Clinical pharmacokinetics of cumulative very high dose of cisplatin in chemotherapy resistant solid tumors

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Summary. - Cisplatin was administered to seven patients with advanced cancer in divided doses of 40 mg/m² body surface daily for 5 consecutive days. The pharmacokinetics of total Pt was studied on the days 1, 3 and 5 of infusion. The renal function was assessed through the parameters usually applied in the clinical practice (serum creatinine level, creatinine clearance, urinary volume). Pt pharmacokinetics and the renal function did not show modifications outside the normal range. However, on day 5 of treatment patients showed increased α-half life and AUC of plasma Pt, as well as decreased Pt total body clearance and Pt renal clearance, associated to a significant (although still within normal range) increase in serum creatinine and a decrease in urinary volume. Moreover, a correlation between Pt pharmacokinetics and renal parameters (measured as the difference between the values of days 1 and 5 of treatment) was also found: the increase in creatinine was directly related to a decrease in Pt renal clearance and inversely related to Pt peak level in urine, while the latter was inversely related to a reduction of Pt renal clearance. It was concluded that very high doses of cisplatin are well tolerated in patients, although some parameters might suggest early impairment of the renal function.

Key words: cisplatin, pharmacokinetics, renal function.

Riassunto (Farmacocinetica clinica di una dose complessiva molto alta di cisplatino in tumori solidi resistenti alla chemioterapia). - Sotto pazienti affetti da malattia tumorale in fase avanzata sono stati sottoposti per 5 giorni consecutivi a trattamento con cisplatino, alla dose giornaliera di 40 mg/m² di superficie corporea. Nei giorni 1, 3 e 5 del periodo di trattamento sono state valutate la farmacocinetica del Pt totale e la funzione renale, attraverso i parametri generalmente applicati nella pratica clinica. La farmacocinetica del Pt e la funzione renale sono rimaste nell'ambito dei valori normali. Tuttavia, al quinto giorno di trattamento, i pazienti presentavano allungamento del τ₂α e aumento dell'AUC del Pt plasmatico, riduzione della clearance totale e della clearance renale del Pt. Tali alterazioni farmacocinetiche si associavano ad un aumento significativo, pur nell'ambito dei valori normali, della creatininemia e ad una riduzione del volume urinario. E' stata anche evidenziata una correlazione tra i parametri farmacocinetici e quelli renali (misurati come differenza tra i valori del primo e quelli del quinto giorno di trattamento): l'aumento della creatininemia era correlato direttamente ad una riduzione della clearance renale del Pt ed inversamente al picco del livello del Pt nelle urine; quest'ultimo era inversamente correlato ad una riduzione della clearance renale del Pt. E' stato possibile concludere che dosi molto alte di cisplatino sono ben tollerate dai pazienti, anche se la sorveglianza di alcuni parametri potrebbe suggerire un precoces seggiamento della funzione renale.

Parole chiave: cisplatino, farmacocinetica, funzione renale.

Introduction

Cisplatin (cis-diamminodichloroplatinum, CDDP) is the best known of a group of Pt coordination complexes which, either alone or in combination with other antineoplastic drugs, has become of primary importance in the treatment of a number of resistant solid tumors (head and neck, testis, ovary, urinary bladder, lung). The clinical management of these tumors is based on the administration of CDDP (40-50 mg/m² body surface), alone or added to other anticancer drugs. A lag of at least 3 weeks is allowed to elapse between two consecutive doses.

Although the optimal dose of CDDP for most cancers is yet to be defined, high doses of CDDP appear to be more effective than standard doses in patients with ovary carcinoma, lung cancer and melanoma [1-3]. Furthermore, when a tumor is unresponsive to the usual total dose of CDDP (100-120 mg/m² as a single agent or in multidrug combinations), or an acquired resistance is developed [4,
5], a total dose as high as 200 mg/m² body surface, divided
in 5 consecutive days in one [6, 7] or repeated [8] courses
can be utilized. When the dose of 40 mg/m²/day was
infused intravenously (i.v.) within a 30-min period
associated with intensive hydration and furosemide,
only 2 out of 17 patients showed increased serum
creatinine [6], and in 7 out of 7 patients no change in the
half life of total and ultrafiltrable Pt values were observed
between days 1 and 5 of treatment [7]. When the total
dose of 200 mg/m² of CDDP was infused continuously
in children (aged 10 months-13 years) for 5 days in 4
repeated courses, Pt clearance was found to decrease
between the first and the last course [8].

