Anti-Cancer Drugs 2000, **11,** pp. 495–501

Report

Overcoming resistance to chronomodulated 5-fluorouracil and folinic acid by the addition of chronomodulated oxaliplatin in advanced colorectal cancer patients

C Garufi,[1] S Brienza,[2] P Pugliese,[3] AM Aschelter,[1] MA Bensmaine,[2] F Bertheault-Cvitkovic,[7] C Nisticò,[1] S Giunta,[4] M Caterino,[4] D Giannarelli,[5] M Cosimelli,[6] F Lévi[7] and E Terzoli[1]

[1]Oncologia Medica Complementare, [2]Debiopharm-France, Charenton Le Pont, [3]Psiconcologia, [4]Radiologia, [5]Biostatistica, [6]Chirurgia, Istituto Regina Elena, Rome, Italy. [7]Hôpital Paul Brousse, Villejuif, France. From the Regina Elena Cancer Institute Multidisciplinary Colorectal Cancer Working Group.

The addition of oxaliplatin (L-OHP) to a 5-fluorouracil (5-FU)/leucovorin (FA) regimen was retrospectively evaluated in 35 consecutive advanced colorectal cancer patients after progression of disease. L-OHP, 25 mg/m^2/day, was infused from 10.00–22.00 with a peak flow at 16.00 while 5-FU, 700 mg/m^2/day and FA, 150 mg/m^2/day of the *l*-form or 300 mg/m^2/day of the racemic form, from 22.00 to 10.00 with a nocturnal peak at 4.00, for 5 days every 3 weeks in 24 patients and for 4 days every 2 weeks in the other 11. Diarrhea and sensitive neuropathy were the most relevant types of toxicity (17% of patients). An objective response was achieved in 8/35 patients (23%) [95% CL 9–37], stabilization in 15 patients (43%) which included five minor responses, and progression in 12. There was no relevant difference in quality of life assessed with the EORTC QLQ C30+3 questionnaire before and after treatment. Median duration of response and median progression-free survival were 6 months; median overall survival was 11 months. This retrospective study showed that it is possible to reverse resistance to chronomodulated 5-FU by adding chronomodulated L-OHP to the previous regimen; comparison with different schedules of this combination should be performed in order to identify the best tolerated and active regimen as second-line treatment of advanced colorectal cancer. [© 2000 Lippincott Williams & Wilkins.]

Key words: Colorectal cancer, chronotherapy, 5-fluorouracil, folinic acid, oxaliplatin.

Correspondence to C Garufi, Oncologia Medica Complementare, Istituto Regina Elena, Viale Regina Elena 291, 00161 Roma, Italy. Tel: (+39) 06 49852237; Fax: (+39) 06 49852388; E-mail: garufi@sirio-oncology.it

Introduction

Management of metastatic colorectal cancer has recently benefited from the availability of new agents such as oxaliplatin (L-OHP) and CPT-11, and from the improved tolerability and efficacy of chronomodulated infusions. L-OHP is a third-generation platinum compound with low hematological toxicity and no renal toxicity, yet does involve cumulative peripheral sensory neurotoxicity.[1] It exerts antitumor activity *in vitro* against colorectal cancer cell lines and is synergistic with 5-fluorouracil (5-FU) against L1210 leukemia transplanted into mice.[2,3] This drug achieved 10 and 24% of the objective responses in phase II trials as a single agent in 5-FU pretreated and untreated patients with metastatic colorectal cancer, respectively.[4–6]

The possibility to simultaneously increase both tolerability and efficacy of anti-cancer drugs administered by chronomodulated infusions in phase I, II and III trials was also demonstrated. Chronobiology is a therapeutic strategy based on the recognition that biological rhythms regulate most metabolic and cellular functions.[7] As a result, both the toxicity and the activity of fluoropyrimidines and platinum compounds vary greatly as a function of time of day with the administration of these drugs. More specifically, the infusion of 5-FU, folinic acid (FA) and L-OHP (FFL), according to circadian rhythms, resulted in a toxic effect up to 5 times less severe and nearly twice as many objective responses than flat infusion of the same drugs in two randomized phase III trials.[8,9]

In patients treated with chronomodulated FFL (chrono-FFL) as second-line therapy, response rate ranged from 38 to 57%, although the degree of clinical resistance to 5-FU had not been extensively defined.[10–12] In analyzing the results of the studies with the FFL combination, the benefits in terms of activity seem to be due to two important factors: drug chronomodulation and introduction of L-OHP.

