Eur J Cancer, Vol. 29A, No. 9, pp. 1280–1284, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00
Pergamon Press Ltd

Oxaliplatin Activity against Metastatic Colorectal Cancer. A Phase II Study of 5-Day Continuous Venous Infusion at Circadian Rhythm Modulated Rate

Francis Levi, Bruno Perpoint, Carlo Garufi, Christian Focan, Philippe Chollet, Petra Depres-Brummer, Rachid Zidani, Silvano Brienza, Moshe Itzhaki, Stefano Iacobelli, Francis Kunstlinger, Julio Gastiaburu and Jean-Louis Misset

Oxaliplatin (L-OHP) is a non-nephrotoxic third generation platinum complex with proven antitumoral activity and minimal haematological toxicity. Circadian scheduling has allowed significant increases in L-OHP dosage and dose intensity and decreases in its toxicities. This phase II trial has tested the antitumour activity of a 5-day circadian schedule of continuous venous infusion of L-OHP against metastatic colorectal cancer. Initial dose was 150 mg/m²/course. An intrapatient dose escalation scheme by 25 mg/m²/course was planned up to 200 mg/m²/course, according to toxicity criteria. The delivery rate of L-OHP was sinusoidally modulated along the 24-h time scale, and was highest at 1600 h. A programmable-in-time ambulatory pump was used, so that all patients could receive their treatment at home. 29 of 30 patients registered were eligible. 25 had failed previous chemotherapy. Three objective responses were observed (response rate: 10%), in patients progressive while on chemotherapy with 5-fluorouracil and folinic acid. Toxicity was moderate. Dose-limiting toxicities were diarrhoea and peripheral sensitive neuropathy. The latter adverse effect appeared to be cumulative. L-OHP, as delivered under this circadian schedule, exhibits clinical antitumour activity against metastatic colorectal cancer. These results, which await further confirmation, support the place of L-OHP in combination regimens including 5-fluorouracil.

Eur J Cancer, Vol. 29A, No. 9, pp. 1280–1284, 1993.

INTRODUCTION

OXALIPLATIN (L-OHP), a diammino cyclohexane (DACH) platinum (Pt) complex [1] displayed similar antitumour effectiveness as cisplatin against several transplanted murine tumours. At equiactive doses, L-OHP lacked any renal toxicity and exhibited minimal haematological toxicity [2, 3]. Clinical antitumour activity has been described in bladder, lung, ovarian and breast cancers and in lymphoma, glioblastoma and malignant melanoma, during its early phase I–II development [3–5].

In mice, the extent of toxicity of L-OHP, like that of cisplatin or carboplatin, was significantly lessened by dosing either Pt complex near the middle of the active span of the circadian sleep–wakefulness cycle [6–10].

As a result, Pt complexes constitute a class of drugs which may legitimate an assessment of chronotherapy in cancer patients. Chronotherapy aims at improving the therapeutic index of medications through an adequate selection of dosing times and/or timed infusion schedules [11]. As an example, cisplatin was less toxic to cancer patients if administered in the late afternoon (1600–2000 h) as compared to late night or early morning (0400–0800 h) [12, 13].

Programmable-in-time pumps now allow testing of the relevance of such strategy in outpatients, thus in larger patient populations. In the case of L-OHP, the validity of this experimentally based concept was supported by the results of a randomised phase I clinical trial: L-OHP was continuously infused for 5 consecutive days either at a constant rate or according to a 24-h chronomodulated rate, with peak delivery at 1600 h. Circadian scheduling resulted in significantly less haematological and neurological toxicity and allowed delivery of 30% more drug than flat infusion. The recommended dose of L-OHP for phase II trials with this schedule was 175 mg/m² [14]. The dose schedule used in phase II trials of L-OHP given as a single 2-h venous infusion is 130 mg/m² every 21 days (J.L. Misset and J. Gastiaburu, personal communication).

