Cumulative Pharmacokinetic Study of Oxaliplatin, Administered Every Three Weeks, Combined with 5-Fluorouracil in Colorectal Cancer Patients

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ABSTRACT

The cumulative pharmacokinetic pattern of oxaliplatin, a new diamminecyclohexane platinum derivative, was studied in patients with metastatic colorectal cancer. Oxaliplatin was administered by i.v. infusion (130 mg/m²) over 2 h every 3 weeks, and 5-fluorouracil and leucovorin were administered weekly. A very sensitive method, inductively coupled plasma-mass spectrometry, allowed for the determination of total and ultrafiltrable (UC) and RBC platinum concentrations on day 1, at 0, 2, and 5 h, and on days 8, 15, and 22. Sixteen patients underwent three or more courses, and six of them underwent six or more courses. The platinum concentration curves were quite similar from one course to another, with a high peak value 2 h after administration (day 1, Cmax = 3201 ± 609 µg/liter) and a rapid decrease (day 8, 443 ± 99 µg/liter). Cmax of both total and UC platinum levels in plasma remained unchanged throughout the treatment. The mean total platinum half-life in plasma was 9 days. We found residual levels of total platinum on day 22 (161 ± 45 µg/liter), but we observed no significant accumulation for the four first cycles (P = 0.57). In contrast, platinum accumulated significantly in RBCs after three courses (+91% at day 22 of the third cycle versus day 22 of the first cycle, P = 0.000018), and its half-life there was equivalent to that of RBCs. The patterns of UC and total platinum concentration curves were very similar and correlated significantly (P < 10^-6) at all sampling times. The mean UC:total platinum ratio was 15% at day 1 and 5% at days 8, 15, and 22 in the 3-week treatment course. Unlike cisplatin, which rapidly accumulates in plasma as both free and bound platinum, oxaliplatin does not accumulate in plasma, but it does accumulate in RBCs, after repeated cycles at the currently recommended dose (130 mg/m²) and schedule of administration (every 3 weeks).

INTRODUCTION

Oxaliplatin is a diammine cyclohexane platinum complex that is active in several solid tumor types, especially in some cisplatin/carboplatin refractory diseases such as colorectal cancers (1–3). Its toxicity profile is different from that of cisplatin because it is devoid of nephrotoxicity at the recommended doses and schedule (2). Oxaliplatin induces acute peripheral sensitive neurotoxicity, characterized by acral paresthesia or dysesthesia affecting the laryngo-pharyngeal area and the upper and lower limbs. Acral paresthesia increases in incidence, intensity, and duration with repeated treatments and is consistently reversible (4).

Some preliminary results concerned the early pharmacokinetics, distribution, and elimination of ultrafiltrable and total platinum after a single oxaliplatin administration to patients (5), but the long-term platinum kinetics remain unknown. The parent drug, cisplatin, accumulates in plasma with repeated administrations (6), and it induces a peripheral neurotoxicity dependent on the cumulative dose, as does oxaliplatin. Thus, for the detection of any accumulation occurring with iterative courses of therapy, the evaluation of oxaliplatin pharmacokinetics appeared to be of major interest.

Previous studies have been carried out regarding the long-term behavior of free and bound platinum after administration of organoplatinum drugs. They were hampered due to the lack of sensitivity of the analytical technique used, which was atomic absorption spectrometry (7–9). A more recent technique, ICPMS, is much more sensitive (10–13). This technique has allowed us to establish the long-term pharmacokinetics of platinum after iterative cisplatin administrations (6). We detected significant levels of total and UC platinum in plasma, up to 3 weeks after cisplatin administration, showing that a progressive...
accumulation of both total and UC platinums occurred upon iterative infusions.

We have applied this technique to the study of platinum pharmacokinetics after several administrations of oxaliplatin. Actually, little is known about oxaliplatin metabolites. In plasma, oxaliplatin loosens oxaloacetate residue and is quickly metabolized in dach-platinum. No oxaliplatin is detectable 2 h after administration. Other metabolites probably exist, but they are not known. The techniques currently used measure platinum and do not permit the separate study of oxaliplatin and other platinum derivative metabolites.

