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Pharmacokinetic study of oxaliplatin iv chronomodulated infusion combined with 5-fluorouracil iv continuous infusion in the treatment of advanced colorectal cancer

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Abstract

We investigated the pharmacokinetics (PK), preliminary clinical results and toxicity of chronomodulated oxaliplatin (OHP) plus 5-fluorouracil (5-FU) without folinic acid (FA) in 13 patients with metastatic colorectal cancer. 5-FU (200 mg/m^2/day as 14-day continuous iv infusion for six cycles) plus OHP at increasing doses (25–30–35 mg/m^2/day, as 12 h chronomodulated iv infusion on days 1-2-3-4, every 14 days for six cycles) were administered to reach maximum tolerated dose (MTD). At MTD (30 mg/m^2/day), a PK study of 5-FU and OHP (in total and ultrafiltered-UF plasma) was performed. 5-FU plasma levels were fairly stable, below that reported in similar studies and closely related to the lack of the most typical 5-FU toxicities. OHP C_{max} occurred 7 h after infusion start; a progressive accumulation of free Pt and ultrafiltered Pt (UF-OHP) through cycles 1-6 was noted. A marked difference between total plasma and UF Pt was seen in the elimination phase. OHP plasma clearance decrease was related to V_z (volume of distribution of late elimination phase), whereas in UF-OHP was due to a change in K_e or $t_{1/2}$. In conclusion, the association of 5-FU with chronomodulated OHP do not seem to influence PK parameters of either drugs. Toxicity was modest/acceptable and clinical efficacy good: preliminary data showed a threshold neurotoxicity at total plasma Pt concentrations >1500 ng/ml and UF plasma Pt concentrations >150 ng/ml.

Keywords: Oxaliplatin; Pharmacokinetic; 5-Fluorouracil; Folinic acid; Advanced colorectal cancer

1. Introduction

The most widely used chemotherapy agent for patients with colorectal cancer (CRC) over the past 30 years has been fluorouracil (5-FU). 5-FU bolus alone gives an objective response rate (ORR) of ca. 11% [1]. Recent means of enhancing its efficacy have involved biochemical modulation of its cytotoxicity through combination with folinic acid (FA) [2] or administration by continuous iv infusion [3]. In patients with metastatic disease, both protocols usually improve tumor response rate (30%), compared with standard 5-FU treatment. FA is known to stabilize the ternary complex of 5-fluorodeoxyuridine monophosphate (the intracellular cytotoxic form of 5-FU) with thymidilate synthetase (TS) and 5,10-methylene-tetrahydrofolate. Recently new cytotoxic drugs, with different mechanisms of action and no cross-resistance between with 5-FU, have been found to be clinically active in treating CRC patients. OHP is one of these new drugs and is the first platinum compound to be active in advanced CRC [4]. OHP is a diaminocyclohexane platinum compound with an oxa-

Abbreviations: OHP, oxaliplatin; 5-FU, 5-fluorouracil; FA, folinic acid; TS, thymidilate synthetase; MTD, maximum tolerated dose; UF, ultrafiltered; CRC, colorectal cancer; ORR, objective response rate; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTP, time to progression; OS, overall survival.

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late ligand as the leaving group and a *trans*-1,1,2-diaminocyclohexane as the transport ligand. OHP acts as an alkylating cytotoxic agent, inhibiting DNA replication by forming adducts that are bulkier and more hydrophobic than cisplatin ones. Several in vitro and in vivo studies demonstrated OHP superior activity over 5-FU [5]. Particularly, OHP has shown significant in vitro and in vivo synergism with 5-FU and FA [6]. OHP clinical development thus concentrated on its use in combination with 5-FU or 5-FU plus FA, as frontline therapy in patients with advanced CRC, with an ORR ranging from 46 to 71% (FOLFOX 2-6) [6]. Chronomodulated drug delivery is based on preclinical and clinical evidence of a relationship between the time of day at which the drug is administered and its effectiveness and toxicity [7]. Some clinical development of the 5-FU/OHP combination took place in the context of a chronomodulation research program [8].

