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Pharmacokinetics of oxaliplatin in patients with normal versus impaired renal function

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Abstract *Purpose*: The pharmacokinetics (PK) of platinum was investigated and compared in patients with normal (NRF) and impaired renal function (IRF), after they had received oxaliplatin at the recommended dose and delivery modality. *Methods*: Oxaliplatin was administered at 130 mg/m^2 as a 2-h infusion without hydration. Patients were recruited and classified according to their creatinine clearance (CrCl > or < 60 ml/min), calculated using the Cockcroft and Gault formula. Blood was taken for PK analysis during and after the infusion. Twenty-three patients were included in the PK analysis (13 NRF and 10 IRF). At inclusion, the median CrCls were 70.5 ml/min (range 63–136) for the NRF group and 42 ml/min (range 27–57) for the IRF group. Three patients underwent a second course of treatment and additional blood sampling for analysis. Platinum levels in the plasma, ultrafiltrate and red blood cells (RBCs) were measured using flameless atomic absorption spectrophotometry (FAAS). *Results*: Following the administration of oxaliplatin, platinum binding to plasma proteins and RBCs was rapid and extensive; at the end of the 2-h infusion, 27% of the platinum in the plasma remained free (40% bound to RBCs, 33% bound to plasma proteins). Neither the mean maximal concentration (C_{max}) of total platinum in the plasma, the mean C_{max} of ultrafilterable platinum in the plasma, nor the maximal platinum content in the RBCs differed significantly between the two groups (2.59 vs 2.58 μg/ml, 1.09 vs 1.28 μg/ml and 2.06 vs 2.17 μg/ml, respectively, for patients with NRF vs IRF). After the end of the infusion, levels of total and free (ultrafilterable) platinum in the plasma declined biexponentially. The plasma clearance of both total and free platinum as well as the area under the curve (AUC) of the free platinum fraction correlate with the calculated CrCl ($P = 9 \times 10^{-3}$, $P = 3.1 \times 10^{-5}$ and $P = 9 \times 10^{-6}$, respectively). After a single course of oxaliplatin, toxicities reported in the two groups of patients were similar. *Conclusions*: Our results are in agreement with the in vitro data concerning the extensive binding of oxaliplatin to plasma proteins and RBCs. They also reveal a strong negative correlation between free drug plasma availability and renal function, with a corresponding positive correlation between clearance of the plasmatic platinum and renal function. Thus, renal impairment entails a greater overall exposure to platinum in the plasma. However, this study failed to elicit any relationship between moderate renal impairment and the acute toxicity associated with oxaliplatin.

Key words Erythrocytes · Oxaliplatin · Pharmacokinetics · Plasma binding · Renal function

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Introduction

Oxaliplatin (trans-l-diaminocyclohexane oxalatoplatinum), is a third-generation platinum complex of the diaminocyclohexane (DACH) family, currently in use for the treatment of colorectal cancer. It was selected for clinical development more than a decade ago, based on its favourable activity/toxicity profile. In vitro, oxaliplatin showed cytotoxicity in L1210 cisplatin-resistant cell lines. It was demonstrated to be active against a wide

range of murine and human cell lines, with a higher cytotoxic potency in the majority of cell lines tested than the more commonly used cisplatin and carboplatin. Its toxicity profile was characterized during phase I trials as being markedly different from both of the other available organoplatin agents. No renal impairment was recorded, and its administration does not require hydration measures. Myelosuppression, mainly thrombopenia, was very infrequent and seldom severe, even at the maximum tolerated dose level (200 mg/m^2). The recommended dose of oxaliplatin elicited from the Phase I trials was fixed at 130 mg/m^2 every 3 weeks when administered as a 2- to 4-h infusion. Subsequently, an alternative schedule of 85 mg/m^2 every 2 weeks was established, which offers the same dose intensity. At the dose level of 130 mg/m^2 every 3 weeks, the incidences of grade 3–4 neutropenia and thrombopenia, as reported in a recent oxaliplatin single-agent phase II study, were 5.2% and 7.9% of cycles, respectively. Oxaliplatin is not ototoxic. The dose-limiting toxicity observed was neurologic, affecting the peripheral sensory system with a different clinical profile than that of cisplatin. The standard, moderately incapacitating symptoms associated with oxaliplatin are also cumulative and generally appear beyond a median total dose of 780 mg/m^2. They are consistently but slowly reversible over the course of a few months after discontinuation of treatment.