The patients presented with advanced colorectal cancer that was resistant to 5-FU. They were treated with oxaliplatin plus 5-FU and leucovorin, because some publications have shown previously the synergistic clinical activity between both drugs and a good response rate in 5-FU-resistant colorectal cancer (3, 14). The objective of the present study was to characterize the long-term retention of oxaliplatin, by determining total and UC plasma platinum levels, as well as RBC platinum concentrations. We can assume that 5-FU does not modify oxaliplatin pharmacokinetics. It also does not influence the pharmacokinetics of cisplatin and carboplatin. Moreover, it is poorly bound to proteins, and its metabolism is completely different from that of oxaliplatin.

PATIENTS AND METHODS

Patients. All of the patients had histologically proven, metastatic colorectal cancer that was refractory to the 5-FU and leucovorin combination. All patients gave written informed consent and were more than 18 and less than 70 years old. Performance status < III (by WHO criteria) was required, as well as normal bone marrow function. Nomination of critical criteria were brain metastasis, expected survival of <3 months, and a cardiac condition contraindicating 5-FU treatment. All patients except two had normal renal function (creatinine clearance, >65 ml/min/1.73 m²). All of them had normal hepatic function and no sign of ascitis or pleural effusion.

Treatment. Chemotherapy consisted of oxaliplatin given in combination with 5-FU and folinic acid. All patients had long-term venous access, established either by means of a catheter or by means of an implantable chamber device. Oxaliplatin was given at 130 mg/m² in 250 ml of sterile 5% glucose solution as a 2-h infusion, every 3 weeks. 5-FU was administered after oxaliplatin infusion and repeated weekly, by means of an 8-h infusion in 1 liter of 0.9% saline serum through a battery-operated pump. The initial dose of 1300 mg/m² was adjusted weekly for each patient, according to 5-FU plasma assays and to a table of 5-FU dose adjustment (15). Folinic acid was administered at 200 mg/m² by i.v. bolus just before (0 h) and at 4 h after 5-FU infusion. Oxaliplatin was administered in association with prophylactic antiemetics, ondansetron, and corticosteroids at conventional doses. Other symptomatic treatments were allowed whenever required. Previous treatments for concomitant conditions were continued at the same dose.

Blood Sampling. For each cycle, on the basis of oxaliplatin infusion, collection times of 5-ml blood samples were: day 1, 0, 2, and 5 h; days 8, 15, and day 22, before the next oxaliplatin infusion. They were collected in heparinized tubes. The plasma was immediately separated by centrifugation at 4°C. Globular pellets were stored, and plasma was split into two aliquots, one for the total platinum assay, without further preparation, and one for the UC platinum assay.

Platinum Assay. Platinum quantification was performed with the ICPMS method described previously (10). The spectrometer used was an Elan 5000 (Perkin-Elmer Corp.).

Total platinum in plasma and RBC platinum levels were measured after a 20-fold dilution in a solution containing Europium (Sigma Chemical Co.; 100 g/liter), an internal standard. For UC platinum assay, the plasma was centrifuged for 3 h at 100,000 rpm using rotor TLA 100.2 (Beckman Instruments, Fullerton, CA). The supernatant was subsequently diluted 10-fold in the Europium solution.

The calibration was performed with 1 g/liter platinum standard solution (Sigma), diluted in a saline solution (Titrisol; Merck) that contained 8.39 g/liter NaCl. The diluted solutions were introduced into the nebulization chamber of the ICPMS, using a peristaltic pump from Gilson.

The method was linear between 0 and 5000 µg/liter of platinum. The recoveries were close to 100%. The within- and between-day coefficients of variation were lower than 2% for total, UC, and RBC platinum. The estimated limit of quantification was 1 µg/liter.

Under the conditions of this study, the limit of quantification was estimated at 1 µg/liter in plasma. The sample concentrations ranged from 1 to 5000 µg/liter.

Platinum levels in RBC were expressed both as µg/liter of cell volume and as µg/g of Hb.