In preclinical research, to investigate the synergistic interaction between OHP and 5-FU, a biochemical mechanism was hypothesized, based on the similarity of OHP and cisplatin, in terms of additive cytotoxic effect of cisplatin/5-FU combination [9]. Cisplatin has been shown to block methionine entry into tumor cells, resulting in increased intracellular methionine synthesis and subsequent increased TS activity; as a result, tumor cells become more susceptible to 5-FU, a direct inhibitor of TS. So, it could be supposed that a similar biochemical mechanism may occurs with OHP. Indeed, OHP undergoes a series of spontaneous, non-enzymatic conversions in biological fluids (like cisplatin), giving several transient reactive species including dichloro-, monochloro- and diaquated-1,2-diaminocyclohexane (DACH) platinum, complexing with nucleophile species like proteins and aminoacids [4,5]. An adduct between an aquated derivative of OHP and methionine, very similar to that formed with cisplatin, has been previously described [10].

The present work studied for the first time pharmacokinetics (PK) parameters of both OHP and 5-FU, combining an OHP chronomodulated iv infusion with a 5-FU continuous 14-day iv infusion.

2. Material and methods

2.1. Patients population and treatment plan

A non-randomized open clinical trial was conducted to investigate PK behaviour of oxaliplatin/5-FU combination in 13 patients affected by metastatic CRC (stage IV). Eligibility criteria included: measurable or evaluable disease; ECOG Performance Status ≤ 2; normal bone marrow, liver and renal functions. Eligible patients underwent a complete work-up including complete medical history, physical examination and double venous access port implantation (Port-a-cath, Pharmacia, Sweden). Standard WHO criteria for solid tumor responses and toxicity criteria were used. Informed consent was required from patients, following Helsinki–Tokio Declaration.

5-FU was administered as a 14-day continuous iv infusion at 200 mg/m^2/day fixed dose, for six 14-day cycles (13 patients). OHP was administered on days 1-2-3-4 of each 14-day cycle for six cycles, by a chronomodulated plan providing sinusoidally-modulated delivery from 10:00 to 22:00 with peak flow rate at 16:00. OHP dose-finding plan comprised three different doses: 25–30–35 mg/m^2/day (3-8-2 patients, respectively). OHP and 5-FU were administered to outpatients by means of a multichannel programmable pump (Mélodie® Aguettant, France).

2.2. Blood sampling and analytical procedures

Fifteen 10 ml blood samples per cycle were drawn from a peripheral vein, during cycles 1-3-6. On days 1-2-3-4, three samples/day were collected: at 10:00 (start of OHP infusion), at 17:00 (experimentally evaluated C_{max}) and at 22:00 (end of OHP infusion). On days 5-10-15, one sample/day was collected at 10:00, respectively corresponding to patient discharge, outpatients check-up and next cycle start. Blood samples were placed immediately on ice and centrifuged (2500 rpm for 10 min) within 2 h. A portion of plasma was transferred into polypropylene tubes and stored at $-80\,^{\circ}$C until analysis; the remainder was processed for ultrafiltration.

2.3. OHP analysis

Fraction of ultrafiltrate (UF) plasma was obtained by ultrafiltration in Centricon 10® membranes (Amicon Division, Danvers, USA). A 3030-Z Zeeman spectrometer, equipped with an AS-60 autosampler (Perkin Elmer, USA), was used to analyze platinum in total and UF plasma. Platinum hollow-cathode lamp (Perkin Elmer) operated at 30 mV voltage. The pyrolytically-coated partitioned graphite tubes (Perkin Elmer) were routinely replaced after ca. 100 firings. During atomization stage, absorbance was monitored with Zeeman correction and peak heights of absorbance profiles were recorded at 265.9 nm [11].