This paper presents the final report of the retrospectively assessed activity of the addition of chronomodulated L-OHP to chronomodulated 5-FU–FA (chrono-FF) in patients with colorectal cancer metastasis and an adequate follow-up.[13] The effect of L-OHP addition on patient quality of life was also investigated through the EORTC QLQ C30+3 questionnaire.[14]

Patients and methods

Thirty-five patients with metastatic colorectal cancer were included in this study. All patients had advanced measurable disease and displayed clinical resistance to chrono-FF. Clinical resistance was defined as a CT scan documentation of disease progression while under chrono-FF treatment. These patients were considered to be resistant to chrono-FF. The rationale of the study is described in Figure 1.

All patients had adequate bone marrow reserve, hemoglobin >10 g/dl, leukocytes >3000 mm^3, platelets $>100\,000$ mm^3, normal renal function with serum creatinine <2 mg/dl, adequate liver function, serum bilirubin <2 mg/dl and prothrombin activity $>70\%$.

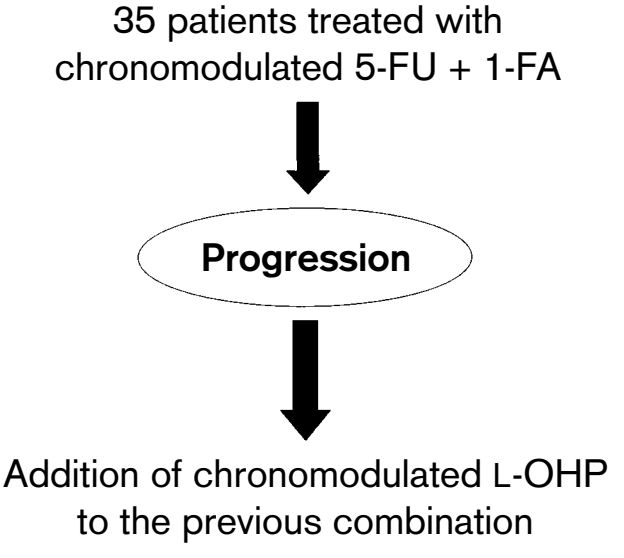

Figure 1. Design of the study.

Treatment regimen

Prior to inclusion, all patients received chrono-FF for 5 consecutive days every 3 weeks with a median dose of 5-FU per course of 3500 mg/m^2 (range 2500–5500 mg/m^2). After inclusion, the three-drug chrono-FFL was administered according to previous reports.[10,11] FFL was either administered for 5 consecutive days following a 16 day interval (chrono-FFL 5–16) in 24 patients or for 4 consecutive days followed by a 10 day rest period (chrono-FFL 4–10) in the other 11 patients. L-OHP (25 mg/m^2/day) was given from 10.00 to 22.00 with a peak at 16.00. 5-FU (700 mg/m^2/day) and FA (150 mg/m^2/day of the levogyral form or 300 mg/m^2/day of the racemic form) were infused from 22.00 to 10.00 with a nocturnal peak at 4.00. Dose reduction and escalation of L-OHP and 5-FU were performed according to toxicity criteria as previously described.[10] All three drugs were administered with a programmable pump (Intelliject; Aguettant, Lyon, France) via a double-lumen Port-a-Cath. Anti-HT_3 antiemetics were not routinely administered before the first course but only after vomiting occurred.

Assessment criteria

The World Health Organization (WHO) criteria for evaluating toxicity and response was used with the exception of a specific scale for neurological toxicity.[8] All computed tomography scans were examined by the same radiologists (SG and MC) for progression during FF and response confirmation during FFL.

Dose intensity (mg/m^2/week) and cumulative dose (mg/m^2) for 5-FU and L-OHP were calculated according to Hryniuk.[15] Dose intensity was calculated after the third and sixth course and for the entire duration of treatment. In an attempt to investigate whether response to therapy was influenced by the extent of 5-FU therapy before and during L-OHP addition, the following factors were analyzed: the number of 5-FU courses given, the duration of 5-FU exposure (expressed in weeks), the cumulative 5-FU dose and the cumulative 5-FU-DI.

