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ORIGINAL ARTICLE

Oxaliplatin in patients with metastatic colorectal cancer: efficacy and pharmacokinetics parameters

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Summary

Purpose: *The aim of this study was to investigate the efficiency of the FOLFOX-4 regimen and to evaluate the pharmacokinetics of oxaliplatin in untreated patients with metastatic colorectal cancer.*

Methods: *43 patients were enrolled in the study. Patients received oxaliplatin 85 mg/m^2 as 2-h i.v. infusion, on day 1, and bolus 5-fluorouracil (5FU) 400 mg/m^2 plus leucovorin (LV) 200 mg/m^2 followed by 5FU 600 mg/m2 as 22-h infusion on day 1 and 2, every 2 weeks. The pharmacokinetics of oxaliplatin evaluated in 4 patients was performed in blood, plasma and ultrafiltered plasma (UFT) by Inductively Coupled Plasma Mass Spectrometry (ICP-MS).*

Results: *The overall response rate and the median time to progression (TTP) were 53.49% and 7.1 months, respectively. Grade 3-4 toxic effects were observed in 11 (25.5%) patients. Grade 3 neuropathy was observed in 13.95% of the cases. In univariate analysis only Eastern Cooperative Oncology Group (ECOG) performance status (PS) was correlated with response. No correlation was found between grade 3-4 adverse events and the patient characteristics. The area under the time-concentration curve (AUC) in UFT was 4.8±0.72 standard deviation (SD) μg·h/ml and the total clearance 30.17±7.75 l/min. The values for volume of distribution and the maximum concentration were 567±20 liters and 0.38±0.17 ug/ml, respectively.*

Conclusion: *FOLFOX-4 was an effective regimen with good tolerability in previously untreated metastatic colorectal cancer patients. The pharmacokinetics of oxaliplatin was triphasic with a short initial distribution phase and a long terminal elimination phase.*

Key words: chemotherapy, colorectal cancer, oxaliplatin, pharmacokinetics

Introduction

Colorectal cancer represents a major public health problem, being the second cause of death from malignancies in the world [1]. Over the last decades, 5FU has been the mainstay for colorectal cancer chemotherapy [2,3]. Addition of oxaliplatin or irinotecan to 5FU/LV therapy significantly increased response rates and TTP compared with FU/LV alone in the first-line treatment of colorectal cancer [4]. Oxaliplatin is a third-generation platinum analog in which 1,2-diaminocyclohexane (DACH) substitutes the amine groups of cisplatin. It is distinguished from the two older platinum derivatives, cis and carboplatin, by its different spectrum of activity and toxicity. Oxaliplatin is the only platinum derivative to have activity in colon cancer. The main toxicity of oxaliplatin is neurotoxicity [5].

However, the clinical efficacy and toxicity for the individual patient are still largely unpredictable, and depend on a diversity of factors including inherited and acquired drug resistance of tumor tissue or the host. Oxaliplatin undergoes biotransformation into aquated

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forms in the blood, where 3 species can be found: total platinum, unbound or "free" platinum that represents the active form with antitumor activity, and erythrocyte platinum [6].

This article summarizes the benefits and side effects of oxaliplatin in chemotherapy-naive patients with colon cancer. A pharmacokinetic study of oxaliplatin during a constant-rate infusion was performed by analyzing the platinum [Pt+] concentrations in plasma, UFT and whole blood using ICP-MS.

Methods

Clinical study

Patient population

A retrospective database was established for 61 patients with metastatic colorectal cancer who were administered FOLFOX-4 first-line chemotherapy. Only 43 patients were finally eligible for this study. The diagnosis was confirmed by both histological and imaging examinations. All of the patients had at least one measurable lesion. Pleural effusion, ascites, bone lesions, or previously irradiated lesions were not accepted as measurable disease. Other exclusion criteria included prior therapy with oxaliplatin, history of previous malignancy in the previous 5 years, clinically significant heart disease, radiotherapy or surgery within 4 weeks before treatment, severe renal function impairment, abnormal hematological or liver function. Pregnant or lactating women were excluded from the study.

Ethics

Prior to therapy all patients gave written informed consent to participate in the study after having been informed about the purpose of this evaluation.