This study was aimed at further evaluating Pt kinetics
during a single course of CDDP, according to the schedule
proposed by Cordes et al. [7], in 7 patients resistant to
previous anticancer treatment. Six patients had been
previously treated with CDDP therapy at the conventional
dose; one patient with ovary carcinoma, never exposed
to CDDP, was included in this study because she was
refractory to previous treatment. In addition, the possible
relationship between Pt pharmacokinetics and renal
toxicity was analyzed during days 1, 3 and 5 of CDDP
therapy.

Table 1: Patients' characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Clinical evaluation</th>
<th>Renal function assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 weeks after treatment</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Previous chemotherapy schedule</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total dose of CDDP in previous cycles (mg/m²)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weeks after the last Pt cycle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Creatinine (mg/dl)</td>
<td>Creatinine clearance (mL/m²)</td>
</tr>
<tr>
<td>AA</td>
<td>F</td>
<td>64</td>
<td>ovary</td>
<td>PD</td>
<td>PD</td>
</tr>
<tr>
<td>PA</td>
<td>F</td>
<td>56</td>
<td>ovary</td>
<td>PD</td>
<td>CR</td>
</tr>
<tr>
<td>CB</td>
<td>M</td>
<td>46</td>
<td>SC oropharynx</td>
<td>PD</td>
<td>SD</td>
</tr>
<tr>
<td>DE</td>
<td>M</td>
<td>69</td>
<td>SC nasal mucosa</td>
<td>PD</td>
<td>PD</td>
</tr>
<tr>
<td>PG</td>
<td>M</td>
<td>67</td>
<td>SC rhinopharynx</td>
<td>PD</td>
<td>SD</td>
</tr>
<tr>
<td>ST</td>
<td>M</td>
<td>58</td>
<td>SC skin</td>
<td>PD</td>
<td>CR</td>
</tr>
<tr>
<td>TA</td>
<td>M</td>
<td>48</td>
<td>SC oral mucosa</td>
<td>PD</td>
<td>SD</td>
</tr>
</tbody>
</table>

SC = squamous carcinoma
AC = adriamycin, cyclophosphamide
PD = progressive disease
SD = stable disease
PAC = cisplatin, adriamycin, cyclophosphamide
CR = complete remission
PR = partial remission

Materials and methods

Treatment of patients

All subjects were inpatients. Pretreatment assessment
of the extent of disease was made by physical examination,
X-rays, CT scan and multiple studies of the liver and
renal functions. Patient eligibility criteria included
progressive or recurrent disease, a life expectancy of at
least 8 weeks, a performance status ≤ 2, according to the
European Cancer Oncology Group (ECOG) [9], and
adequate cardiac and renal functions (serum creatinine
< 1.2 mg/dl and creatinine clearance > 60 mL/min)
and bone marrow (WBC ≥ 4,000/m³ and platelets
≥ 100,000/m³, Hb ≥ 10 g/l).

Patients' characteristics are reported in Table 1. All
patients but one had previously received 3 to 8 cycles of
polychemotherapy, each consisting of a single dose
infusion of either CDDP (50 mg/m²) associated with
methotrexate, bleomycin and vincristine (CABO), or
adriamycin and cyclophosphamide (PAC). Four to 66
weeks (median 28) elapsed between the last cycle of
polychemotherapy and the present therapy. The patient
with ovary carcinoma, not previously exposed to CDDP,
had received chemotherapy with Adriamycin and cyclophosphamide (AC). All patients were unresponsive or scarcely responsive to the previous polychemotherapy treatment, and their clinical condition was considered "progressive disease", following ECOG group criteria [9]. Six weeks after the end of CDDP cycle, patients underwent again a complete assessment of disease. Each patient was given a score of 4 through 1, where 4 was "progressive disease"; 3 was "stable disease"; 2 was "partial remission", and 1 was "clinical complete remission".