Phase II studies with single-agent oxaliplatin have focused mainly on colorectal and ovarian cancers, but significant activity has also been reported in non-Hodgkin's lymphomas and non-small-cell lung cancer. In colorectal cancer patients, oxaliplatin was shown to be active against both 5-fluorouracil (5-FU)-resistant and previously untreated patients; it also significantly enhanced the anti-tumoural efficacy of front-line 5-FU-based regimens and partially reversed clinical 5-FU resistance. In cisplatin-pretreated ovarian cancer, oxaliplatin induced a 26% response rate in potentially platinum-sensitive tumours (disease-free interval > 6 months) while it has exhibited limited but definite efficacy in cisplatin/carboplatin-refractory disease.

The reference agent, cisplatin, is known to cause renal toxicity and is excreted to a large degree in urine. Carboplatin, which is nephrotoxic only at high doses also has its major clearance from the body via the kidneys and its pharmacodynamics and dosing are determined according to the level of renal function. Oxaliplatin is also mostly excreted through the kidneys, as noted both during the preclinical pharmacodynamic studies and confirmed later in clinical studies. Since the pharmacokinetics (PK) and pharmacodynamics of cisplatin and carboplatin compounds are affected by renal function, it was considered appropriate to evaluate the PK of oxaliplatin in patients with impaired renal function, a condition fairly prevalent in old patients and those pretreated with nephrotoxic drugs, both common situations in oncology, especially in cases of advanced disease.

We report the PK study of the platinum species, as determined by flameless atomic absorption spectrophotometry (FAAS) after a single 2-h infusion of oxaliplatin in patients with normal renal function (NRF) and impaired renal function (IRF).

Patients and methods

Patients

Patients were required to have advanced-stage tumours, and to have received and failed at least one recommended chemotherapy regimen for their disease. Patients were also required to have a potentially platinum-sensitive tumour type, and not to have been administered any platinum compound (cisplatin, carboplatin) in the 4 months preceding the study. The protocol was approved by the local ethics committee (Centre Hospitalier Universitaire, Kremlin Bicêtre). Before inclusion, written informed consent was obtained from each patient. All patients were treated during a 2-day hospitalization. Patient selection was based on the determination of creatinine clearance (CrCl), calculated with the Cockcroft and Gault formula and taking into account age, sex, weight and serum creatinine levels. Patients were assigned to one of the two following groups according to their calculated CrCl: a normal renal function (NRF) group (CrCl > 60 ml/min) versus an impaired renal function (IRF) group (CrCl < 60 ml/min). The 60-ml/min CrCl value was selected as the lower limit for NRF because it is a standard value for dose adaptation in kidney-cleared drugs and was expected to provide a useful distribution of patients between the NRF and IRF groups.

Drug administration

All patients received oxaliplatin at the recommended dose (130 mg/m^2). The drug was supplied by Debiopharm SA (Lausanne, Switzerland). The oxaliplatin was diluted in 500 ml of a 5% glucose solution and administered as a 2-h infusion every 3 weeks, using a syringe infusion pump when possible. No pre- or post-treatment hydration was given. Prophylactic antiemetic treatment was systematically given (granisetron, 3 mg IV bolus before the oxaliplatin administration).

Sampling

For the PK studies, blood samples of 5 ml were taken in citrate tubes just before treatment (control), and at 30 min, 1 h, and 1 h 30 min after the start of infusion, at 2 h (end of infusion), 2 h 15 min, 2 h 30 min, 4 h, 5 h, 7 h, 15 h, 24 h, 36 h, 48 h, 63 h, 72 h, 120 h and 144 h; the last four points were obtained according to the availability of the individual patient. The last three patients received a second cycle of oxaliplatin. An additional blood sample was collected from these patients on day 22 (504 h), just before the drug infusion, after which the same PK protocol was performed as above. Blood samples were immediately placed on ice and centrifuged at 3000 *g* for 15 min at +4 °C; the plasma was divided into two aliquots: one was directly stocked for total platinum assay without any further preparation, the other was ultrafiltrated (2000 *g* for 30 min at +4 °C) using the MPS-1 system with a cut-off at 25,000 Da (Amicon, Denver, Colo., USA). Total plasma, plasma ultrafiltrate and red blood cells (RBCs) were stored at −80 °C until analysis.