Although no Pt complex has revealed any clinical antitumour efficacy in such disease [15–20], L-OHP testing appeared justi-

Correspondence to F. Levi.
F. Levi, P. Depres-Brummer, R. Zidani, M. Itzhaki and J.-L. Misset are at the Laboratoire "Rythmes Biologiques et Chronothérapeutique", Institut du Cancer et d'Immunogénétique; F. Levi, P.Depres-Brummer, R. Zidani, S. Brienza, M. Itzhaki, F. Kunstlinger, J. Gastiaburu and J.-L. Misset are at the Centre de Chronothérapie, Service des Maladies Sanguines, Immunitaires et Tumorales, Hôpital Paul Brousse, 14–16, avenue Paul Vaillant-Couturier, 94800 Villejuif; B. Perpoint is at the Service de Médecine et de Thérapeutique, CHRU St-Etienne, France; C. Garufi is at the Università degli Studi "G. d'Annunzio", Chieti, Italy; C. Focan is at the Hôpital Saint-Joseph Sainte Elisabeth, Liège, Belgium; P. Chollet is at the Centre Jean Perrin and INSERM U71, Clermont-Ferrand, France; and S. Brienza and J. Gastiaburu are at the Laboratoire Debiopharm, S.A. Lausanne, Switzerland.
Presented in part at the 82nd conference of the American Association for Cancer Research, May 15–18 1991, Houston, Texas, U.S.A.
Revised 12 Oct. 1992; accepted 26 Nov. 1992.

fied based on the following data: first, L-OHP, like other DACH–Pt complexes, was found to be active against cisplatin-resistant human cell lines from colorectal cancer [21]. Second, one major clinical response in this disease was observed during a pilot screening phase II clinical trial (B. Chevallier and M. Bayssas, L-OHP pilot study at the recommended dose for phase II studies. Report on file, S.A. Debiopharm, Lausanne). Moreover, a combination chronotherapy schedule of L-OHP, 5-fluorouracil (5-FU) and folinic acid has resulted in a 58% objective response rate in 93 consecutive patients with such disease, half of whom had previously failed standard chemotherapy [22]. The present phase II trial was designed to determine the activity of L-OHP by itself as delivered with a circadian rhythm modulated administration schedule. Most patients had failed 5-FU-containing chemotherapy.

PATIENTS AND METHODS

Patients with metastatic colorectal cancer were eligible for entry into the study between May 1990 and May 1991. The present trial had been approved by the local ethics committee and a written informed consent was obtained from each patient. Three French centres, a Belgian one and an Italian one also participated in this trial. Registration was made through a central coordinating office in Villejuif. Inclusion and follow-up data were transmitted by Fax within 1 month following their collection. Admission criteria included biopsy-proven adenocarcinoma, measurable recurrent or metastatic cancer of the colon or rectum, a life expectancy greater than 1 month and informed consent.

Exclusion criteria were surgically resectable metastases, or cerebral metastases, a performance status (PS) greater than II on the WHO scale or age above 75 years. Previous chronotherapy with 5-FU, folinic acid and L-OHP or a cumulative dose of 400 mg/m^2 of cisplatin were also exclusion criteria.

Eligible patients had a complete work-up including complete history, physical examination and surgical placement of a totally implanted venous access port (Port-a-Cath^R, Pharmacia, Upsala, Sweden). Weight and height, complete blood cell count, serum bilirubin, creatinine, urea, ionogram, calcium, magnesium, total proteins, alkaline phosphatase, serum glutamate-pyruvic/oxaloacetic transaminase (SGPT and SGOT), glutamyl transpeptidase (gamma-GT), lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA) and CA 19-9 were determined. Initial radiological examinations included chest X-ray, abdomino-pelvic ultrasound and computed tomography (CT) of the abdomen, pelvis and thorax not older than 1 month at onset of therapy. Radioisotopic bone scan and/or cardiac echography and/or colonoscopy were obtained when indicated. Clinical examination, and blood determinations were performed before each therapy course and radiological investigations after every third treatment course.

Chemotherapy regimen

Treatment consisted of a 5-day course of circadian-scheduled continuous venous infusion of L-OHP (30 mg/m^2/day × 5 days; total dose: 150 mg/m^2), which was repeated every 21 days (16-day interval). In the absence of grade III toxicity or greater after the first course, intrapatient dose escalation was mandatory. Daily doses were escalated up to 35 mg/m^2 at the second-course (175 mg/m^2) and 40 mg/m^2/day (200 mg/m^2) at the third course.

L-OHP was infused for 5 consecutive days with a sinusoidally varying delivery rate over 24 h, with a daily peak at 1600 h (Fig. 1). Such chronomodulated delivery schedule was performed in outpatients with a programmable-in-time multichannel ambulatory pump (IntelliJect, Aguettant, Lyon, France).