All patients received a daily CDDP dose of 40 mg/m² body surface area, dissolved in 250 ml of 3% saline and infused over 30 min. Treatment was given for five consecutive days. The drug was administered at approximately the same time each day to avoid potential circadian variations in CDDP urinary kinetics. Intensive hydration, based on the infusion of 6 liter/day (250 ml/h) of a 0.9% NaCl solution containing 20 mEq KCl/l, was started 12 h before the first dose of CDDP and was continued up to 12 h after completion of the treatment. Furosemide i.v. at the dose of 20 mg, 20-30 min before each dose of CDDP, and antiemetic therapy (metoclopramide) were also administered.

Serum creatinine and blood urea nitrogen (BUN) levels were measured before, during and 3 days after the end of treatment. Creatinine clearance was determined from the 24 h urine collection prior to the administration of the drug. Blood and urine samples were analyzed for electrolytes (sodium, potassium, chloride) and BUN levels determined on days 1, 3 and 5 of therapy.

Sampling and analytical procedure

Blood (10 ml) and urine samples (through a catheter in urinary bladder) for the determination of Pt and all the parameters listed above were collected before administration of the drug and at 0, 20, 40, 60, 120 and 180 min after the end of infusion. Urine collection was continued also at 6, 12 and 24 h after drug infusion on days 1, 3 and 5. The average urine concentration of Pt was determined over 24 h. Blood samples were allowed to clot for 30 min at room temperature and subsequently centrifuged at 2500 x g for 10 min. The separated serum was immediately frozen and stored at -20°C until analysis began. Urine samples were frozen at -20°C.

Determination of Pt were accomplished by inductively coupled plasma atomic emission spectrometry (ICP-AES). Biological fluids were analyzed without any pretreatment except 1+3 and 1+1 dilution with double distilled water for serum and urine, respectively. All calibrants and samples were added with La as the internal standard.

Pharmacokinetic analysis

Pharmacokinetic analyses were carried out for all patients during days 1, 3 and 5 of therapy. The following information was obtained using a software developed for statistical and pharmacological calculations [10]:
- the elimination half-life of total Pt was derived by the least-squares regression analysis of the concentration-time curve, as applied to a mono- and biexponential model; 
  \[ C = C_0e^{-\alpha t} + Be^{-\beta t} \]
  (where C is the concentration at time t and A, B and α, β are the concentration and first-order rate constants, respectively). The F-test [11] was used to differentiate between the two models. For the determination of β half-life, further calculations were performed, i.e., simulated levels were added at 24 h, at different levels between 0 and the baseline on days 3 or 5 before the treatment of the day.
- the area under the curve (AUC) of the concentration vs time for Pt levels in plasma samples (total Pt) was determined by the trapezoidal method including extrapolation to infinity;
- the total body clearance (Cl) was obtained from the equation \[ Cl = \frac{D}{AUC} \]
  where D is the dose administered;
- the volume of distribution (Vd) was calculated by dose/C0, where C0 is the extrapolated concentration at time zero;
- the calculation of renal clearance (CLR) for Pt was made by determining the amount of Pt excreted over the time interval from 0 to 180 min and the plasma Pt concentration during the same time interval.

Statistical methods

The values are given as means and standard error of means (SEM). Parametric and non-parametric methods were used as indicated. Correlations between Pt pharmacokinetics and renal parameters were checked by using the one-tailed Spearman rank correlation coefficient (R) and the linear correlation coefficient (r). The two-tailed paired t-test and Wilcoxon matched pairs signed ranks test were applied to differences between groups. A significance level of p < 0.05 was adopted.