Analytical procedures

All samples were thawed just before analysis. Thawed RBCs (0.5 ml) were first digested for 24 h at room temperature with 0.5 ml fuming nitric acid (33.3%). Six microlitres of each sample was mixed with 3 µl of tensioactive agent (Triton), and a final volume of 10 µl of each sample was introduced into the furnace.

Platinum concentrations were measured using FAAS with Deuterium correction, on a VARIAN 1475-GTA 95 analyser at 263.9 nm, following the methods described by Leroy. The limit of sensitivity was 10 ng/ml except in the case of RBCs, where it was 40 ng/ml. Reproducibility was always over 90%. The values of the platinum concentrations were calculated from a standard calibration curve prepared the same day using plasma and RBCs taken from healthy volunteers. A standard curve was established every ten samples to compensate for any variation in the FAAS furnace.

The data gathered allowed the determination of platinum concentrations in the biological fluids. Area under the curve (AUC), distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), clearance (CL) and volume of distribution (VD) were calculated using Microparm (INSERM) PK software after non-linear regression with Simplex and Gauss-Newton algorithms. Correlations were assessed using the Spearman's rank order test. The Mann-Whitney U test was used to compare PK parameters between the two groups of patients (NRF and IRF). Statistical analysis was performed using the Statistica 5.1 software program. Toxicity was evaluated after the first cycle using the WHO scale [29], except in the case of neuropathy, where a specific scale developed by Lévi et al., which takes into account both intensity and duration of symptoms, was used [16].

Results

A total of 24 patients with advanced solid tumours refractory to standard treatment (14 men and 10 women, aged 43–76 years) were enrolled in this PK study in two different French centres (Hôpital Paul Brousse, Villejuif, and Centre Val d'Aurelle, Montpellier). Twenty-seven cycles of oxaliplatin were administered, with three patients receiving a second course of treatment, and PK determinations were made at 3-week intervals. One patient with altered renal function (CrCl = 12 ml/min) was administered one cycle of oxaliplatin at a total dose of 130 mg (instead of the calculated dose of 250 mg); he was excluded from the final analysis. Twenty-three patients (26 cycles) were finally considered to be evaluable for the PK study analysis. Their characteristics are displayed in Table 1. Nine patients (three NRF, six IRF) had received prior treatment with cisplatin, only one of whom had received the treatment within the preceding 4 months. According to the Cockcroft and Gault formula, thirteen patients were calculated to have CrCl >60 ml/min (median 70, range 63–136 ml/min) and were placed in the NRF group. Ten patients had low CrCl (median 42, range 27–57 ml/min) and were included in the IRF group; in six cases, prior cisplatin treatment was at the origin of the renal function impairment; one patient had had a prior nephrectomy.

Platinum plasmatic pharmacokinetics

The platinum PK parameters (total platinum in plasma, ultrafilterable or free platinum in plasma, and platinum in RBCs) were determined and compared between these two patient groups.

Table 1 Characteristics of the patients. *NRF* normal renal function, *IRF* impaired renal function

Characteristics of the patients	NRF (n = 13)	IRF (n = 10)	Total (n = 23)
Median age (range)	62 (43–75)	58 (43–76)	62 (43–76)
Sex			
Male	7	6	13
Female	6	4	10
Diagnosis			
Colorectal	4	3	7
NHL	3	2	5
Ovary	–	2	2
Breast	1	–	1
Lung	1	–	1
Pancreas	1	1	2
Uterus	1	–	1
Mesothelioma	2	–	2
Corticosurrenaloma	–	1	1
Biliary tract	–	1	1
PS			
0–1	9	8	17
2–4	4	2	6
Previous CT lines			
0	3	0	3
1–2	9	8	17
>2	1	2	3
Patients receiving cisplatin prior to treatment	n = 3	n = 6	n = 9
Cumulative cisplatin dose (mg/m^2) median (range)	500 (30–1000)	600 (10–139)	600 (100–1390)
Etiology of IRF	n = 13	n = 10	n = 23
Patient characteristics			
Cisplatin		4	
Disease progression		1	
Cisplatin + disease progression		2	
Other	–	3	–
	(1 nephrectomy,	1 vancomycin,	1 unknown)
Calculated creatinine clearance (ml/min)	70 (63–136)	42 (27–57)	

The individual mean PK parameters for the total and free platinum in the NRF and IRF patients are displayed in Table 2. The representative mean plasma concentration-time profiles of these two platinum species are shown in Fig. 1 (NRF) and in Fig. 2 (IRF). Following the end of the infusion, plasma levels of total and free platinum declined biexponentially in both groups.