RESULTS

Patient Characteristics. Seventeen patients were included in the study between June 1994 and April 1995. One patient refused plasma assays after inclusion. Sixteen patients could be investigated throughout their treatment (mean number of cycles, 5; range, 3–12). Eight of them underwent 3 courses, two underwent 4 courses, two had 6 courses, two had 7 courses, one patient had 11 courses, and one patient had 12 courses. Eighty-five courses of oxaliplatin were administered. The 3-week interval between courses was maintained in 58 of 68 intervals (85%), and 64 of 68 intervals were no longer than 4 weeks. Treatment was delayed for 10 courses in nine patients due to gastrointestinal toxicity (2 courses), myelosuppression (2 courses), personal convenience (2 courses), surgery (1 course), and other reasons not related to toxicity (3 courses). The intervals between delayed courses were 28 (six courses), 36 (one course), 43 (two courses), and 108 days (one course, for surgery).

The treatment was stopped due to: (a) tumor progression in seven cases (three after 3 cycles and four after 4, 6, 7, and 12 cycles); (b) drug-related toxicity in four cases (cardiac toxicity, gastrointestinal tract toxicity, myelosuppression, and skin toxicity); (c) a quite stable disease in two cases (after 8 and 11 cycles); and (d) patient treatment refusal in two cases, after 3 and 4 courses.

All oxaliplatin treatments were administered at the recom-
mended dose of 130 mg/m² and given as a 2-h infusion. The median cumulative dose of oxaliplatin was 520 mg/m² (range, 260-1560 mg/m²).

**Toxicity.** Toxic events, evaluated before each new cycle according to WHO criteria, are displayed in Table 1. No toxic death occurred during this trial. A patient presented with 5-FU related acute angina pectoris at home, the night after a treatment. It spontaneously resolved before the physician came. Another patient had a toxidermia. In these two cases, the treatment was stopped, and the toxic event disappeared.

**Total Platinum Characteristics.** The mean plasma levels of total platinum are presented in Fig. 1. All courses are characterized by a high peak value at 2 h after the end of administration, followed by a rapid decrease. The plasma levels measured after 5 h were 70% of the levels measured after 2 h, and those measured after 8, 15, and 22 days were 15, 7, and 3% of the peak value, respectively. It should be noticed that significant plasma levels of platinum (161 ± 45 µg/liter after the first course) were still measured 22 days after administration. The mean terminal half-life of total platinum in plasma determined from three points, measured on days 8, 15, and 22, was 9 ± 0.7 days (range, 8.42–9.66; Table 2). These results illustrate the reproducibility of the kinetics after iterative administrations.

For 12 patients, late samplings performed on days 28 (six patients), 36 (four patients), 58 (one patient), and 108 (one patient) showed residual platinum levels: 183 µg/liter (range, 111–272 µg/liter), 109 µg/liter (range, 94–129 µg/liter), 52 µg/liter, and 13 µg/liter, respectively. These results illustrate the very long retention of platinum in plasma. In these cases, a breakdown of the platinum concentration slope was observed on day 22, and the terminal half-life was 15 days.

Total platinum levels at early sampling times did not increase significantly between courses (Fig. 1 and Table 3). Only a trend toward a slow increase of residual levels was observed from the first to the seventh course (+50%). The slope of the residual levels regression curve was 0.71 (P < 0.05). However, the difference was not statistically significant when all of the sampling times were taken together and when the first course was compared with the third (P = 0.13) or the fourth (P = 0.57) course.

**Pharmacokinetics of UC Platinum.** The pattern of the UC platinum plasma concentration curves is similar to that of...
Table 2. Mean platinum half-lives in plasma (total and UC platinum) and in RBCs for successive courses. Half-lives were very stable throughout the treatment. Mean platinum half-life in RBCs was almost equivalent to that of RBCs, suggesting that the binding might be covalent.