Treatment plan

Each cycle comprised a 2-h infusion of 200 mg/m^2 LV followed by bolus 5FU 400 mg/m^2 and then a 22-h infusion of 600 mg/m^2 5FU given on 2 consecutive days, every 14 days, plus a 2-h infusion of 85 mg/m^2 oxaliplatin (Eloxatin®, Sanofi-Synthelabo) on day 1 (FOLFOX-4). Side effects were registered after each cycle and image evaluation every 3-4 cycles. The oxaliplatin dose was reduced by 25% in the event of grade 3 or 4 thrombocytopenia, grade 4 neutropenia, or any other severe organ toxicity, and for paresthesias with pain or functional impairment, or paresthesias with pain persisting between cycles. If paresthesias with functional impairment persisted between cycles, oxaliplatin was discontinued.

Study assessments

The primary endpoint was to determine the activity of FOLFOX-4 in an intent-to-treat population. Secondary endpoints were safety profile, response rate and TTP.

Clinical response was determined according to Response Evaluation Criteria in Solid Tumors [7] by radiological imaging at baseline, every 3 cycles thereafter and every 3 months until tumor progression. The response was graded as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). TTP was defined as the interval between the first chemotherapy cycle and the first sign of PD or death. For toxicity evaluation, the National Cancer Institute Common Toxicity Criteria (NCI-CTC) were used. For the assessment of neurotoxicity of oxaliplatin, we used the special criteria established by Levi et al. [8].

Statistical methods

Univariate analysis was used to evaluate the rate of objective response or grade 3/4 adverse events depending on age, gender, ECOG PS, primary tumor localization (rectum or colon) or the site of metastasis. Statistical level of significance was chosen at 5%, whereas the confidence interval was evaluated at 95%. Survival curves were generated by Kaplan-Meier method and differences between them were evaluated by log-rank test. Differences in percentages were evaluated by chi-square method and Student's t-test.

Pharmacokinetics study

Blood sampling

The pharmacokinetics of oxaliplatin was performed in 4 patients. During the oxaliplatin infusion blood samples were collected into NH4-heparinized tubes every 30 min for 2 h, and every hour until up to 4 h after the end of infusion and at 3 time-points after the end of infusion (12, 15, 24 h).

The blood samples were immediately centrifuged to separate plasma and red blood cells (RBC). An aliquot of the plasma was stored for total platinum assay and the remainder was ultrafiltered using Amicon ultrafiltration filters (Milipore, MA, USA) at 3000 rpm for 30 min. The ultrafiltered and total plasma samples were immediately stored at –20° C for a maximum of 2 weeks.

Determination of platinum levels

The pharmacokinetics of oxaliplatin during a constant rate infusion was performed by analysing the [Pt+] concentration in plasma, UFT, and whole blood by ICP-MS using a quadrupole mass spectrometer (Perkin Elmer SCIEX, Elan DRC II, Toronto, Canada). Liquid samples were introduced into the mass spectrometer using the Meinhard nebulizer with default cyclonic chamber. Skimmer and samples cones were made of nickel to avoid any contamination that could be generated by the default platinum cones set. Samples were diluted 10 times. Ultrapure water used was prepared using an Milli-Q system and all the other reagents used were purchased from Merck (Darmstadt, Germany). Only ultrapure level or ICP-MS quality reagents were used. All readings were done in detector's pulse mode for enhanced precision. Direct determination of Pt was performed using an usual quantitative method.

Pharmacokinetic evaluation

The plasma concentration-time data following oxaliplatin administration were analyzed by a noncompartmental method using the computer software Winnonlin, Pharsight, USA. The peak plasma concentration (C_{max}) and the time to reach the peak concentration (T_{max}) were obtained directly from the experimental observation. AUC from time 0 to T (AUC_{0-T}), where T is the time of the last measurable concentration, was calculated by the trapezoidal method.

Results

Clinical study

Patients

The group of patients comprised 23 (53%) females and 20 (47%) males, aged from 26 to 73 years (median 53.1). Patients had ECOG PS 0-1, with life expectancy of at least 3 months. There were 32 colon and 11 rectal cancer cases. Baseline patient and tumor characteristics are summarized in Table 1.

Chemotherapy

A total of 200 chemotherapy cycles were administered, with a median of 6 per patient (range 2-7). Six (14%) patients received less than 3 cycles of FOLFOX-4, due to disease progression.