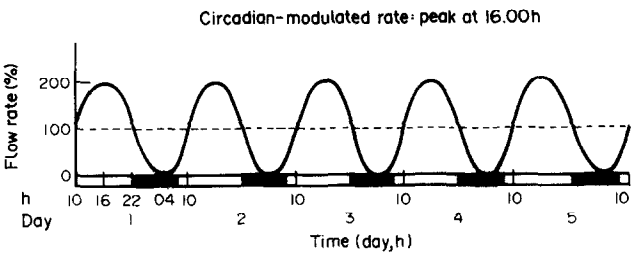

Fig. 1. Circadian schedule of oxaliplatin (L-OHP) delivery. L-OHP delivery rate followed a sinusoidal pattern ranging from 0% at 0400 h up to 200% of the 24-h mean at 1600 h. Such 24-h cycle was automatically repeated each day for 5 consecutive days.

The pump is equipped with four 30-ml disposable syringes connected to the same central venous line via a manifold. The plunger of each syringe is indepently driven by a step motor. The rotation rate of the latter varied in time according to the program which has been written in a PROM (Programmable Read Only Memory) chip located within the pump; this chip is programmed via an IBM-PC computer using the Intellimed^R software. Two 9-V batteries allow a 15-day power autonomy of the pump, far beyond what was needed for one course.

L-OHP (Debiopharm, S.A. Lausanne, Switzerland) was suspended in 5% glucose solution at a concentration of 3 mg/ml. L-OHP stability has been documented for 5 days or more in these conditions, according to the manufacturer.

Efficacy endpoints

Indicator lesions were considered as measurable if not located within any prior radiotherapy field or in bone. All indicator lesions were assessed with computer tomography (CT) scans, and/or echography. Response was measured after every third treatment course and defined according to the following criteria: (a) complete response (CR), complete disappearance of all symptoms and signs of disease for a minimum of 4 weeks; (b) partial response (PR), a 50% reduction (or more) in the sum of the products of the perpendicular diameters of measurable disease and the appearance of no new malignant lesion for a minimum of 4 weeks; (c) stable disease (SD), no appearance of new areas of disease, less than 50% decrease or less than 25% increase in the above described measurements; (d) progressive disease (PD), more than 25% increase in these measurements and/or the appearance of new lesions.

All radiological assessments were centrally reviewed by the same two radiologists both highly specialised in hepatic imaging interpretation. Duration of response, time to disease progression and survival were determined from date of first treatment course. Progression-free survival were estimated according to Kaplan and Meier [23].

Toxicity endpoints

The toxicity of each course was evaluated and recorded before the next one, and graded according to the WHO criteria for haematological, skin, mucosal and hair toxicity. A specific grading system was used for nausea and vomiting, diarrhoea and paresthesias, similar to that used in the phase I trial of L-OHP chronotherapy [14].

Nausea or vomiting. Nausea only, without any antiemetic (grade I); two or fewer vomiting episodes per day, well controlled

with standard daily antiemetics (grade II); vomiting poorly controlled with standard antiemetics (grade III); protracted vomiting despite any therapy (grade IV).

Diarrhoea. 3–5 daily stools and no need for symptomatic treatment (grade I); > 5 daily stools, with < 3 stools with loperamide (grade II); > 5 daily stools (but < 10), despite loperamide (grade III); profuse diarrhoea requiring parenteral hydration (grade IV).

Peripheral paresthesias. Moderate intensity and lasting less than 7 days (grade I); moderate intensity, lasting 8–14 days (grade II); incomplete recovery between courses or mild hypoesthesias of finger tips or footplant (grade III); and beginning functional impairment (grade IV).

RESULTS

Patients' characteristics

From 3 May 1990 to 15 April 1991, 30 patients with metastatic colorectal cancer were registered. 1 patient had received more than 400 mg/m^2 cisplatin prior to inclusion and was not eligible. Another patient was lost to follow-up after the second course but was nevertheless included in the assessment of both toxicity and efficacy. As a whole, 29 patients were evaluated (Table 1).

25 of 29 patients (86%) had failed previous chemotherapy. 27 patients (93%) had tumour in the liver and 13 (45%) had two or more metastatic sites. A total of 108 courses were administered. The median number of courses given was three (range: two to nine). 7 patients received six or more courses. The median total dose received was 500 mg/m^2 (range 275–1550).