<table>
<thead>
<tr>
<th>Course (days)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total platinum</td>
<td>8.4 ± 1.1</td>
<td>8.4 ± 1.31</td>
<td>8.7 ± 0.78</td>
<td>9.7 ± 0.47</td>
<td>9.3 ± 0.94</td>
<td>9.5 ± 0.5</td>
<td>9.4 ± 0.7</td>
<td>8.5 ± 0.5</td>
</tr>
<tr>
<td>UC platinum</td>
<td>6.8 ± 2</td>
<td>6.4 ± 1</td>
<td>7.2 ± 0.7</td>
<td>8</td>
<td>6.5</td>
<td>6.8 ± 0.8</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>RBC platinum</td>
<td>50 ± 10</td>
<td>46.6 ± 11</td>
<td>45.5 ± 14</td>
<td>8.09</td>
<td>5.05</td>
<td>5.09</td>
<td>5.09</td>
<td>5.09</td>
</tr>
</tbody>
</table>

Table 3. Comparison of platinum concentrations in plasma and RBCs at the third and sixth courses vs. the first course. Total platinum did not accumulate in plasma, and neither did UC platinum. In contrast, platinum significantly and rapidly increased in RBCs.

<table>
<thead>
<tr>
<th>Sampling time</th>
<th>C3 vs. C1</th>
<th>C6 vs. C1</th>
<th>C6 vs. C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 h</td>
<td>TP</td>
<td>UP</td>
<td>RBC P</td>
</tr>
<tr>
<td>% change</td>
<td>-1%</td>
<td>-5%</td>
<td>+73%</td>
</tr>
<tr>
<td>P</td>
<td>NS*</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>5 h</td>
<td>% change</td>
<td>-5%</td>
<td>-24%</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>8 days</td>
<td>% change</td>
<td>+18%</td>
<td>-20%</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>15 days</td>
<td>% change</td>
<td>+27%</td>
<td>+40%</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>22 days</td>
<td>% change</td>
<td>+16%</td>
<td>+21%</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* NS, not significant.

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Oxaliplatin (Fig. 2). Early high peaks appeared at 2 and 5 h after oxaliplatin administration and were followed by a rapid decrease. The UC platinum elimination half-lives were somewhat shorter than the total platinum ones and did not change throughout the treatment (7.15 ± 0.7 days; Table 2). UC platinum did not accumulate in plasma (Table 3), although small but significant levels of UC platinum (10 μg/liter) were measured until 22 days after every course (Fig. 2). The values were not statistically different between the courses, whatever the sampling time.

UC platinum plasma levels were closely and strongly correlated with total platinum plasma levels. The mean ratio of UC versus total platinum was 7.7%, and the coefficient of correlation was \( r = 0.94 \) (\( P < 10^{-6} \)). It did not change throughout the courses but changed with the sampling time within each course, and two different patterns could be observed. For early samplings (2 and 5 h), with platinum levels > 1,000 μg/liter, the mean percentage of UC versus total platinum was 15%, and the coefficient of correlation was \( r = 0.69 \) (\( P < 10^{-6} \); Fig. 3). For late samplings (days 8, 15, and 22) and for total platinum plasma levels less than 1000 μg/liter, the percentage was 5%, and the coefficient of correlation was \( r = 0.65 \) (\( P < 10^{-6} \); Fig. 3).

Platinum Accumulation in RBCs. Platinum was measured in RBCs for eight patients over three courses of treatment (Fig. 4). Platinum levels in RBCs increased rapidly during infusion and reached a maximal value at 2 and 5 h; afterward, they declined slowly (Fig. 4). Compared to the values obtained after the first course, the levels at the second and third cycles were significantly higher (Fig. 4 and Table 3). For the first cycle, platinum levels in RBCs were close to the total platinum values on day 1, 2 and 5 h (83 ± 12 and 130 ± 9%, respectively), but they were strikingly higher afterward, reaching 810 ± 40% of plasma levels on day 22. On day 22, the residual platinum concentrations in RBCs represented one-half of the peak values, indicating a long storage in this compartment. The mean platinum terminal half-life in RBCs, calculated with the concentrations on days 8, 15, and 22, was 48 ± 10.5 days. It did not change with the course (Table 2). In three instances, it reached 70 days.