Table 1. Patient and tumor characteristics

Characteristics	*Patients, n (%)*
Gender	
Male	20 (46.51)
Female	23 (53.49)
Age (years)	
30-45	6 (13.96)
46-55	18 (41.86)
56-65	13 (30.23)
66	5 (11.63)
ECOG PS	
0	18 (41.86)
1	25 (58.14)
Primary site	
Rectum	11 (25.58)
Colon	32 (74.41)
Prior chemotherapy	
Adjuvant*	24 (55.81)
Untreated	19 (44.18)
Metastatic site	
Liver	24 (55.81)
Peritoneal	8 (18.60)
Lung	5 (11.62)
Lymph nodes	2 (4.65)
Osseous	1 (2.32)
Multiple sites	12 (27.92)

*FUFOL regimen

Efficacy

The response rate was 53.49% including CR 6.98% (3/43), PR 37.21% (16/43) and SD 9.3% (4/43) (Table 2). In univariate analysis only ECOG PS was correlated with response rate (Table 3). The median TTP for all the patients was 7.1 months (95% CI 3.9-7.8; Figure 1).

Six patients underwent resection of their metastases after chemotherapy (2 with liver metastasis, 2 with pulmonary metastasis and 2 with peritoneal carcinomatosis) with improvement in TTP compared to those without metastasectomy. TTP between operated (12 months) and non operated patients (6 months) was significantly different ($p < 0.001$).

Safety

Treatment was well tolerated. The majority of treatment-related adverse events were mild to moder-

Table 2. Objective response to treatment

Response	*Patients, n (%)*	*95% CI*
CR	3 (6.98)	0.00-14.59
PR	16 (37.21)	22.76-51.66
SD	4 (9.30)	0.62-17.99
PD	20 (46.51)	31.60-61.42
Total	43 (100)	

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, 95% CI: 95% confidence interval

Table 3. Univariate analysis of objective response in relation to clinical and tumor parameters

Parameters	*Objective response*		*p-value*
	CR, PR, SD *n (%)*	*PD* *n (%)*	
Age (years)			0.56
<50	7 (58.33)	5 (41.67)	
50-60	9 (45)	11 (55)	
60+	7 (63.64)	4 (36.36)	
Gender			0.67
Male	10 (50)	10 (50)	
Female	13 (56.52)	10 (43.48)	
Histological grade			0.58
G1	7 (70)	3 (30)	
G2	7 (53.85)	6 (46.15)	
G3	6 (50)	6 (50)	
mucinous	3 (37.5)	5 (62.5)	
Primary site			0.60
Ascites & transverse & descending	5 (41.67)	7 (58.33)	
Sigmoid & rectosigmoid	12 (60)	8 (40)	
Rectum	6 (54.55)	5 (45.45)	
Metastasis			0.82
Peritoneal carcinomatosis	5 (62.5)	3 (37.5)	
Hepatic	12 (50)	12 (50)	
Others	6 (54.55)	5 (45.45)	
ECOG PS			p<0.01
0	14 (77.78)	4 (22.22)	
1	9 (36)	16 (64)	

For abbreviations see footnote of Table 2

ate in intensity. Grade 3-4 toxicities were observed in 11 (25.5%) patients: neutropenia 2.33%, thrombocytopenia 2.33%, vomiting 2.33%, allergy 2.33%, elevation of liver transaminases 2.33%. Grade 3 neurotoxicity was seen in 13.95% of the patients (Table 4).

Univariate analysis did not detect any relationships between the appearance of grade 3-4 neurotoxicity and age, gender, ECOG PS, and metastatic localizations (Table 5).

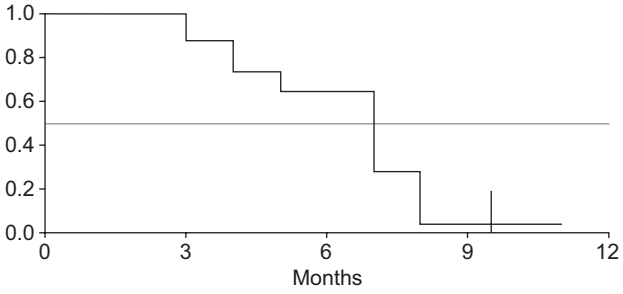

Figure 1. Progression free survival (Kaplan-Meier). The median progression free survival was 7.1 months.