In NRF patients, the mean peak plasma levels of total platinum (C_{max} for P) and free platinum (C_{max} for U) obtained at the end of the 2-h oxaliplatin infusion were 2.59 μg/ml (range 1.78–3.15) and 1.09 μg/ml (range 0.65–2.14), respectively. Large interindividual variations were observed.

The PK of the free platinum in the plasma was characterized by a $t_{1/2\beta}$ of 25.2 h (range 10.2–109), while for the total form it was 37.5 h (range 24.3–51). The mean AUC for the free platinum in the NRF group was 5.21 mg/ml · h (range 3.1–20). The free platinum had a large volume of distribution (VD) with a mean of 338 l (range 164–632) while that of the total form was 70 l (47–102).

In IRF patients, parameter values varied more widely. C_{max} for P and C_{max} for U after the end of the 2-h oxaliplatin infusion were 2.58 μg/ml (range 2.11–3) and 1.28 μg/ml (range 0.82–2.31), respectively. These values did not differ significantly from those measured in the NRF group ($P = 0.69$ and 0.37, respectively). For this second group of patients, the free platinum exhibited a mean $t_{1/2\beta}$ of 23 h (range 5–49), while that of the total form was 49 h (range 21–78).

The free platinum AUC values varied almost as widely in the IRF patient group as in the NRF group (mean 9.15 μg/ml · h, range 4.45–17.4 μg/ml · h). However, when compared with the mean free-platinum AUC value obtained for the NRF group, this parameter was significantly higher in the IRF group ($P = 3 \times 10^{-3}$). Again, the free platinum had a large VD, with a mean of 280-l (range168–696), while that of the total form was 60 l (range 42–80). Neither the mean VD of the total nor

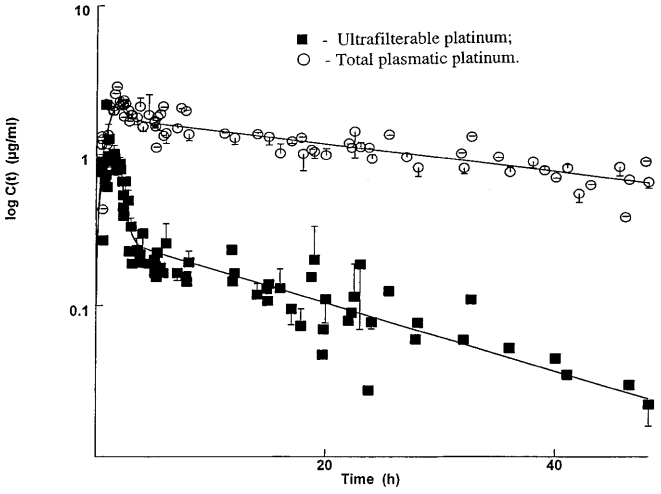

Fig. 1 Mean concentration curves of plasmatic total and ultrafilterable platinum in patients with normal renal function

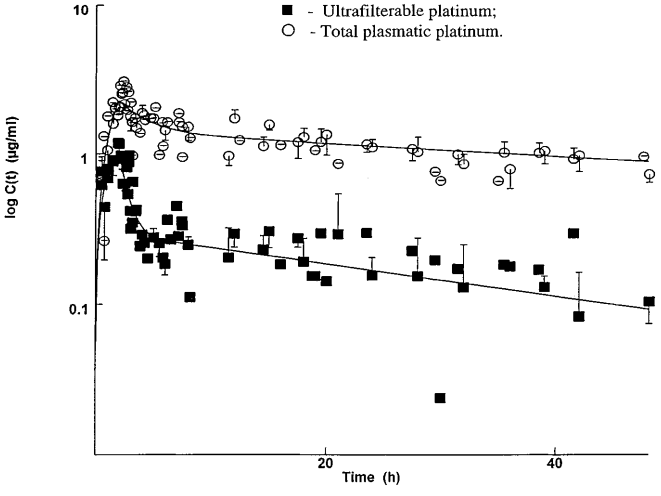

Fig. 2 Mean concentration curves of plasmatic total and ultrafilterable platinum in patients with impaired renal function