2.4. 5-FU analysis

The HPLC system consisted of a Shimadzu LC-10ADvp pump and a Shimadzu SPD-10Avp UV spectrophotometer. The analytical column was a symmetry C_{18} (250×4.6 mm i.d.) with a symmetry C_{18} precolumn (Waters, USA). 5-FU was determined using an UV detector at 254 nm fixed wavelength. 5-FU was assayed in plasma using the above HPLC system after

liquid/liquid extraction, as described by Gamelin et al. [12].

2.5. Pharmacokinetic study design

PK analysis was performed by Kinetica 3.0 (Inna-Phase Corp., USA). The chosen approaches are non-compartmental analysis for OHP and Steady State Kinetica proprietary model for 5-FU; their only assumption is that terminal elimination phase can be approximated by an exponential equation, so that a straight line can approximate the logarithmic transformation of data belonging to the terminal removal process. Statistical evaluation was performed by Mann–Whitney non-parametric test, using Instat 3.05 (Graphpad, USA).

3. Results

3.1. Pharmacokinetics of 5-FU

5-FU PK was tested in 20 courses/13 patients during the first 96 h of each cycle (18 courses/11 patients treated with OHP 25 and 30 mg/m^2/day) (Fig. 1). Differences in 5-FU plasma concentrations among different patients/cycles/OHP dosage regimen were not statistically significant (Mann–Whitney test). At OHP 30 mg/m^2/day, median values of maximum plasma (C_{max}), trough plasma (C_{min}) and average plasma concentrations (C_{av}) were 98.9, 62.1 and 66.3 ng/ml respectively, while $AUC_{ss(0-72)}$ was 4596.1 ng h/ml. A general overview of 5-FU PK parameters at two OHP different doses (25 and 30 mg/m^2/day) is reported in Table 1.

Table 1
5-FU PK steady state parameters (median values) in 18 courses/11 patients

5-FU	OHP 25 mg/m^2/day 9 courses/3 patients	OHP 30 mg/m^2/day 9 courses/8 patients
Dose/24 h (mg)	366	426.5
C_{min} (ng/ml)	49.83	62.15
C_{max} (ng/ml)	68.99	98.86
C_{av} (ng/ml)	41.79	66.29
$AUC_{ss(48-72\ h)}$ (ng h/ml)	1003.09	1590.97
Cl_{ss} (l/h)	364.87	219.46

3.2. Pharmacokinetics of OHP

OHP PK was evaluated in 30 courses/13 patients (among 61 totally administered courses). At 30 mg/m^2/day level, eight patients were evaluated to calculate OHP PK (in total and UF patients) (Table 2). We found that, on each day, C_{max} was reached at the seventh hour of infusion (17:00), therefore deciding to optimize blood sample timing. OHP maintained the same behaviour in the subsequent days [2,3] of the first cycle: Cp progressively increased on days 2-3-4, reaching the highest level at 17:00 of day 4. During the following cycles, OHP Cp again increased from day 1 to day 4, with a progressive drug accumulation from cycle 1 to 6. Median OHP C_{max} raised from 0.96 mg/l (cycle 1) to 1.88 mg/l (cycle 6) (Figs. 2 and 3). Table 2 reports OHP main PK parameters; OHP progressive accumulation from cycle