Pharmacokinetic analysis of oxaliplatin

Patients

Pharmacokinetic analysis was performed in 4 patients during the first cycle of oxaliplatin. In 2 patients pharmacokinetic analysis was carried out during 2 consecutive cycles of chemotherapy. The characteristics of patients included in the pharmacokinetic study are shown in Table 6.

Results

The mean C_{max} value of total plasma platinum was 1.61 ± 0.21 μg/ml (range 1.38-1.85), whereas the mean C_{max} value in RBC was 1.89 ± 0.19 μg/ml (range 1.72-2.1). The mean C_{max} value of ultrafiltrable platinum, which represents the active form, was 0.38 ± 0.17 μg/ml (range 0.29-0.64). The mean AUC_{total} values were lower in UFT (4.8 ± 0.72 μg/ml-h) than in plasma (51.4 μg/ml-h ± 6.32) or in RBC (54.2 ± 3.27 μg/ml-h). $T_{1/2\ max}$ was 12.1 ± 3.47 h in UFT, 26.1 ± 7.60 h in plasma, and 23.5 ± 3.47 h in RBC.

Concerning the volume of distribution, platinum showed a high volume of distribution in UTF plasma (567 ±20 l) and the clearance of UFT platinum was also relatively high (30.17 ±7.75 l/min) compared with the clearance of platinum in plasma (2.77± 0.61 l/min) or in RBC (2.71± 0.84 l/min) (p=0.0051; p=0.0046).

The pharmacokinetic parameters are displayed in Figures 2-5.

The pharmacokinetics of platinum after oxali-

Table 4. Treatment toxicity

Variables	*G0* *n (%)*	*G1* *n (%)*	*G2* *n (%)*	*G3* *n (%)*	*Total* *n (%)*
Leukocytes	32 (74.42)	7 (16.28)	3 (6.98)	1 (2.33)	11 (25.6)
Hemoglobin	34 (79.07)	6 (13.95)	3 (6.98)	0	9 (20.93)
Platelets	35 (81.4)	6 (13.95)	1 (2.33)	1 (2.33)	8 (18.61)
Digestive	32 (74.42)	6 (13.95)	4 (9.3)	1 (2.33)	11 (25.6)
Hepatic	36 (83.72)	4 (9.3)	2 (4.65)	1 (2.33)	7 (16.28)
Allergies	39 (90.7)	2 (4.65)	1 (2.33)	1 (2.33)	4 (9.3)
Mucositis	40 (93.02)	2 (4.65)	1 (2.33)	0	3 (6.98)
Diarrhea	36 (83.72)	6 (13.95)	1 (2.33)	0	7 (16.28)
Neurotoxicity	17 (39.53)	11 (25.58)	9 (20.93)	6 (13.95)	26 (60.46)

Table 5. Univariate analysis of neurotoxicity

Variables	*Neurotoxicity*				
	G0 *n (%)*	*G1* *n (%)*	*G2* *n (%)*	*G3* *n (%)*	
Age (years)					p=0.96
<50	5 (41.67)	4 (33.33)	2 (16.67)	1 (8.33)	
50-60	7 (35)	5 (25)	5 (25)	3 (15)	
60+	5 (45.45)	2 (18.18)	2 (18.18)	2 (18.18)	
Gender					p=0.14
M	7 (35)	8 (40)	2 (10)	3 (15)	
F	10 (43.48)	3 (13.04)	7 (30.43)	3 (13.04)	
Metastatic localization					p=0.88
PC	3 (37.5)	3 (37.5)	1 (12.5)	1 (12.5)	
Liver	8 (33.33)	6 (25)	6 (25)	4 (16.67)	
Others	6 (54.55)	2 (18.18)	2 (18.18)	1 (9.09)	
ECOG PS					p=0.27
0	4 (22.22)	6 (33.33)	5 (27.78)	3 (16.67)	
1	13 (52)	5 (20)	4 (16)	3 (12)	
Total	17 (39.53)	11 (25.58)	9 (20.93)	6 (13.95)	