Table 2 Comparison of pharmacokinetic parameters in NRF and IRF patients. *NRF* normal renal function, *IRF* impaired renal function, *CrCl* creatinine clearance, *AUC* area under the curve, C_{max}, *VD* volume of distribution, $t_{1/2\alpha}$ distribution half-life, $t_{1/2\beta}$

PK parameters		NRF Mean (± SD)	RF Mean (± SD)	*P* value
CrCl		78.00 (19.63)	42.20 (10.63)	6×10^{-5}
Total dose oxaliplatin		237.69 (16.65)	218.50 (21.71)	0.038
Total platinum in plasma	C_{max} (μg/ml)	2.59 (0.37)	2.58 (0.32)	0.69
	AUC (μg/ml · h)	49.02 (8.95)	64.40 (29.64)	0.15
	CL (l/h)	2.51 (0.54)	1.94 (0.66)	0.07
	$t_{1/2\alpha}$ (h)	0.45 (0.34)	0.66 (0.88)	0.83
	$t_{1/2\beta}$ (h)	37.52 (8.24)	49.22 (18.62)	0.09
	VD (l)	69.72 (17.06)	60.12 (11.27)	0.17
Free platinum in plasma (ultrafilterable)	C_{max} (μg/ml)	1.09 (0.37)	1.28 (0.55)	0.35
	AUC (μg/ml · h)	5.21 (2.12)	9.16 (4.28)	4×10^{-3}
	CL (l/h)	25.70 (8.53)	14.23 (6.04)	5×10^{-3}
	$t_{1/2\alpha}$ (h)	0.42 (0.23)	0.61 (0.78)	0.46
	$t_{1/2\beta}$ (h)	25.18 (26.54)	23.23 (13.81)	0.69
	VD (l)	338.38 (155.49)	279.56 (168.57)	0.77
C_{max} ratio	Total/free	2.59 (0.73)	2.20 (0.71)	0.29
RBC	C_{max} (μg/ml)	2.06 (0.66)	2.17 (0.60)	0.62

that of the free platinum was found to differ statistically when compared with those determined for the NRF patients ($P = 0.17$ and $P = 0.32$, respectively).

Erythrocytic platinum pharmacokinetics

RBCs from ten NRF and ten IRF patients were stored for platinum level measurement. The peak platinum content in RBCs (C_{max} for RBCs) was measured between hour 2 and hour 7 [median time to peak serum concentration (tmax) 3 h] and the mean value was found to be 2.05 μg/ml (NRF) and 2.17 μg/ml (IRF). After this, platinum concentrations in RBCs declined monoexponentially with a long $t_{1/2\beta}$ (230 h); the time profile curve of the mean platinum levels measured in RBCs is presented in Fig. 3. At the end of the oxaliplatin infusion (data not shown), the ratio between platinum levels in the plasma and RBC compartments was 1.55 (NRF) and 1.42 (IRF), showing that approximately half of the blood platinum was bound to RBCs.

Platinum accumulation

For three patients (one NRF, two IRF), sampling was performed again before and after a second oxaliplatin administration; their initial calculated CrCls were 66, 49 ml/min and 38 ml/min, respectively. Residual platinum levels were measured on day 22, just before the new oxaliplatin treatment. Total platinum concentrations in plasma were 0.12, 0.26 mg/ml and 0.18 mg/ml, respectively, representing about one tenth of the total platinum peak value measured on day 1. PK data obtained during the two courses of oxaliplatin were compared for each patient. We observed that the AUC (0–48 h) values of the free platinum measured at cycle 1 and 2 did not differ significantly.