The Italian version of the EORTC QLQ-C30+3 questionnaire was used to evaluate L-OHP addition on quality of life in the 24 patients treated in Rome. This questionnaire incorporates five functioning scales, three global functioning scales, and eight symptom scales and/or items. The questionnaire was completed before starting FFL, and after the third and sixth course of treatment.

Statistical analysis was performed by *t*-test for the comparison between the averages and the Wilcoxon test was used for non-parametric analyses. Time to

disease progression and survival were determined from the date of inclusion and estimated by the Kaplan–Meier method.[16]

Results

Patient characteristics

Patient data are shown in Table 1. Forty-nine percent of the patients had an altered performance status, twenty-three patients showed metastasis in two or more organs and the liver was involved in 30 (86%). Chrono-FFL was given as third-line chemotherapy in 16 patients.

Toxicity

Chrono-FFL was generally well tolerated. No patient displayed grade 3 anemia or thrombocytopenia while a single patient experienced grade 4 leukopenia. Six patients (17%) had grade 3–4 vomiting or diarrhea. Severe mucositis was encountered in two patients. Clinically relevant neurological toxicity (WHO-modified Grade 2) affected six patients (17%). The incidence of severe toxicity per course, including modified neurological grade 2 toxicity, is 23 of 211 courses (11%). The incidence of severe toxicity per patient and per course is shown in Table 2.

Table 1. Patient characteristics

	Patients	(%)
No. of patients	35	
Sex (M/F)	22/13	(63/17)
Median age (years)	60	
range	25–75	
PS (WHO)		
0	18	(51)
1	13	(37)
2	3	(9)
3	1	(3)
Primary tumor		
colon	22	(63)
rectum	13	(37)
No. of metastatic sites		
1	12	(34)
2	12	(34)
3	11	(32)
Metastatic site		
liver	30	(86)
lung	12	(34)
pelvis	7	(20)
Previous adjuvant treatment		
chemotherapy	3	(9)
radiotherapy	4	(12)
Previous treatment for advanced disease:		
chrono-FF	35	(100)
other 5-FU-based therapies	16	(48)
radiotherapy	8	(23)

Table 2. Incidence of WHO graded toxicity per patient ($n=35$) and per course ($n=211$)

	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hemoglobin					
patient	29 (83)	2 (6)	4 (11)	0	0
course	195 (92)	13 (6)	3 (2)	0	0
Leukocytes					
patient	27 (77)	5 (14)	2 (6)	0	1 (3)
course	173 (82)	26 (11)	12 (6)	0	1 (0.5)
Platelets					
patient	29 (83)	5 (14)	1 (3)	0	0
course	193 (91)	16 (8)	2 (1)	0	0
Vomiting					
patient	6 (17)	13 (37)	10 (28)	5 (14)	1 (3)
course	129 (61)	46 (22)	30 (14)	5 (2.5)	1 (0.5)
Mucositis					
patient	17 (47)	13 (37)	3 (8)	0	2 (6)
course	174 (81)	28 (13)	7 (3.3)	0	2 (1)
Diarrhea					
patient	12 (34)	7 (20)	10 (28)	3 (8.5)	3 (8.5)
course	146 (69)	35 (17)	24 (11)	3 (1.5)	3 (1.5)
Skin					
patient	23 (66)	3 (8)	8 (23)	1 (3)	0
course	176 (83)	19 (9)	10 (5)	1 (0.5)	0
Neuropathy					
patient	7 (20)	12 (34)	7 (20)	3 (8)	6 (17)
course	78 (37)	88 (42)	35 (17)	3 (1.5)	7 (3)
Neuropathy[8]	Grade 0	Grade 1a	Grade 1b	Grade 1c	Grade 2

Dose and dose intensity

Two-hundred and twenty-one courses of chrono-FFL were administered; the median number of courses was 6 and range 1–15. The median dose per course was 3500 mg/m^2 (range 3000–7500) for 5-FU and 125 mg/m^2 (range 50–125) for L-OHP. There was no difference between chrono-FF and chrono-FFL regarding the number of 5-FU courses given, 5-FU exposure and 5-FU cumulative dose. Median 5-FU-DI over the entire duration of chrono-FF treatment was significantly larger than that of the chrono-FFL; 1250 versus 1152 mg/m^2/week (p=0.006) (Table 3). During chrono-FFL, the median DIs at the third course (DI_3) for 5-FU and L-OHP were 1166 mg/m^2/week (range 700–1639) and 41 mg/m^2/week (range 21–51), respectively, and 1179 mg/m^2/week for 5-FU-DI_6 (range 900–1787) and 37 mg/m^2/week for L-OHP-DI_6 (range 31–51) at the sixth course.