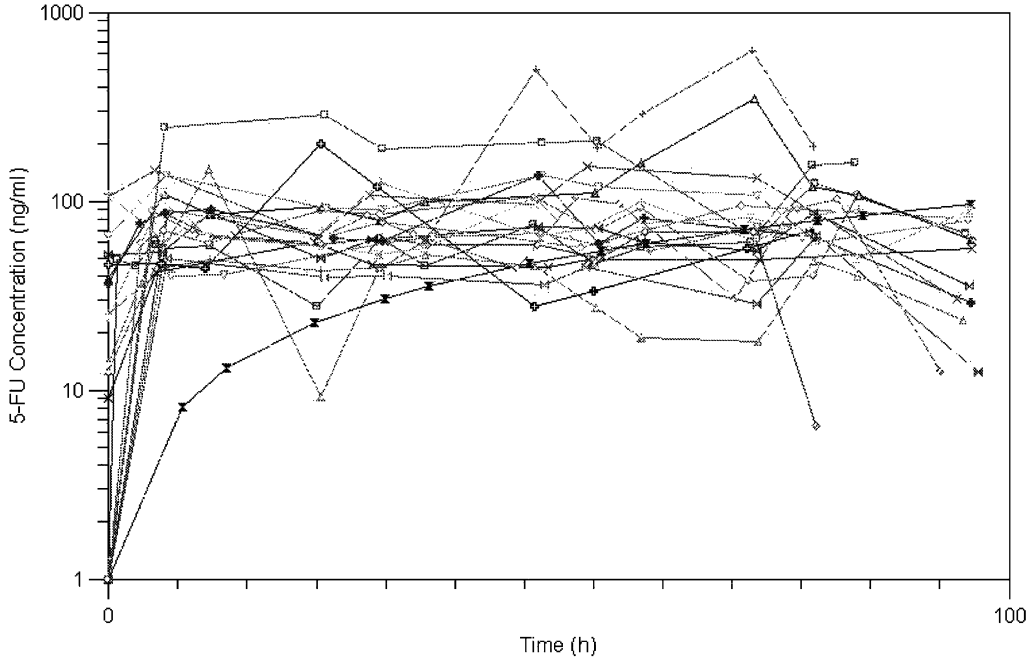

Fig. 1. 5-FU plasma concentrations in 20 courses/13 patients at all OHP doses.

Table 2
OHP (dose 30 mg/m^2/day) PK parameters in total and UF plasma

OHP	Pt in total plasma			Pt in UF plasma		
	1st Course Median	6th Course Median	P [a]	1st Course Median	6th Course Median	P [a]
C_{min} (ng/ml)	0	319	<0.05	0	0	
C_{max} (ng/ml)	961.7	1881.0	<0.05	137.8	166.6	<0.05
AUC_{tot} (mg h/l)	185.01	379.22	<0.05	866.91	19.50	<0.05
K_e (l/h)	0.0061	0.0061	n.s.	0.018	0.009	<0.05
$t_{1/2}$ (h)	145.9	168.9	n.s.	38.3	73.8	<0.05
MRT (h)	219.4	235.5	n.s.	72.3	125.5	n.s.
Cl_{tot} (l/h)	1.04	0.59	<0.05	25.8	10.3	<0.05
V_z (l)	243.9	95.6	<0.05	1601.6	1270.9	<0.05

n.s., Statistically not significant.
[a] Mann–Whitney test.

1 to 6 was also evident for AUC_{tot}, as for trough level C_{min}. Median residual platinum concentration was equal to 378.3 and 319.35 ng/ml, when measured at the end of cycle 3 and 6, respectively. In plasma UF, OHP levels were 10–15 times lower; a progressive drug accumulation was clear again, shown by the C_{max} and AUC_{tot} values. A marked difference between total plasma and UF platinum levels occurred during elimination phase. In total plasma, from cycle 1 to cycle 6, the progressive increase of C_{max} and AUC_{tot} was accompanied by the parallel decrease of clearance (Cl_{tot}) (from 1 to 0.6 l/h), probably related to the marked reduction of V_z (from 244 to 95 l). The elimination constant (K_e) remained constant throughout. Cl_{tot} also decreased in plasma OHP-UF (from 25.8 to 10.3 l/h): this could be due to a change in K_e (from 0.02 to 0.009/h) or $t_{1/2}$ (from 38 to 74 h). A general overview of main OHP PK parameters at two different doses (25 and 30 mg/m^2/day) is reported in Table 3, Pt accumulation trend (OHP dose 30 mg/m^2/day) is reported in Table 4.