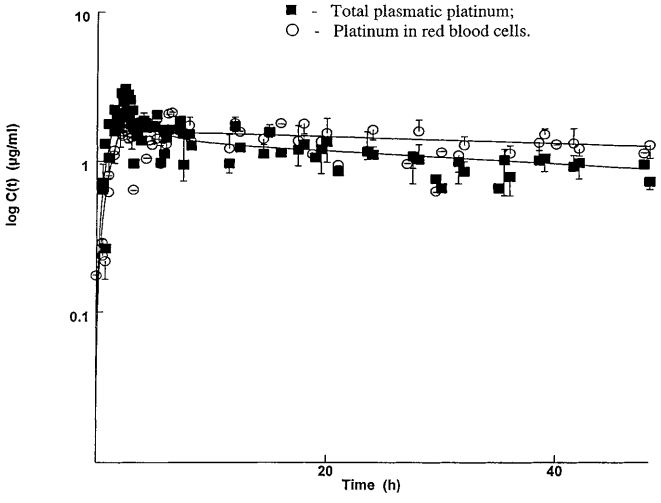

Fig. 3 Mean concentration curves of total plasmatic platinum and red-blood-cell platinum

Table 3 Toxicities in first cycle (WHO scale). *NRF* normal renal function, *IRF* impaired renal function

	NRF patients (n = 13)				IRF patients (n = 10)			
Grades (WHO)	1	2	3	4	1	2	3	4
Toxicities								
Nausea/vomiting	4	2	–	–	–	3	1	–
Diarrhoea	2	–	–	–	5	–	–	–
Haematological	0	1	–	–	3	–	–	–
Neurological	7	1	–	–	7	–	–	–

Toxicity

All patients were evaluable for toxicity after they had received a single course of oxaliplatin. Toxicities were graded according to the WHO scale [29]. Tolerance was good. The haematological, neurological and digestive toxicities are presented in Table 3; no statistical difference in toxicity was found between the NRF and IRF groups. There was one case of asthenia, one of alopecia and two cases of constipation. The only unexpected event that occurred was a transient dyspnoea episode, which appeared at the end of infusion without consequences.

Discussion

In this study, we have defined and compared the PK parameters for the different platinum species of oxaliplatin in patients with NRF and IRF, following a single course of oxaliplatin. The clearance of free platinum in plasma decreased significantly in the IRF group ($P = 4 \times 10^{-3}$). The free platinum AUC in plasma was consistently and significantly higher in these patients ($P = 3 \times 10^{-3}$). More specifically, our results show that the clearance of both total and free platinum as well as the free platinum AUC correlated strongly with the calculated CrCl ($P = 9 \times 10^{-3}$, $P = 3.1 \times 10^{-5}$ and $P = 9 \times 10^{-6}$), while the total platinum AUC differences did not reach, but nevertheless closely approached statistical significance ($P = 0.06$). There were no differences in peak levels of total or free platinum between the two groups that were compared (Figures 4, 5 and 6).

The unbound platinum fraction is usually considered to be the active drug and free platinum levels measured in plasma have been reported to influence both the antitumour activity and the toxicity of the drug. In the case of carboplatin, a good correlation has been demonstrated between the percentage reduction in platelet count and the platinum AUC.

We have also confirmed that a major fraction of platinum species was bound to plasma proteins or to RBCs. These data may reflect the low stability of the oxalate leaving group, the rapid hydrolysis of oxaliplatin giving rise to 1,2-DACH platinum dichloride species and related biotransformation products which react with

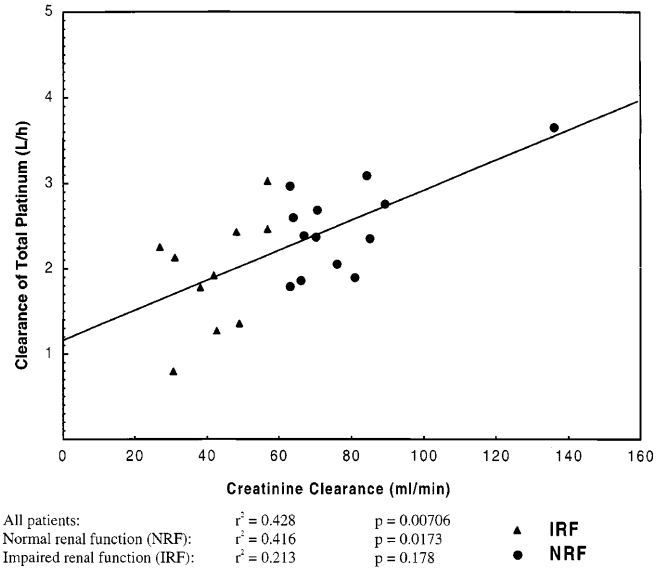

Fig. 4 Total platinum clearance plotted against creatinine clearance. Footnote: All patients: $r^2 = 0.428$, $P = 0.00706$. Normal renal function (*NRF*): $r^2 = 0.416$, $P = 0.0173$. Impaired renal function (*IRF*): $r^2 = 0.213$, $P = 0.178$