PC: peritoneal carcinomatosis, M: male, F: female

Table 6. Characteristics of patients included in the pharmacokinetic study

No.	*Age (years)*	*Gender*	*Weight (kg)*	*Height (cm)*	*Serum creatinine (mg/dl)*	*Dose (85 mg/m^2)*
1	56	Female	43	154	0.58	100 mg TD
2	58	Male	77	174	0.8	150 mg TD
3	45	Female	63	165	0.63	140 mg TD
4	57	Female	63	157	1.06	120 mg TD

TD: total dose

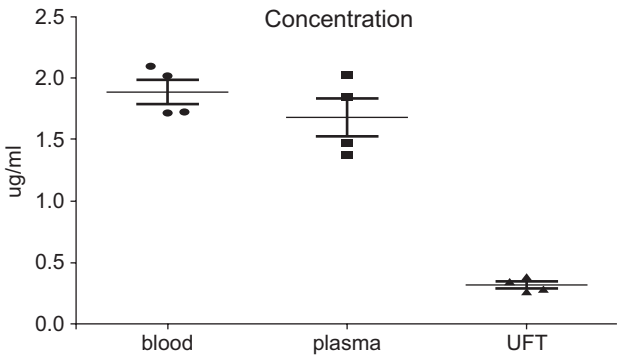

Figure 2. Treatment toxicities.

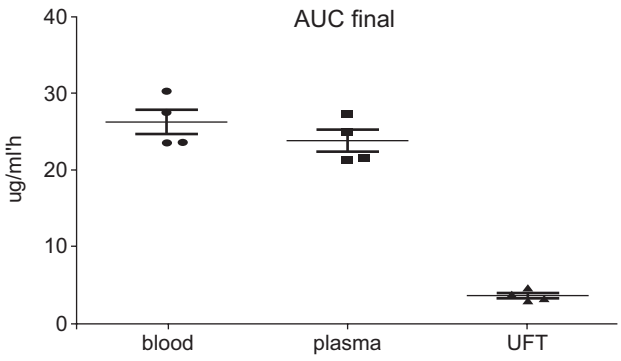

Figure 3. C_{max} of platinum in blood, plasma, UFT.

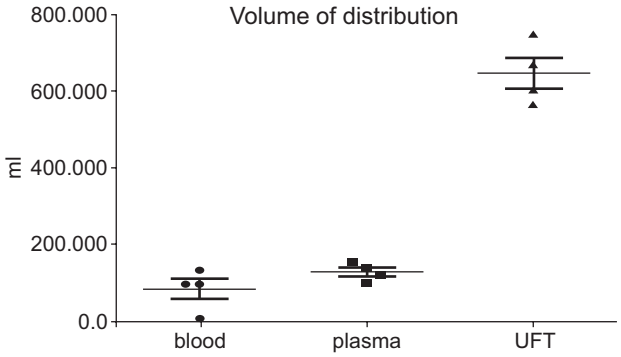

Figure 4. AUC final of platinum in blood, plasma, UFT.

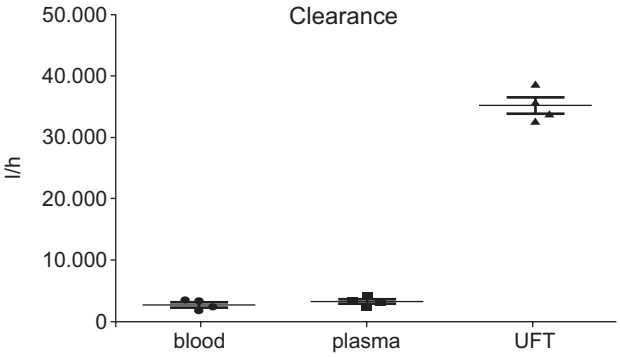

Figure 5. Volume of distribution of platinum in blood, plasma, UFT.

platin administration was triphasic, characterized by a short initial distribution phase and a long terminal elimination phase (Figure 6).

Discussion

Currently, metastatic colorectal cancer, a leading cause of cancer-related deaths worldwide, represents a serious health problem due to its growing incidence and high mortality rate [9]. In the past 40 years 5FU has been the mainstay in the chemotherapy of colorectal cancer with a response rates of 10-15% [2,3]. Addition of the biomodulator leucovorin has successfully increased the response rate to 23% but without improvement in survival [10]. Oxaliplatin is a third-generation platinum analog which, in combination with 5FU/LV, has improved the response rate and survival in advanced colorectal cancer [11-17].