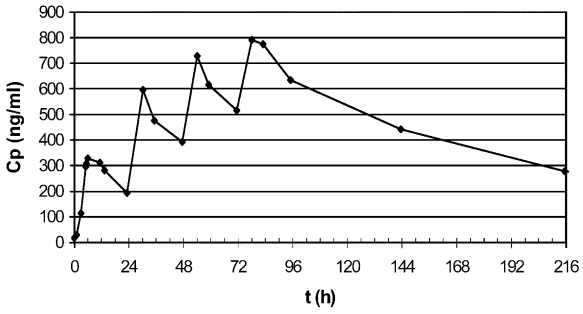

Fig. 3. A representative plasmatic curve of a 1st cycle of 30 mg/m^2/day chronomodulated OHP.

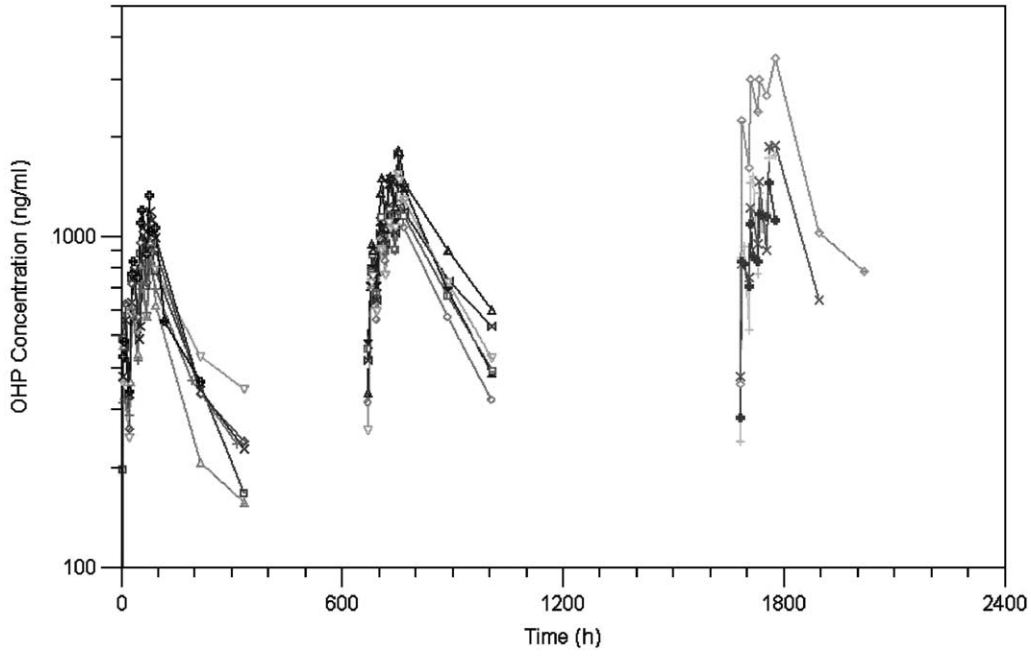

Fig. 2. OHP plasma concentrations in 17 courses/8 patients (OHP dose: 30 mg/m^2/day): Pt progressive accumulation during cycles 1-3-6.

Table 3
Total plasma OHP PK parameters (median values) in 18 courses/11 patients

OHP	OHP 25 mg/m^2/day 9 courses/3 patients	OHP 30 mg/m^2/day 9 courses/8 patients
Dose/4 days (mg)	188	209
C_{min} (ng/ml)	198.3	327.8
C_{max} (ng/ml)	1074.4	1509
AUC_{tot} (mg h/l)	252.26	361.73
K_e (l/h)	0.005	0.005
$t_{1/2}$ (h)	147.2	145.4
MRT (h)	220.2	221.3
Cl_{tot} (l/h)	0.492	0.648
V_z (l)	109.4	151.6