We looked for a link between the variations of RBC platinum levels and those of Hb because, for three patients, platinum RBC levels increased unexpectedly from day 8 to day 15. A spontaneous rise of Hb level occurred at the same time, which could explain the trapping and the increase of platinum in RBCs. Thus, we calculated platinum RBC concentrations in μg/g Hb, and these platinum/Hb ratios were always lower on day 15 than on day 8. We observed a progressive accumulation from the first to the third treatment course. Thus, we calculated platinum RBC concentrations in μg/g Hb, and these platinum/Hb ratios were always lower on day 15 than on day 8. We observed a progressive accumulation from the first to the third treatment course: on day 1, 2 h, 7.4 ± 1.67, 10.4 ± 2.11, and 14.28 μg/g Hb; on day 8, 4.91 ± 1.23, 8.43 ± 1.98, and 10.78 μg/g Hb on day 15: 4.82 ± 1.51, 7.02, and 8.8 μg/g Hb; and on day 22, 3.92 ± 0.77, 6.2 ± 1.43, and 7.14 ± 0.64 μg/g Hb (values are for C1, C2, and C3, respectively).
Fig. 2 Mean UC platinum concentrations in plasma throughout seven courses. UC platinum did not accumulate, although small but significant levels of UC platinum were measured until 22 days after every course.

At late sampling times (days 8, 15 and 22), RBC platinum levels were higher than total plasma platinum levels but correlated significantly with them (coefficients of correlation: $r = 0.67$ on day 8, $r = 0.75$ on day 15, and $r = 0.55$ on day 22, $P < 10^{-6}$; Fig. 5). The same observation could be made with UC platinum. This relationship was not found for the early samplings.

As mentioned above, two patients had a renal function at baseline characterized by a low creatinine clearance (26 and 32 ml/min). At all of the sampling times, their total and RBC platinum levels were 20–40% higher than the whole group. Likewise, UC platinum levels in these patients on day 1.5 h, were either higher or very close to those on day 1.2 h. Because these two patients had a different pharmacokinetic behavior, a separate statistical analysis compared the different courses after their exclusion and showed no difference (data not shown).

We looked for a link between accumulation of platinum in RBCs and anemia incidence. RBC levels were higher in patients who experienced subsequent anemia ($n = 4$). The differences of the mean levels between the two groups were significant at day 8 ($P = 0.015$), day 15 ($P = 0.05$), and day 22. 2 h ($P = 0.014$), after the first administration of oxaliplatin.
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**Fig. 4** Mean platinum concentration in RBCs throughout three courses. Platinum levels increased rapidly after infusion and reached a maximal value at 2 and 5 h; afterward, they declined slowly, and, thus, a progressive accumulation could be observed.

**Fig. 5** Correlation between RBCs and total platinum in plasma (120 samples). A, there was no correlation at early sampling times. B, the correlation was high for late sampling times: $r = 0.65, P < 10^{-4}$, and the linear regression curve was 1.009.

**DISCUSSION**

Some preliminary results on early pharmacokinetics of oxaliplatin have been reported after a single course (5). However, no data were available regarding its long-term retention. ICPMS allowed us to study total, UC, and RBC platinum concentrations for successive courses of chemotherapy, as had been done for other organoplatinum drugs (6, 10–13). Eighty-five cycles have been administered, with a median number of 5 cycles per patient. Toxicity was consistent with the data previously reported with this type of association (1, 2). Myelosuppression remained moderate, and mucositis resulted from 5-FU, whereas neurotoxicity was related to oxaliplatin.

The platinum concentration curves were very similar throughout the treatment, and the terminal half-lives remained unchanged. The $C_{max}$ of total platinum were constant over eight courses. Significant residual levels of total platinum persisted until the beginning of the following course and showed a slightly increasing trend. These results, combined with a prolonged terminal half-life of total platinum, may cause us to fear a significant platinum accumulation if the interval between two
courses is reduced to 15 days. This accumulation could increase the incidence of neurotoxicity.