7 patients withdrew from treatment for progressive disease before receiving the third course.

Table 1. Patients' characteristics

No. included	30
Eligible	29
Centre	
Villejuif (France)	12
Saint-Etienne (France)	5
Chieti (Italy)	5
Liège (Belgium)	4
Clermont-Ferrand (France)	3
Previous treatment	
None	3
Chemotherapy	20
Radiotherapy	1
Both	5
Sex ratio (M:F)	24:5
Age (years)	
Median	60
Range	33–75
Colon : rectum	19:10
Performance status	
0–I	27 (93%)
II	2
Number of metastatic sites	
One	16 (55%)
Two	10
Three or more	3
Organs involved	
Liver	27 (93%)
Lung	7
Bone	4
Abdomen-pelvis	3
Lymphnodes	2
Tumour markers median (range)	
CEA (ng/ml)	76 (6 to 5816)
CA 19.9 (u/ml)	204 (3 to 1267)
% of patients with	
CEA > 10 ng/ml	89%
CA 19.9 > 40 iu/ml	70%

Toxicity

There were no treatment-related deaths. 4 patients withdrew from this trial owing to toxicity. 2 of these 4 patients also had disease progression at time of withdrawal. 1 had severe diarrhoea (grade III after first course; grade IV after second course), the 3 other patients developed peripheral sensitive neuropathy after four or six courses (1 and 2 patients, respectively, cumulative doses: 725, 900 and 925 mg/m^2). Neutropenia and thrombocytopenia (WHO grade II) were associated with neurological toxicity in 2 patients.

Toxicity was assessed in 103 (95%) to 106 (98%) courses, according to the endpoint considered (Table 2). No grade II or greater toxicity was observed with regard to anaemia, liver function tests, central nervous system (consciousness), audition (no patients reported hearing change, but audiogram was not mandatory), allergy, hair or skin.

Serum creatinine remained normal in all courses in all patients. Haematological or mucosal toxicities were minimal. Nausea was usually mild, and required antiemetic medications (oral or intramuscular metoclopramide or alizapride) in 20 courses (19%). Severe vomiting was observed in two courses only despite no 5-HT$_3$ receptor blocker being used. Diarrhoea was usually well controlled with oral loperamide (18% courses); nonetheless, grade III or IV diarrhoea occurred in six courses (6%) and was responsible for one toxic withdrawal.

Dysesthesias, consisting of cold-induced sensations of electric discharges in hands and/or feet occurred in 84 courses (79%). Such transient symptoms usually started on day 4 or 5 of infusion and completely regressed within 1 week or less in 50 courses (47%), or within 1 to 2 weeks in 21 courses (20%). In 13 courses (12%), such symptoms of peripheral sensitive neuropathy did not regress during treatment intervals and were associated with hypoesthesia of tips of fingers and toes, which could gradually extend to whole fingers and footplant. In 2 patients, transient muscle cramps involving jaws and/or shoulders were observed during L-OHP infusion and led to course interruption in one of them (150 mg/m^2 at first course, then 125 mg/m^2 at second course). L-OHP was reintroduced for several courses at a lower

Table 2. Toxicity of L-OHP chronotherapy

Endpoint	No. of courses	0	I	II	III	IV
Leucocytes*	105	97	6	2	0	0
Neutrophils*	105	97	5	2	1	0
Platelets*	106	98	3	4	1	0
Mucositis†	105	97	5	3	0	0
Nausea or vomiting†	105	44	41	18	1	1
Diarrhoea†	105	62	18	19	5	1
Peripheral sensory neuropathy‡	106	22	50	21	10	3

*Graded according to WHO scale.
†Graded according to WHO modified scale.
‡Grading described in Patients and Methods.

dose level in the other patient, with similar yet acceptable symptoms. An electromyogram was obtained in 3 patients, which documented a decrease in conduction velocity of median, peroneal and sural nerves in 2 patients. Electromyographic findings were in favour of moderate sensori-motor axonal degeneration and myelin loss.

Peripheral sensitive neuropathy (hypoesthesia of fingers or footplant—grade III or more) appeared to depend upon the total dose of L-OHP received. Thus, its incidence doubled in those patients who had received a cumulative dose of 700–1550 mg/m^2 (4/10 patients, 40%) as compared to patients receiving a total dose less than 699 mg/m^2 (3/19 patients, 16%). Of those 7 patients with grade III–IV peripheral sensitive neuropathy, only 1 had received the dose level of 200 mg/m^2 (for two courses).