3.3. Preliminary toxicity and clinical data

Preliminary data showed a threshold neurotoxicity at total plasma Pt Cp > 1500 ng/ml and UF plasma Pt Cp > 150 ng/ml, corresponding to C_{max} values in cycle 3 at 30 mg/m^2/day dose and in cycle 1 at 35 mg/m^2/day dose. The higher toxicity at 35 mg/m^2/day is probably due to faster rise in OHP plasma levels. Two patients began treatment at 35 mg/m^2/day of OHP: both suffered grade 3 neurological toxicity with severe asthenia, depression and weight loss. Chemotherapy was stopped and OHP dose reduced to 30 mg/m^2/day; this dose constitutes OHP maximum tolerated dose in our study [13].

All 13 patients were evaluable for clinical response. A partial response (PR) was achieved in seven patients (53.8%), stable disease (SD) was recognized in four patients (30.8%) and progressive disease (PD) occurred in two patients (15.4%). Median time to progression disease (TTP) was 7 months and overall survival (OS) 9.6 months. Among PR, in two cases hepatic metastases were reduced in their dimension by chemotherapy, becoming operable: these patients are now in complete response (CR).

4. Discussion

In this paper, OHP and 5-FU PK parameters and toxicity are studied, when administered in an original protocol to patients affected by advanced CRC. The rationale of this pilot study was to assess whether: (1) OHP chronomodulated iv infusion associated to 5-FU 14-day continuous iv infusion, without the biochemical modulator FA, may cause severe toxicity and (2) OHP and 5-FU PK parameters may be altered.

Table 4
Accumulation trend in total plasma Pt (AUC median values, OHP dose 30 mg/m^2/day)

OHP 30 mg/m^2/day	Cycle 1	Cycle 3	Cycle 6
$AUC_{(0-24)}$ (ng h/ml)	8347.68	11 754.75	17 468.65
$AUC_{(24-48)}$ (ng h/ml)	11 607.9	13 141.8	23 300.45
$AUC_{(48-72)}$ (ng h/ml)	13 398.9	11 791.75	32 821
$AUC_{(72-96)}$ (ng h/ml)	18 015.7	29 804.8	36 065.85

5-FU steady state plasma concentrations, analyzed in 20 courses/13 patients during the first 96 h of each cycle, were fairly constant, as shown by the relatively low inter-subject variability (CV 24%). These values are below those reported in other studies [14] and are closely related to the lack of typical 5-FU toxicity produced by our clinical protocol (hand–foot syndrome, stomatitis and anemia). Moreover, the low-dose prolonged infusion of 5-FU produces C_{av} levels (median 66.3 ng/ml, at OHP 30 mg/m^2/day) below the minimal toxic value (> 80 ng/ml) [15]. Among all the analyzed courses, there were no anomalous C_{ss} values, probably due to the absence of any dehydropyrimidine dehydrogenase deficient patient [3]. Median values of C_{max}, C_{min} and $AUC_{(0-72)}$ were similar to those reported in the literature [15,16]. Consequently, the association with chronomodulated OHP did not influence the PK parameters of 5-FU. OHP PK analyses were more complex, as no PK studies have been previously devoted to chronomodulated administration. At first, we had to determine chronomodulated OHP daily C_{max} during infusion length (12 h), corresponding to maximum daily activity of glutation-oxidoreductase (usually at mid-cycle). We observed a daily C_{max} 7 h after the start of OHP administration, corresponding to the theoretical values found in a simulated OHP chronomodulated study [17]. Secondly, we determined the progressive accumulation of plasma OHP from day 1 to day 4 of each cycle, which doubled OHP levels in total plasma from cycle 1 to 6, increasing AUC_{tot} and C_{min}. A parallel decrease of clearance, mostly related to V_z decrease, was also reported. OHP undergoes rapid non-enzymatic biotransformation, forming a variety of reactive platinum intermediates, which bind rapidly and extensively to plasma protein and erythrocytes [4,5]. This leads to the progressive increase of plasma-bound drug, on one hand, and to a reduced distribution volume of OHP in total plasma, on the other hand. The literature reports that, after OHP flat infusion, the extent of protein-bound platinum increases too [4]. On the other hand, C_{max} and AUC_{tot} of UF OHP also increased over time, although their Cp values were 10–15 times lower and free drug was below the limit of detection near the end of the cycle. By contrast, in the plasma UF, Cl_{tot} decrease could be more closely related to K_e or $t_{1/2}$ than to the distribution volume. These results may be rationalised by taking into account the elimination pattern of OHP and its reactive derivatives [18,19]. The short initial half life of OHP in plasma UF is linked to the rapid clearance of intact OHP and its related