The aim of our study was to evaluate the efficacy and safety of FOLFOX-4 in patients with metastatic colorectal cancer and also to determine the pharmacokinetics of oxaliplatin at a dose of 85 mg/m^2.

All 43 patients in our group received FOLFOX-4 as first-line chemotherapy. The response rate was of 53.49%. This result is congruent with other important studies, like the Intergroup N9741 trial [18] and V308

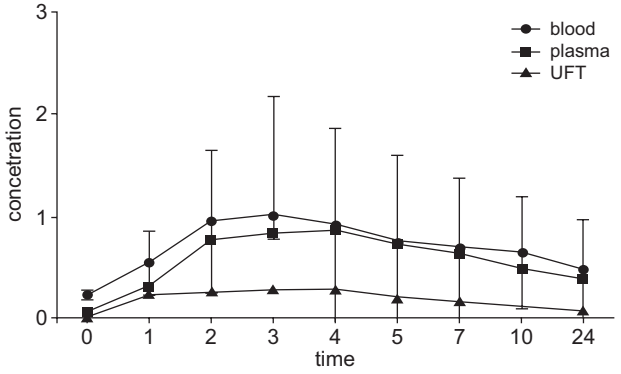

Figure 6. Clearance of platinum in blood, plasma and UFT.

[19] which showed that oxaliplatin, when combined with 5FU/LV, produced a response rate of 47-54% in first-line chemotherapy of advanced colorectal cancer patients. Concerning TTP, it was 7 months in our study, lower than in the above mentioned studies. Interestingly, 6 patients underwent metastasectomy after chemotherapy with improvement in TTP compared to those not undergoing metastasectomy ($p < 0.001$). In univariate analysis only ECOG PS was correlated with response.

FOLFOX-4 was generally well tolerated. The majority of treatment-related adverse events were mild to moderate in intensity. Grade 3-4 toxicities were observed in 11 (25.5%) patients. The main toxicity of oxaliplatin was dose-limiting peripheral neuropathy which can be aggravated by exposure to cold. The incidence of grade 3 peripheral neurotoxicity in our group was 13.95%, similar with others reports. Other grade 3-4 toxicities included neutropenia, thrombocytopenia and vomiting, whose incidence rates were also similar with other studies.

Pharmacokinetics studies of oxaliplatin at a dose of 85 mg/m^2 are poorly represented [6,20]. For a description of oxaliplatin pharmacokinetics it is important to separate bound and free platinum. UFT platinum which comprises non-protein bound drug and biotransformation products in plasma water represents the active form with antitumor and toxic properties.

In our study we found relatively small differences in AUC, volume of distribution, and clearance in comparison with the results reported by Kho et al. [21] and Graham et al. [22] (Table 7).

Concerning the C_{max}, the lower values obtained in our study could be secondary to the increase of infusion duration. Prolongation of the infusion from 2 to 4 h has been used in 2 patients due to acute allergic reaction. These results are in concordance with those obtained by Marty et al. who indicated that prolonging the infusion from 1 to 6 and 12 h decreased the mean C_{max} by 56 and 71% [23].

In summary, our results are congruent with others studies regarding the pharmacokinetics and safety and

Table 7. Main pharmacokinetic variable (mean ±SD) of UFT platinum across studies following 2-h infusion of oxaliplatin 85 mg/m^2

	Mean (±SD)	*Range*	*Graham [21] Patients=3*	*Kho et al [22] Patients=33*
C_{max} (mg/mL)	0.38 (0.17)	0.29-0.64	0.681 (0.077)	0.977 (0.224)
AUC_{024} (mg/mL/h)	4.8 (0.72)	4.14-5.51	4.25 (1.18)	6.86 (2.31)
Vss (liters)	567 (20)	284-750.1	295 (142)	514.7 (139.7)
Cl (liters/h)	30.17 (7.75)	18.6-35.6	18.5 (4.71)	25.2 (6.3)

SD: standard deviation, AUC: area under plasma concentration vs. time curve, C_{max}: maximum concentration, Vss: volume of distribution, Cl: clearance, UFT: ultrafiltered plasma

provide a scientific basis for effective use of oxaliplatin in the chemotherapy of colorectal cancer.

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