Antitumor activity

An objective response was achieved in eight of 35 patients (23%) [95% confidence limit (CL) 9–37]. Disease remained stable in 15 patients (43%) with five of them achieving a reduction in tumor size ranging from 36 to 46%. Disease progressed in 12 patients (34%) including all eight patients previously pretreated with radiotherapy. Objective responses were obtained in four of 11 patients treated with FFL 4–10 (36%) and in four of 24 patients (17%) receiving FFL 5–16. FFL-responders received higher 5-FU and L-OHP DIs than non-responders but this reached statistical significance only for 5-FU-DI_3; 1292 versus 1098 mg/m^2/week (p=0.04). The median response duration was 6 months (range 3–8 months). Median progression-free survival was 6 months. Median overall survival was 11 months.

Quality of life

We did not find any significant difference between the mean scores of the questionnaire on quality of life before and after the addition of L-OHP at the third and sixth course, with the exception of fatigue which increased significantly at the third course (p=0.02) but not at the sixth. See Figure 2.

Discussion

This retrospective study involved 35 patients with clinical resistance to chronomodulated 5-FU–FA. An analysis of these data demonstrated that addition of L-OHP clearly contributed to the activity of the FFL regimen as it achieved 23% of the objective responses and 43% of the stabilizations. As a result, tumor progression was stopped in 66% of the patients. These results are clinically relevant considering that treatment was delivered as a third line in 48% of patients. It was further confirmed that schedule intensification

Table 3. Studies concerning addition of L-OHP to the same previous 5-FU plus FA regimens

Author	5-FU (mg/m^2)	FA (mg/m^2)	L-OHP (mg/m^2)	Days/courses	Grade 3–4 toxicity (% of patients)	Response rate (%)
Chronomodulated Studies						
Bertheault-Cvitkovic *et al.*[11]	800	300	20 × 4 dd	4 days q 2 wk	not reported	11/27 (41)
Giacchetti *et al.*[12]	700	300	25 × 5 dd	5 days q 3 wk	not reported	10/57 (17)
present study						
FFL 5-16	700	150	25 × 5 dd	5 days q 3 wk		4/24 (17)
FFL 4-10	800	150	20 × 4 dd	4 days q 2 wk		4/11 (36)
					17	8/35 (23)
Non-chronomodulated studies						
de Gramont *et al.*[21]						
FolFox2	1500–2000	500	100 dl	2 days q 2 wk	46	10/22 (45)
André *et al.*[22]						
FolFox3	1500–2000	500	85 dl	2 days q 2 wk	27	6/30 (20)
André *et al.*[23]						
FolFox3	1500	200	85 dl	2 days q 2 wk	17.3	5/24 (18.4)
FolFox4	400 bolus					
	600 c.i.	500	85 dl	2 days q 2 wk	36.9	7/20 (23.5)
Gamelin *et al.*[26]	1500	400	130 dl	day 1 q 3 wk	21	14/38 (36)
Büchele *et al.*[25]	2600	500 wk	60 wk	weekly × 6 q 8 wk	42	3/24 (13)
Van Cutsem *et al.*[24]	320 bolus	20 × 5 dd	130 dl	5 days q 3 wk	not reported	15/115 (13)
	2600 i.c.	500 wk	85 dl	weekly × 6		4/57 (7)