dichloro-, monochloro- and diaquo-DACH platinum intermediates from the tissues, and removal from the systematic circulation via glomerular filtration [5,18]. The renal elimination of OHP and related metabolites may account for the progressive decrease of K_e, related to some saturable kinetic processes. Tissues distribution is also an important clearance mechanism: in fact, OHP antitumor and toxic properties are thought to reside in platinum species present in the UF plasma fraction.

In conclusion, preliminary results produced by 5-FU continuous 14-day iv infusion plus OHP chronomodulated 12-h iv infusion are very encouraging, since the omission of FA did not decrease the synergism [20] between 5-FU and OHP, without affecting clinical efficacy and toxicity. Moreover, the two drugs do not alter their PK parameters when used in combination. It may be interesting in future preclinical studies to assess whether chronomodulated OHP, by blocking methionine cellular uptake, could stimulate intracellular TS-complex formation, thus enhancing 5-FU activity.

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References

[1] C.G. Moertel, Chemotherapy of colorectal cancer, New England Journal of Medicine 330 (1994) 1134–1142.
[2] M. Poon, M. O'Connel, C.G. Moertel, H.S. Wieand, S.A. Cullinan, L.K. Everson, J.E. Krook, J.A. Mailliard, J.A. Laurie, L.K. Tschetter, Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma, Journal of Clinical Oncology 7 (1989) 1407–1417.
[3] J. Lokich, J. Ahlgren, J. Gullo, S.S. Lokich, J.D. Ahlgren, J.J. Gullo, J.A. Philips, J.G. Fryer, Prospective randomized comparison of continuous infusion fluorouracil with conventional bolus schedule in metastatic colorectal carcinoma: A Mid-Atlantic Oncology Program study, Journal of Clinical Oncology 7 (1989) 425–432.
[4] C.R. Culy, D. Clemett, L.R. Wiseman, Oxaliplatin. A review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies, Drugs 60 (2000) 895–924.
[5] E. Raymond, C. Buquet-Fagot, S. Djelloul, J. Mester, E. Cvitkovic, P. Allain, C. Louvet, C. Gespach, Antitumor activity of oxaliplatin in combination with 5-fluorouracil and the thymidylate synthase inhibitor AG337 in human colon, breast, and ovarian cancers, Anticancer Drugs 8 (1997) 876–885.
[6] E. Cvitkovic, M. Bekradda, Oxaliplatin: a new therapeutic option in colorectal cancer, Seminars in Oncology 26 (1999) 647–662.
[7] F. Levi, Chronopharmacology of anticancer agents, in: P.H. Redfern, B. Lemmer (Eds.), Handbook of Experimental Pharmacology: Physiology and Pharmacology of Biological Rhythms—Cancerchemotherapy, Springer, Berlin, 1997, pp. 299–331.
[8] F. Levi, R. Zidani, J.L. Misset, Randomised multicenter trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. International Organization for Cancer Chronotherapy, Lancet 350 (1997) 681–686.
[9] T. Shirasaka, Y. Shimamoto, H. Ohshimo, H. Saito, M. Fukushima, Metabolic basis of the synergistic antitumor activities of 5-fluorouracil and cisplatin in rodent tumor models in vivo, Cancer Chemotherapy and Pharmacology 32 (1993) 167–172.