Dose modifications

8 patients withdrew from treatment for progressive disease before receiving the third course. 21 patients (72%) completed the first three courses of therapy and were evaluated for the dose escalation scheme. Among these, 1 remained at 150 mg/m^2 courses, 12 reached 175 mg/m^2 and 8 received 200 mg/m^2. Reasons for not reaching this third dose level in 13 patients included grade II or greater peripheral sensitive neuropathy (10 patients), diarrhoea (5 patients) and nausea or vomiting (3 patients). 6 of the 7 patients who received six or more courses had three or more courses at a dose level of 175 mg/m^2 or higher. Such a dose level (175 mg/m^2) was delivered in 49/108 courses (45%), 150 mg/m^2 were given in 37 courses (34%), 200 mg/m^2 were administered in nine courses (8%) and 125 mg/m^2 in 13 courses (12%).

Antitumour efficacy (Table 3)

19 patients had PD (66%). Metastatic lesions were stabilised in 7 patients (24%) for 17 to 31 weeks. 2 of these patients (7%) had a minor response (decrease in tumour size by 40%).

Three objective responses (10%) were documented after three courses, all in patients with liver metastases of colon cancer. All had prior disease progression, while receiving 5-FU and folinic acid (5-day schedule). Objective response was documented with both CT scan and liver echography in 2 patients, and by echography in 1 patient in whom CT scan was not contributory. One of these patients had developed liver metastases from colon cancer in October 1987 for which he had received 21 courses of chemotherapy (5-FU and folinic acid) until March 1990. In June 1990, his disease progressed and multiple liver lesions were found in segments IV (major indicator lesion: 50 × 58 mm^2), VI, VII and in the left lobe. Tumour size decreased by more than 50% at all measurable sites after three courses, as assessed both with CT scan and liver echography. CEA and CA 19-9, respectively, decreased by 40 and 50%. This objective response lasted 29 weeks. Both other responses lasted 20 and 26 weeks, respectively.

Table 3. Antitumor efficacy of L-OHP in 29 patients with metastatic colorectal cancer

Prior treatment	No. of patients	Progression	Stabilisation	PR > 50%
No	3	3	0	0 (0%)
Yes				
5-FU + FOL	12	5	4	3 (25%)
id. + Ptc*	3	2	1	0
id. + other	3	3	0	0
5-FU	2	1	1	0
id. + Ptc	1	0	1	0
id. + other†	5	5	0	0
All treated	26	16	7	3 (12%)
All patients	29	19 (66%)	7 (24%)	3 (10%)

*Platinum complex (Ptc), †except folinic acid (FOL), PR = partial response.

Median progression-free survival was 20 weeks. Median estimated overall survival was 40 weeks. Objective responders lived for 25, 33 and 34 weeks, respectively, whereas 5 of the 7 patients with stable disease are alive with 39 to 67 weeks follow up.

DISCUSSION

Circadian scheduling of L-OHP has allowed delivery of high doses of drug (150–200 mg/m^2) without any life threatening toxicity, confirming the results of the phase I study [14]. Dose-limiting toxicities were mostly diarrhoea and peripheral sensitive neuropathy. The latter adverse effect was cumulative, as had been previously observed [3, 14, 22, 24]. Since most patients had a poor prognosis, recovery from this condition could not be adequately documented. Nonetheless, a complete recovery of all clinical symptoms of peripheral sensitive neuropathy had been observed within 2–6 months in large series of patients treated with L-OHP, in association with 5-FU and folinic acid [22]. Nausea and vomiting were generally mild, and required no antiemetic medication in 81% of courses. No renal toxicity was encountered, and haematological toxicity was minimal. All patients were treated as outpatients.

Such well-tolerated circadian schedule of L-OHP resulted in three objective responses in 29 patients, 25 of whom had failed previous chemotherapy. This 10% response rate is modest although rather unusual in previously treated patients with such disease. It indicates that L-OHP has clinical antitumour activity against metastatic colorectal cancer. 5-FU has remained the most active drug against this disease for the past 30 years, with a 10–15% response rate as first-line single-agent bolus therapy [25].