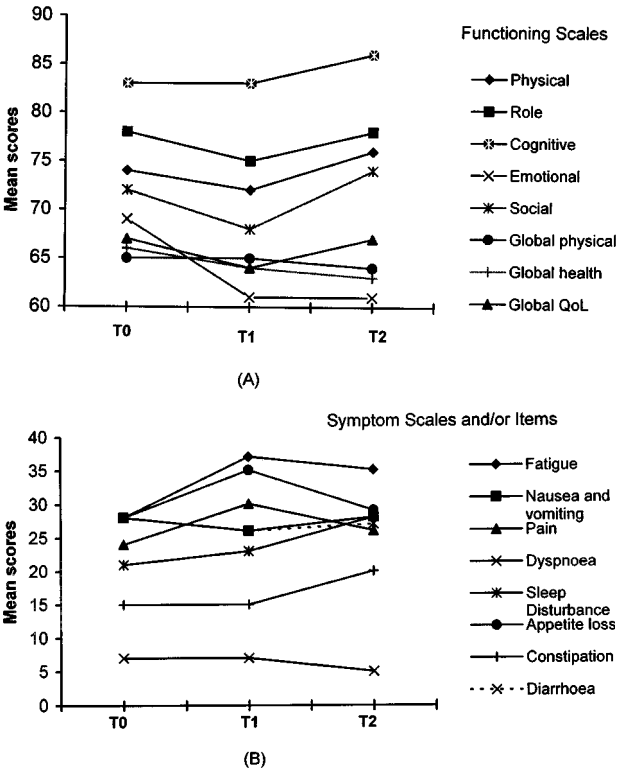

Figure 2. Evaluation of functioning scales (A) and symptom scales and/or items (B) before starting treatment (T0), after the third course (T1) and after the sixth course (T2).

every 2 weeks yielded a higher response rate than the 3-weekly schedule. The present study confirmed the excellent toxicity profile of the chronomodulated infusion with severe toxicity being observed in 11% of all courses and mostly consisting of vomiting or diarrhea. It should be emphasized that 5-HT_3 receptor antagonists were used only after the first course of patient discomfort. Diarrhea was the dose-limiting toxicity, encountered in 17% of the patients. Peripheral sensory neuropathy with functional impairment was observed in 17% of all patients. Leukopenia was severe in only one patient and no severe anemia or thrombocytopenia was encountered.

Although L-OHP activity is no greater than 10% in 5-FU-resistant patients, the combination of 5-FU, FA and L-OHP allowed 5-FU resistance to be overcome by a synergistic effect which has yet to be completely explained. Different hypotheses, based on the *in vitro* synergy between cisplatin and 5-FU, have recently been summarized by Fischel *et al.*[17] In particular, platinum-induced reduction of methionine uptake by tumor cells stimulates methionine synthesis and reduces folate pool expansion, which in the presence of 5-FU leads to the stabilization of the ternary complex (5-fluoro-dUMP-TS and 5-10 methylenetetrahydrofolate). However, Raymond *et al.* showed synergy of platinum compounds with TS inhibitors that do not always require folates for their action.[18] Gamelin suggested that L-OHP could inhibit dihydropyrimidine dehydrogenase activity since he observed increased 5-FU plasma concentrations after repeated L-OHP administrations.[19] 5-FU might increase platinum cellular toxicity through an effect on DNA repair systems.[20] Finally, an appropriate timing of 5-FU–FA and L-OHP during the 24 h time scale may further favor the synergistic activity of these agents in tumor cells, while normal cells remain partly protected as a result of their circadian rhythms in the susceptibility for these drugs.

The results obtained in 5-FU refractory patients point to a synergistic and specific activity of L-OHP. This original study model, i.e. the addition of L-OHP to 5-FU-refractory patients, first demonstrated in this series of patients, was subsequently confirmed by other regimens of 5-FU and FA very common in Europe as the De Gramont schedules[21] (Table 3). Patients included in each study range from 20 to 115, the response rate varies from 7 to 45% and the patient rate with grade 3–4 toxicity from 17 to 42%. Because of the limited sample numbers and data available, it is difficult to reach a conclusion on the role of 5-FU and L-OHP doses, schedule (weekly, bi- or tri-weekly) and modality of infusion (bolus and/or continuous infusion versus chronomodulated infusion).

André *et al.* found that reduction of L-OHP from 100 mg/m^2 (FOLFOX2) to 85 mg/m^2 (FOLFOX3) every 2 weeks was followed by a drop in response rate from 45 to 20% in a similar set of patients.[20] In a recent prospective study with FOLFOX3, 40 patients, and with FOLFOX4, 57 patients, response rates of 18.4 and 23.5%, respectively, were reported.[23] The largest experience with the Mayo Clinic schedule and the German weekly regimen was recently reported by van Cutsem *et al.*:[24] an objective response, externally reviewed, was observed in 19 of 172 patients (11%).