[10] O. Heudi, S. Mercier-Jobard, A. Cailleux, P. Allain, Mechanism of reaction of L-methionine with carboplatin and oxaliplatin in different media: a comparison with cisplatin, Biopharmaceutics and Drug Disposition 20 (1999) 107–116.
[11] L.J.C. van Warmerdam, O. van Tellingen, R.A.A. Maes, J.H. Beijnen, Validated method for determination of carboplatin in biological fluids by Zeeman atomic absorption spectrometry, Fresenius Journal of Analytical Chemistry 351 (1995) 777–781.
[12] E. Gamelin, M. Boisdron-Celle, A. Turcant, F. Larra, P. Allain, J. Robert, Rapid and sensitive high-performance liquid chromatographic analysis of halogenopyrimidines in plasma, Journal of Chromatography B, Biomedical Sciences and Applications 695 (1997) 409–416.
[13] J. Grem, 5-Fluoropyrimidines, in: B.A. Chabner, D.L. Longo (Eds.), Cancer Chemotherapy and Biotherapy, second ed., Lippincott–Raven, Philadelphia, 1996, pp. 149–211.
[14] F. Levi, J.L. Misset, S. Brienza, R. Adam, G. Metzger, M. Itzakhi, J.P. Caussanel, F. Kunstlinger, S. Lecouturier, A. Descorps-Declere, C. Jasmin, H. Bismuth, A. Reinberg, A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid, and oxaliplatin using an ambulatory multichannel programmable pump, Cancer 69 (1992) 893–900.
[15] T. Yoshida, E. Araki, M. Iigo, T. Fujii, M. Yoshino, Y. Shimada, D. Saito, H. Tajiri, H. Yamaguchi, S. Yoshida, M. Yoshino, H. Ohkura, M. Yoshimori, N. Okazaki, Clinical significance of monitoring serum levels of 5-fluorouracil by continuous infusion in patients with advanced colon cancer, Cancer Chemotherapy and Pharmacology 26 (1990) 352–354.
[16] F.A. Levi, R. Zidani, J.M. Vannetzel, B. Perpoint, C. Focan, R. Faggiuolo, P. Chollet, C. Garufi, M. Itzhaki, L. Dogliotti, S. Iacobelli, R. Adam, F. Kunstlinger, J. Gastiaburu, H. Bismuth, C. Jasmin, J.L. Misset, Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial, Journal of the National Cancer Institute 86 (1994) 1608–1617.
[17] W. Kern, J. Braess, B. Bottger, C.C. Kaufmann, W. Hiddemann, E. Scheyler, Oxaliplatin pharmacokinetics during a four-hour infusion, Clinical Cancer Research 5 (1999) 761–765.
[18] E. Gamelin, A. Le Bouil, M. Boisdron-Celle, A. Turcant, R. Delva, A. Cailleux, A. Krikorian, S. Brienza, E. Cvitkovic, J. Robert, F. Larra, P. Allain, Cumulative pharmacokinetic study of oxaliplatin, administered every three weeks, combined with 5-fluorouracil in colorectal cancer patients, Clinical Cancer Research 3 (1997) 891–899.
[19] M.A. Graham, G.F. Lockwood, D. Greenslade, S. Brienza, M. Bayssas, E. Gamelin, Clinical pharmacokinetics of oxaliplatin: a critical review, Clinical Cancer Research 6 (2000) 1205–1218.
[20] J.L. Fishel, M.C. Etienne, P. Formento, G. Milano, Search for the optimal schedule for the oxaliplatin/5-fluorouracil association modulated or not by folinic acid: preclinical data, Clinical Cancer Research 4 (1998) 2529–2535.