A possible dose–response relationship of L-OHP against colorectal cancer is suggested by the fact that, in this study, all 3 objective responders and both patients with a minor response had received two or more courses at a dose level of 175 mg/m^2 or more. Nonetheless, no dose–response relationship has been documented for the activity of any Pt complex against colorectal cancer, as opposed to ovarian cancer [26]. This may be due to the lack of activity of cisplatin, carboplatin or CHIP against this disease at conventional dosages [15–20]. However, human cell lines derived from colorectal cancer may exhibit *in vitro* susceptibility to cisplatin [27, 28]. Moreover, cisplatin-resistant cell lines from human colorectal cancer were indeed susceptible to L-OHP [21]. This indicates a possible lack of cross-resistance between both Pt complexes at the clinical level.

Further trials are needed to document more precisely the antitumour activity of L-OHP in previously untreated patients with metastatic colorectal cancer. Nonetheless, Pt complexes also modulate the cytotoxicity of 5-FU with a mechanism different from that of folinic acid [29]. The acceptable toxicity of circadian-scheduled oxaliplatin makes it a good candidate for its association with 5-FU and folinic acid. The results already obtained in 93 patients with metastatic colorectal cancer with circadian scheduling of L-OHP, 5-FUra and folinic acid (58% response rate) warranted testing of L-OHP alone under a similar schedule in previously treated patients [22]. The dose intensity

of L-OHP as delivered by this chronomodulated schedule, was substantially higher than the dose intensity of a currently ongoing trial of L-OHP (130 mg/m^2 over 2 h every 3 weeks) in a similar patient population. Taken together, the data from both trials will possibly indicate any schedule dependency of L-OHP activity. The chronomodulated modality of L-OHP delivery allows a higher dose intensity on an outpatient basis and will likely constitute a major option in the routine administration of this promising new agent. We believe that future clinical trials should further explore the benefits brought about by the addition of L-OHP to 5-FU and folinic acid.