If we compare the pharmacokinetics of oxaliplatin and cisplatin after repeated administrations, the main difference is the absence of clear accumulation of plasma UC and total platinum after iterative administrations of oxaliplatin, whereas a quite significant accumulation of platinum in plasma has been described after repeated cisplatin administration (6, 16, 17). We have shown previously for cisplatin that there was a progressive and significant increase in both \( C_{\text{max}} \) and \( C_{\text{min}} \) of total and UC plasma platinum, with a doubling of these levels after three courses (6). In contrast, the increase of total platinum residual levels after oxaliplatin administration is much lower (50% increase after seven courses), at the limit of statistical significance. This difference between oxaliplatin and cisplatin may be due to a different platinum binding to plasma proteins and/or to a difference in the volume of distribution of the two drugs. We used an ultracentrifugation technique for measuring free platinum concentrations in plasma, as we did previously for studying free platinum after cisplatin administration (6). Ultracentrifugation was compared previously with other techniques and was found comparable for reliability to equilibrium dialysis, which is the technique of reference (8, 18–21). It appeared superior for reproducibility, especially when measuring low free drug concentrations. Moreover, ultracentrifugation, as a physical method, does not involve a membrane and does not take into account the binding of drugs to low molecular weight proteins or peptides, as can be the case with low-density lipoproteins (21). Thus, this technique appeared to be particularly adapted for the assessment of non-protein-bound platinum. A methodological study was carried out in our laboratory comparing ultracentrifugation and ultrafiltration (Amicon, model 4104) with 22 plasma samples. The results of the two techniques were closely correlated (Pearson correlation test, \( r = 0.994 \)).

UC platinum did not accumulate in plasma after iterative courses of oxaliplatin. \( C_{\text{max}} \) as well as residual levels remained constant, although significant amounts of UC platinum persisted throughout the whole treatment period and until 22 days after oxaliplatin administration (Figs. 3 and 4).

Three of four studies of cisplatin administration reported free platinum accumulation after cisplatin was administered (6, 7, 22). In the fourth discrepant study, the platinum determination method in plasma had a high detection limit that did not allow for the detection of small variations in free platinum concentrations (16). Two mechanisms could explain the progressive accumulation of free platinum: either a reduced ability to clear ultrafiltrable platinum with repeated courses (22) or a close correlation between total and free platinum, the free species following the progressive accumulation of the total one (6). These results could explain, in part, the differences of toxicity between oxaliplatin and cisplatin, especially the long-term cumulative nephrotoxicity of cisplatin (23–25). A quick distribution, a progressive accumulation, and a very long-term platinum retention in deep compartments characterize cisplatin pharmacokinetics (12, 13, 26, 27). This slow storage for several months is linked with long-standing nephrotoxicity and irreversible chronic nephrotoxicity (12, 13, 17, 23, 26–30). In contrast, the absence of oxaliplatin accumulation in plasma could explain why oxaliplatin neurotoxicity is most often reversible upon treatment discontinuation (4).

UC platinum levels are closely correlated with total platinum values after oxaliplatin administration. Two studies showed a similar correlation between UC and total platinum after cisplatin administration (6, 31), but most authors reported that the platinum binding to proteins after cisplatin administration was irreversible (8, 9, 29, 32, 33). It is important to stress that these two studies were either carried out ex vivo, so that the influences of rate constants between different compartments other than the protein binding system were eliminated or they were not sensitive enough to detect platinum level modifications lower than 100 \( \mu \)g/liter. These studies concluded that the half-life of free platinum was very short, with a maximum of a few hours (9, 31, 34–37), whereas with ICPMS, we could detect significant levels throughout the whole cycle (6). The proportion of UC platinum in plasma after oxaliplatin administration varied according to the sampling time. It was approximately 15% at early sampling times, reaching even 25–30% in some patients, and was 5% from day 8 to day 22 after each administration. No study has reported this phenomenon with cisplatin, for which the ratio between UC and total platinum was constant at approximately 6% throughout the sampling period, from day 1 to day 22 (6, 33, 38).

It has been shown previously that for the first 2 h after cisplatin administration, platinum could bind to several protein species, including low molecular weight thiols such as sulfhydryl groups, cysteine, methionine, and glutathione (30, 39, 40). Later, it binds with a high affinity to high molecular weight proteins (>25 kDa) such as albumin, globulins, and transferrin (8, 9, 33, 38, 40). On the other hand, after carboplatin administration, platinum only had affinity with low molecular weight thiols and did not bind with high molecular weight proteins (40). These results and ours suggest that, after oxaliplatin administration, platinum binds first with both high and low molecular weight proteins and only later with high molecular weight proteins.