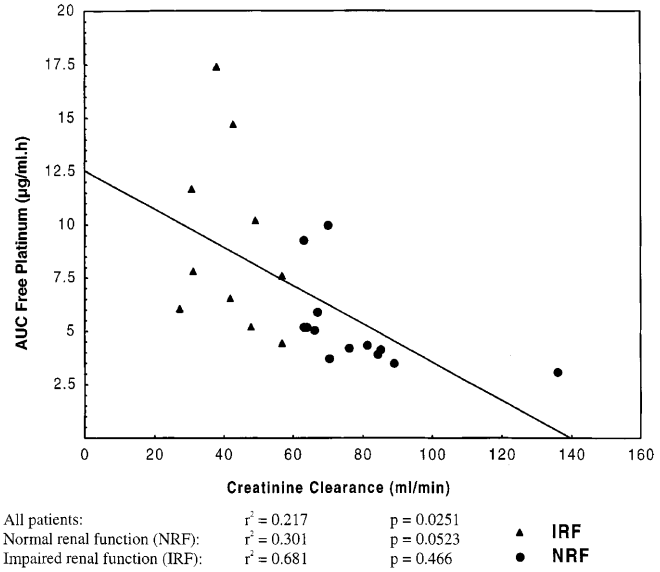

Fig. 6 AUC of free platinum plotted against creatinine clearance. Footnote: All patients: $r^2 = 0.217$, $P = 0.0251$. Normal renal function (*NRF*): $r^2 = 0.301$, $P = 0.0523$. Impaired renal function (*IRF*): $r^2 = 0.681$, $P = 0.466$

plasma proteins. Data from clinical studies with the other available organoplatinum compounds, cisplatin and carboplatin, indicate that the protein binding of oxaliplatin is intermediate between them. For cisplatin, 50% of the plasma platinum was still free at the end of a 3-h infusion, while 90% was bound 2 h later. After a 1-h carboplatin infusion, the binding of platinum to plasma proteins was much lower, 24% after 4 h, increasing to 87% after 24 h. These results had to be compared with the in vitro binding characteristics determined for the three drugs. The comparative binding of oxaliplatin and cisplatin to human plasma proteins has been evaluated.

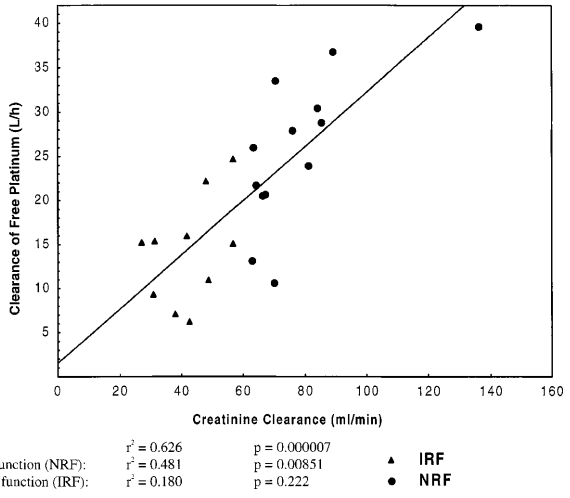

Fig. 5 Free platinum clearance plotted against creatinine clearance. Footnote: All patients: $r^2 = 0.626$, $P = 0.000007$. Normal renal function (*NRF*): $r^2 = 0.481$, $P = 0.00851$. Impaired renal function (*IRF*): $r^2 = 0.180$, $P = 0.222$

When oxaliplatin was incubated in human plasma at 37 °C, 85–88% of all platinum species were bound to plasma proteins after 5 h. In the same study, cisplatin was shown to exhibit protein binding in plasma to a similar extent and over a similar course of time; the $t_{1/2}$ for the decline in concentration of free platinum in plasma was 1.64 h, compared with 1.65 h for oxaliplatin. In vitro binding to human plasma proteins has also been investigated for carboplatin. Carboplatin was shown to bind more slowly than the other two platinum compounds, with the $t_{1/2}$ of carboplatin from plasma ultrafiltrate ranging from 33 to 49 h. Our work also shows that the pharmacokinetic parameters of oxaliplatin have more similarity with those of cisplatin than with those of carboplatin.

