of drugs" and the efficacy, toxicity and cost of each therapy. In light of all these results, it was not possible to decide which of the family could win the match, while it was possible to define the different toxicity profile which could influence the choice of a first or second-line therapy. The significantly lower rates of nausea, vomiting, diarrhea, dehydration and febrile neutropenia associated with oxaliplatin as compared with the CPT11 regimen are notable because these toxic effects generally occur in early treatment cycles and can lead to treatment-induced morbidity and mortality. Additionally, oxaliplatin may cause sensory neuropathy, an adverse effect that is cumulative but generally reversible and dose-dependent. This tended to become treatment-limiting only in patients benefiting from treatment, as it generally occurred after eight to ten cycles. Oxaliplatin is also associated to treatment-limiting neutropenia, but this is seldom complicated by clinically meaningful toxicity such as infections. Several issues must be considered in integrating these phase II studies data to define optimal treatment because the field is currently too confused (65, 66).

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