In the present study, we showed that platinum underwent a long-term retention process in RBCs. The RBC platinum uptake was rapid. The RBC platinum levels decreased much more slowly than those in plasma and subsequently became higher than the plasma levels in the late samplings. Consequently, RBC platinum levels increased markedly from one course to the following one. The difference between cycle 1 and cycle 3 (an increase of 57–107%) was highly significant for all sampling times.

Our results show that at early times, RBC platinum behaved independently from UC and bound plasma platinum. However, on days 8, 15, and 22, RBC platinum levels show a strong correlation with total and UC platinum in plasma.

Some arguments suggest that Hb, the major protein in RBC, binds with platinum and plays a major role in its storage. When an increase of Hb occurred, RBC platinum levels on day 22 were higher than on day 15. The binding of platinum to Hb might be covalent because the terminal half-life of platinum in RBCs was similar to that of RBCs, as determined by radioactive phosphate labeling techniques, which is about 60 days (41). In three instances, it reached 70 days, which may suggest a secondary uptake by RBCs after a first release.
As for oxaliplatin, a particular accumulation in RBCs has been previously reported for cisplatin, but not for carboplatin. Carboplatin distribution in RBCs and its extrusion of them were very fast so that its half-life was very short (42–44). The concentration-time curves of RBC platinum were similar to those of free platinum. In contrast, after cisplatin administration, the platinum uptake in RBCs was rapid, the concentrations reached high peaks at 2.5 h, and platinum accumulated significantly. A few studies have emphasized the importance of RBCs in the distribution volume and the long-term retention of platinum (8, 9, 38). Of some them reported an irreversible RBC-platinum binding (8, 9, 38), whereas some others found a slow release (45). Vermorken et al. (8, 9) found that the elimination of platinum from RBCs was biphasic, with a second terminal half-life of about 30 days. They concluded that this terminal half-life involved an increased breakdown of RBCs resulting from cisplatin cytotoxicity (8, 9). To our knowledge, the long-term kinetics of platinum in RBCs after repeated administrations of cisplatin has not been studied thus far.

This important and prolonged retention of platinum in RBCs might play a role in some toxic manifestations. The probable interaction with Hb could be of major interest for the study and understanding of platinum adduct formation and liability.

Although a prospective pharmacodynamic evaluation was not the goal of the present study, we did attempt to correlate platinum plasma levels with neurotoxicity, because a pharmacokinetic-pharmacodynamic correlation has been reported for cisplatin (17, 23, 28). Total platinum levels varied, as has been reported with cisplatin (8, 9, 24, 38). However, the number of values was perhaps too small in our limited cohort, and we could not elicit any clear relationship between platinum levels in plasma and the neurotoxicity pattern. Moreover, neurotoxicity occurs after a 700 mg/m² total cumulated dose of oxaliplatin, whereas, in the present study, the mean cumulated dose of oxaliplatin was 520 mg/m².

Likewise, we looked for a relationship between anemia incidence and individual pharmacokinetic data. Patients who experienced subsequent anemia had significantly higher RBC plasma levels at days 8, 15, and 22 after the first administration of oxaliplatin, but once again, the groups were small.

In the present study, we showed that oxaliplatin does not accumulate in plasma but accumulates in RBCs with a very long half-life after repeated administration at the currently recommended dose and schedule of administration. Unlike cisplatin, which rapidly accumulates as both free and bound platinum, Cmax; of total and UC platinum levels in plasma remain unchanged throughout the treatment, despite significant total residual levels on day 22. These differences might explain why oxaliplatin neurotoxicity is consistently reversible.

REFERENCES


Cumulative pharmacokinetic study of oxaliplatin, administered every three weeks, combined with 5-fluorouracil in colorectal cancer patients.

E Gamelin, A L Bouil, M Boisdron-Celle, et al.