In the present study, the mean elimination $t_{1/2}$ of total plasma platinum calculated in the NRF patients was 38 ± 8 h; our values differ from those determined in a similar patient population in another PK study involving oxaliplatin (8.4 ± 1.1 days). The difference between the values can be explained to a large extent by differences in the PK techniques used. Firstly, methods for platinum analysis in the two studies were not identical. Gamelin et al. [10] used a more sensitive assay technique, inductively coupled plasma-mass spectrometry (ICPMS), to measure platinum levels, and the free platinum fraction was isolated from total plasma by ultracentrifugation and not by ultrafiltration.

Another important difference in method which could explain the discrepancy in the results was the duration of the PK study. In our study, blood collection was mandatory only in the first 48 h, while late samplings (days 8, 15 and 22) were available for the determination of pharmacokinetic parameters in the study conducted

by Gamelin et al. [10]. Finally, the mean terminal $t_{1/2}$ we calculated in the three patients who had blood sampling on day 22 (250 h) confirms the long retention of platinum in plasma following an oxaliplatin infusion.

In this study, we also investigated the PK of platinum in RBCs. Following the infusion of oxaliplatin, the uptake of platinum in RBCs was also rapid and extensive; 40% of the platinum levels measured in blood samples at the end of infusion were present in the RBCs. After the end of infusion, platinum content in RBCs declined more slowly than that in plasma, and the ratio of platinum concentration in RBCs to that in plasma was very soon greater than one and increased progressively (Fig. 3). The platinum elimination $t_{1/2}$ was close to the $t_{1/2}$ of the RBCs themselves (400–600 h) and there were no signs of toxanaemia. Gamelin et al. [10], using a more sensitive analysis method, have reported a longer platinum terminal $t_{1/2}$ in RBCs (mean 48 days); this parameter was again determined from late blood sampling (days 8, 15 and 22). RBC binding has also been investigated by in vitro studies and correlated with our in vivo data. When incubated in whole blood, platinum uptake into the RBCs was rapid, being maximal in the first 2 h; the amount of platinum partitioned in the RBCs was 37% of the total, compared with 40% measured in our clinical study. In vitro data have shown that the platinum bound in the RBCs is not exchangeable and does not serve as a reservoir of the drug. Finally, both these observations suggest that oxaliplatin species form stable covalent complexes with RBCs.

It should be borne in mind that there are several possible sources of error in determining the values for the free platinum compounds in the plasma. Although neither the anticoagulants (EDTA, citrate or heparin) nor the separation method interfere in the binding, other sampling conditions, particularly freezing, may do so [30]. Furthermore, the plasma separation methods may not be sensitive enough, and the ultrafiltrate may contain platinum compounds bound to very low molecular weight peptides or amino acids; this binding is known to be irreversible. Such binding may, however, be relevant to the action of the drug, as only the unbound platinum compound can exert a therapeutic or toxic effect (such binding is, however, estimated to be $< 10\%$, which is negligible except for calculating residual rates). Also, the measurement technique used is important. While FAAS and ICPMS are sensitive, they can only detect the presence of platinum, and do not differentiate between the biotransformation products of the organoplatinum compounds. High-performance liquid chromatography (HPLC) techniques, although not as sensitive, do offer the possibility of identifying such entities [28].

In conclusion, we have shown that exposure to free platinum was negatively correlated with renal function (Fig. 6) and that there is a corresponding positive correlation between renal function and the clearance of the plasmatic platinum (Figures 4 and 5). However, after a single course of oxaliplatin, toxicity was not noticeably higher in the IRF group than in the NRF group. No comparative data are available after repeated cycles of treatment, and the impact of this pharmacokinetic difference on toxicity after multiple infusions of oxaliplatin remains an open question.

One recommendation which arises from this study is to monitor the residual level of total plasmatic platinum before a cycle of oxaliplatin therapy when patients have to receive several such cycles. This monitoring might help in adapting the posology of oxaliplatin from one cycle to the next, in order to keep the residual concentration of oxaliplatin constant, and thus prevent accumulation and the emergence of the associated neuropathy. Finally, the PK and pharmacodynamics of oxaliplatin given to patients with severely impaired renal function (creatinine clearance < 30 ml/min) remains a subject of both interest and concern, which also needs to be addressed.

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