Treatment tolerability is even more important in this setting of patients. Although FFL is generally a well-tolerated combination, important differences exist among proposed schedules. Thirty-nine percent of patients receiving the FOLFOX2 regimen displayed grade 3–4 neutropenia and 9% had neutropenic fever. Overall, 21 patients (46%) experienced grade 3–4 toxicity with this regimen. In addition, the subsequent FOLFOX3 and FOLFOX4 versions resulted in an incidence of patients with grade 3–4 neutropenia in 15 and 36.9% of patients with 5% of febrile neutropenia and one toxic death.[22]

Forty-two percent of patients receiving L-OHP with the German regimen displayed grade 3–4 diarrhea.[25] Diarrhea was the most relevant toxic effect reported by Meyer with an overall grade III toxicity in eight of 38 patients (21%).[26]

Finally, this is the first experience on the impact of L-OHP addition on patient quality of life. In spite of an initial slight and brief decrease after the introduction of L-OHP, the final scores returned to baseline values. This corresponds to what was observed in a randomized trial comparing L-OHP versus taxol in resistant ovarian cancer patients.[27] A significant difference was found only in fatigue at the third course; this was considered a transient effect since it disappeared at the sixth course. Similar results were observed during the evaluation of patients randomized between bolus plus infusion 5-FU/leucovorin with or without L-OHP; in this trial quality of life was not significantly affected by the addition of the drug.[28]

In conclusion, oxaliplatin plays an important role in the antitumor activity of chrono-FFL. The addition of chronomodulated L-OHP infusion in patients previously treated with chrono-FF achieved 23% of all objective responses in these patients and stopped tumor progression in 66%. The simple and safe addition of L-OHP to the previous 5-FU-containing regimen can be proposed as an adequate second-line chemotherapy for patients with advanced colorectal cancer. Randomized clinical trials with adequate designs are needed to identify those three-drug schedules from which patients benefit the most in terms of activity and tolerability in 5-FU-resistant disease. We feel that chronomodulated infusions should be an integral part of these studies, considering the results obtained in all reported studies, including the present one.

Acknowledgments

The authors would like to thank Marco Ravaioli for linguistic assistance.

References

1. Raymond E, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol* 1998; **9**: 1053–71.
2. Silvestro L, Anal H, Sommer F, *et al*. Comparative effect of a new platinum analog (*trans*-l-diamine-cyclohexane oxalato-platinum; L-OHP) with CDDP on various cells: correlation with intracellular accumulation. *Anticancer Res* 1990; **10**: 1376 (abstr 115).
3. Raymond E, Djelloul C, Buquet-Fagot F, *et al*. Oxaliplatin (L-OHP) and cisplatin (CDDP) in combination with 5-FU, specific thymidase synthase (TS) inhibitors (AG337, ZD1694) and topoisomerase I (Topo-1) inhibitors (SN38, CPT-11), in human colonic, ovarian and breast cancers. *Proc Am Ass Cancer Res* 1996; **37**: 291 (abstr 1981).
4. Lévi F, Perpoint B, Garufi C, *et al*. Oxaliplatin activity against metastatic colorectal cancer. A phase II study of 5-day continuous infusion at circadian rhythm modulated rate. *Eur J Cancer* 1993; **29A**: 1280–4.
5. Machover D, Diaz-Rubio E, de Gramont A, *et al*. Two consecutive phase II studies of oxaliplatin (L-OHP) for treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines. *Ann Oncol* 1996; **7**: 95–8.
6. Bécouran 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**: 2739–44.
7. Moore RY. Entrainment pathways and the functional organization of the circadian system. *Prog Brain Res* 1996; **111**: 103–19.
8. Lévi F, Zidani R, Vannetzel JM, *et al*. Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid in patients with colorectal cancer metastases: a randomized multi-institutional trial. *J Natl Cancer Inst* 1994; **86**: 1608–17.
9. Lévi F, Zidani R, Misset JL for the International Organization for Cancer Chronotherapy. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. *Lancet* 1997; **350**: 681–6.
10. Lévi F, Misset JL, Brienza S, *et al*. A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid and oxaliplatin using an ambulatory multichannel programmable pump. High antitumor effectiviness against metastatic colorectal cancer. *Cancer* 1992; **69**: 893–900.
11. Bertheault-Cvitkovic F, Jami A, Ithzaki M, *et al*. Biweekly intensified ambulatory chronomodulated chemotherapy with oxaliplatin, 5-fluorouracil and folinic acid in patients with metastatic colorectal cancer. *J Clin Oncol* 1996; **14**: 2950–8.
12. Giacchetti S, Brienza S, Focan C, *et al*. Contribution of second line oxaliplatin (OXA)-chronomodulated 5-fluorouracil-folinic acid (CM-5-FU-FA) and surgery to survival in metastatic colorectal cancer patients (MMC pts). *Proc Am Soc Clin Oncol* 1998; **17**: 1050.
13. Garufi C, Brienza S, Misset JL, *et al*. Addition of oxaliplatin to chronomodulated 5-fluorouracil and folinic acid for reversal of acquired chemoresistance in patients with advanced colorectal cancer. *Proc Am Soc Clin Oncol* 1995; **14**: 192.
14. Aaronson NK, Ahmedzai S, Bergman B, *et al*. The EORTC QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993, **85**: 365–76.
15. Hryniuk WM. The importance of dose intensity in the outcome of chemotherapy. In: De Vita VT, Holman S, Rosenberg SA (eds), *Important advances in oncology*. Philadelphia, PA: Lippincott 1988: 121–42.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958; **53**: 457–81.