1. Kidani Y, Naji M, Tashiro T. Antitumour activity of platinum II complexes of 1,2-diammino-cyclohexane isomers. *Jpn J Cancer Res* 1980, **71**, 637–643.
2. Mathé G, Kidani Y, Noji M, Maral R, Bourrut C, Chenu E. Antitumor activity of L-OHP in mice. *Cancer Lett* 1985, **27**, 135–143.
3. Mathé G, Kidani Y, Eriguchi M, *et al.* Oxalato-platinum or L-OHP, a third generation platinum complex: an experimental and clinical appraisal and preliminary comparison with cisplatinum and carboplatinum. *Biomed Pharmacother* 1989, **43**, 237–250.
4. Extra JM, Espie M, Calvo F, Ferme C, Mignot L, Marty M. Phase I study of oxaliplatin in patients with advanced cancer. *Cancer Chemother Pharmacol* 1990, **25**, 299–303.
5. Misset JL, Brienza S, Burki F, *et al.* Early phase II trial of trans-1-diammino cyclohexane oxalatoplatine (L-OHP) in malignant melanoma, ovarian carcinoma and non-Hodgkin's lymphoma (NHL). Proceedings of ECCO 6. *Eur J Cancer* 1991, **27**, (suppl. 2), S196.
6. Boughattas NA, Lévi F, Fournier C, *et al.* Circadian rhythm in toxicities and tissue uptake of 1,2-diammino-cyclohexane (trans-1) oxaliplatinum (II) in mice. *Cancer Res* 1989, **49**, 3362–3368.
7. Lévi F, Hrushesky W, Blomquist J, *et al.* Reduction of *cis*-diammine dichloroplatinum nephrotoxicity in rats by optimal circadian drug timing. *Cancer Res* 1982, **42**, 950–955.
8. Hrushesky W, Lévi F, Halberg F, Kennedy BJ. Circadian stage dependence of *cis*-diamminedichloroplatinum lethal toxicity in rats. *Cancer Res* 1982, **42**, 945–949.
9. Boughattas NA, Lévi F, Fournier C, *et al.* Circadian time dependence of murine tolerance for carboplatin. *Toxicol Appl Pharmacol* 1988, **96**, 233–247.
10. Boughattas N, Lévi F, Fournier C, *et al.* Stable circadian mechanisms of toxicity of two platinum analogs (cisplatin and carboplatin) despite repeated dosages in mice. *J Pharmacol Exp Ther* 1990, **255**, 672–679.
11. Reinberg A, Labrecque G, Smolensky M. *Chronobiologie et Chronothérapeutique*. Paris, France, Flammarion Méd Sci, 1991.
12. Hrushesky W. Circadian timing of cancer chemotherapy. *Science* 1985, **228**, 73–75.
13. Lévi F, Benavides M, Chevelle C, *et al.* Chemotherapy of advanced ovarian cancer with 4'-0-tetrahydropyranyl doxorubicin and cisplatin: a randomized phase II trial with an evaluation of circadian timing and dose-intensity. *J Clin Oncol* 1990, **8**, 705–714.
14. Caussanel JP, Lévi F, Brienza S, *et al.* Phase I trial of 5-day continuous infusion of oxaliplatin at circadian rhythm modulated rate compared with constant rate. *J Natl Cancer Inst* 1990, **82**, 1046–1050.
15. Kovach JS, Moertel G,Schutt AJ, *et al.* Phase II study of cisdiamminedichloroplatinum in advanced carcinoma of the large bowel. *Cancer Chemother* 1973, **57**, 357–359.
16. Lokich J, Zipoli T, Green SP, *et al.* Protracted low dose cisplatin infusion in advanced colorectal cancer. *Cancer Treat Rep* 1986, **70**, 523–524.
17. Peny D, Weiss R, Creekmore S, *et al.* Carboplatin for advanced colorectal carcinoma: a phase II study. *Cancer Treat Rep* 1986, **70**, 301–302.
18. Pazdur R, Samson M, Baker L. CBDCA: Phase II evaluation in advanced colorectal carcinoma. *Am J Oncol* 1987, **10**, 136–138.
19. Asburry R, Kramer A, Green M, *et al.* A phase II study of carboplatin and CHIP in patients with metastatic colon carcinoma. *Am J Clin Oncol* 1989, **12**, 416–419.
20. Schmoll HJ, Gundersen S, Arnold A, Nys G, Gratton R, Canetta R. Phase II study of carboplatin in colorectal cancer. *Ann Oncol* 1990, **48**, (suppl. 1), 6–22 (abstract).
21. Pendyala L, Creaven PJ, Shah G, Molnar MV, Grandjean EM. *In vitro* cytotoxicity studies of oxaliplatin in human tumor cell lines. *Proc Am Assoc Cancer Res* 1991, **32**, 410 (abstract 2441).
22. Lévi F, Misset JL, Brienza S, *et al.* A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid and oxaliplatinum using an ambulatory multichannel programmable pump: high antitumor effectiveness against metastatic colorectal cancer. *Cancer* 1992, **69**, 893–900.
23. Kaplan E, Meier P. Non parametric estimation for incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
24. Gastiaburu J, Brienza S, Misset JL, *et al.* Oxaliplatinum (L-OHP) tolerance evaluation of 253 two hours infusion cycles (CY). *Proc Am Assoc Cancer Res* 1991, **32**, 173 (abstract 1031).
25. De Vita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer. Principles and Practice of Oncology*, 3rd edition. Philadelphia, U.S.A., J.B. Lippincott, 1992.
26. Levin H, Hryniuk WM. Dose intensity of chemotherapy regimens in ovarian carcinoma. *J Clin Oncol* 1987, **5**, 756–767.
27. Vadi H, Drewinko B. Kinetics and mechanism of 1-β-D-arabinofuranosylcytosine-induced potentiation of cis-diammine dichloroplatinum (II) cytotoxicity. *Cancer Res* 1986, **46**, 1105–1109.
28. Trujillo J, Yang LY. Synergism of 1-β-D-arabinofuranosyl cytosine and *cis*-diammine dichloroplatinum in their lethal efficacies against seven established cancer cell lines of gastro-intestinal origin. *Anticancer Res* 1989, **9**, 197–202.
29. Scanlon K, Newman E, Lu Y, *et al.* Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. *Proc Natl Acad Sci USA* 1986, **83**, 8923–8925.

Acknowledgements—Thanks to E.M. Grandjean M.D. (Debiopharm) and to E. Cvitkovic, M.D. for pertinents comments and advices, to Y. La Torre, M.D. and G. Debotte for their help in data management, and to M. Levi for the edition of this manuscript. C. Garufi is recipient of a fellowship of Consorzio Interuniversitario Nazionale per la Biooncologia (Italy).