17. Fischel JL, Etienne MC, 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**: 2529–35.
18. Raymond E, Buquet-Fagot F, Djelloul C. Antitumor activity of oxaliplatin in combination with 5-fluorouracil and the thymidylate synthase inhibitor AG337 in human colon, breast and ovarian cancers. *Anti-Cancer Drugs* 1997; **8**: 876–85.
19. Gamelin E, Boisdron-Cell M, Allain P. Pharmacokinetic interference between oxaliplatin (LOHP) and fluorouracil: delayed 5-FU metabolism inhibition by LOHP. *Proc Am Soc Clin Oncol* 1997; **38**: 223.
20. Esaki T, Nakano S, Tastumoto T. Inhibition by 5-fluorouracil of cisdiamminodichloroplatinum(II)-induced DNA interstrand cross-link removal in a HST-1 human squamous carcinoma cell line. *Cancer Res* 1992; **52**: 6501–6.
21. De Gramont A, Vignoud J, Tournigaud C, *et al*. Oxaliplatin with high-dose Leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. *Eur J Cancer* 1997; **33**: 214–19.
22. André T, Louvet C, Raymond E, Tournigand C, de Gramont A. Bimonthly high-dose leucovorin, 5-fluorouracil infusion and oxaliplatin (FOLFOX3) for metastatic colorectal cancer resistant to the same leucovorin and 5-fluorouracil regimen. *Ann Oncol* 1998, **9**:1251–3.
23. André T, Bensmaine MA, Louvet C, *et al*. Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J Clin Oncol* 1999; **17**: 3560–8.
24. Van Cutsem E, Szanto J, Roth A. Evaluation of the addition of oxaliplatin (OXA) to the same Mayo or German 5FU regimen in advanced refractory colorectal cancer (ARCRC). *Proc Am Soc Clin Oncol* 1999; **18**: abstr 900.
25. Büchele T, Balleisen L, Beck M *et al*. Weekly high-dose (HD) 5-fluorouracil (5-FU) and folinic acid (FA) with addition of oxaliplatin (LOHP) after documented progression under high-dose infusional 5-FU/FA in patients (pts) with advanced colorectal cancer (CRC). A multicentric phase II study. In: *Abstracts Int. Conf. on Chemotherapeutic Strategies for Treatment of Colorectal Cancer: present and future developments*, organized by the European Cancer Centre in collaboration with the Roswell Park Cancer Institute, Amsterdam 1999: 10–12.
26. Gamelin E, Meyer V, Delva R, *et al*. Oxaliplatin (L-OHP) and 5-fluorouracil (5-FU) synergism in pretreated advanced colorectal patients. *Proc Am Soc Clin Oncol* 1997; **16**: 1102–5.
27. Green JA, Piccart M.J, Lacave A. Oxaliplatin versus taxol in platinum pretreated ovarian cancer patients: a randomized phase II trial by the EORTC-Gynecological Oncology Cooperative Group. In: *8th Int. Symp. on platinum and other metal coordination compounds in cancer chemotherapy (ISPCC '99).* Oxford 1999: 28–31 (abstr 5.03).
28. Seymour MT, Tabah-Fish I, Homerin M. Quality of life in advanced colorectal cancer: a comparison of QOL during bolus plus infusion 5-FU/leucovorin with or without oxaliplatin. *Proc Soc Am Clin Oncol* 1999, **18**: 901 (abstr).

(Received 1 March 2000; revised form accepted 10 April 2000)