Results

Plasma and urine Pt levels

The individual plasma and urine concentration peaks of total Pt soon after the end of the infusion on days 1, 3 and 5 are reported in Table 2. In 5 out of 7 patients the peak plasma values increased throughout the study ranging from 1.47-4.1 mg/l (mean 2.32 ± 0.38 mg/l) after the 1st infusion to 2.5-5.2 mg/l (mean 4.19 ± 0.60 mg/l)
Table 2. - Summary of the effect of high-dose CDDP on Pt peaks in blood and urine, blood creatinine and diuresis in individual patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>CDDP Cumul. dose (mg/tot)</th>
<th>Peaks of Pt (mg/l)</th>
<th>Blood creatinine (mg/dl)</th>
<th>Diuresis (l/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Days of therapy 1° 2° 3°</td>
<td>Days of therapy 1° 2° 3°</td>
<td>Days of therapy 1° 3° 5° 8°</td>
</tr>
<tr>
<td>AA</td>
<td>300</td>
<td>1.9 4.1 m</td>
<td>8.0 9.0 m</td>
<td>0.69 0.76 0.70 0.94 1.19</td>
</tr>
<tr>
<td>PA</td>
<td>240</td>
<td>4.1 4.4 6.5</td>
<td>13.0 11.4 10.6</td>
<td>0.77 0.72 0.70 0.79 0.88</td>
</tr>
<tr>
<td>BC</td>
<td>360</td>
<td>1.47 2.7 4.1</td>
<td>10.5 8.5 10.1</td>
<td>0.92 0.91 0.99 1.01 1.34</td>
</tr>
<tr>
<td>DE</td>
<td>340</td>
<td>1.8 3.4 3.8</td>
<td>11.8 3.4 3.6</td>
<td>0.91 0.76 0.92 1.84 2.84</td>
</tr>
<tr>
<td>PI</td>
<td>350</td>
<td>2.4 2.4 2.5</td>
<td>13.6 12.3 20.6</td>
<td>0.86 0.78 0.81 0.96 1.07</td>
</tr>
<tr>
<td>ST</td>
<td>350</td>
<td>2.9 2.9 3.0</td>
<td>12.2 8.8 12.7</td>
<td>0.86 0.87 0.88 0.99 1.34</td>
</tr>
<tr>
<td>TA</td>
<td>350</td>
<td>2.3 2.2 5.2</td>
<td>16.1 12.4 12.8</td>
<td>0.84 0.79 0.97 0.99 1.13</td>
</tr>
</tbody>
</table>

m = missing

after day 5. After this, blood Pt concentration decreased with a biphasic curve during the three days of the study (Fig. 1, see also pharmacokinetics section).

There was a decrease in Pt peak values in urine throughout the study (days 3 or 3 and 5). Only in 1 out of 7 patients an unexpected increased value was found on day 5 (Table 2). The rapid peak was followed by a slower excretion rate which decreased slightly from day 1 to day 5.

On days 1 and 3 there was a significant correlation between the mean urine Pt concentration and mean plasma Pt levels (day 1: r = 0.903, p < 0.02; R = 1, p < 0.001; day 3: r = 0.9770, p < 0.001; R = 1, p < 0.001; day 5: r = 0.6324, R = 65, p = n.s.).

Pharmacokinetic analysis

The F-test [11] indicated that a biexponential function provides a more appropriate fitting to experimental data. This model was therefore adopted. The mean values of some major pharmacokinetic parameters for days 1, 3 and 5 of CDDP infusion are reported in Table 3.

The decline of plasma concentration of total Pt after CDDP infusion showed a rapid initial phase and a prolonged second phase (biphasic pattern, see Fig. 1). The half-life ranged from 8.28 min (day 1) to 20.3 min (day 5) for the rapid phase (paired t and Wilcoxon test p < 0.05). The half-life for the slow phase decreased from the day 1 (8.22 h) to the day 5 (7.04 h) (difference n.s.).

Cl of Pt decreased in all patients from a mean of 6.92 l/h on the day 1 to 2.58 l/h on the day 5 (paired t test p < 0.01; Wilcoxon test p < 0.03). Also Clp decreased from 13.92 l/h to 5.87 l/h (paired t and Wilcoxon test p < 0.01 and p < 0.03, respectively).

AUC was significant higher in all patients on the day 5 of therapy vs the day 1 (paired t and Wilcoxon test p < 0.01 and p < 0.03, respectively). Also V2 significantly decreased on the days 3 and 5 of infusion vs the day 1 (paired t test p < 0.01 and Wilcoxon test p < 0.02).

Blood and urine chemistry

Only one patient showed an increase in serum creatinine above the normal range (1.84 mg/dl) on the last day of therapy and a further enhancement three days later (2.84 mg/dl). For the other patients data on serum creatinine during the five days of treatment and three days later showed a trend to increase: the mean creatinine level before treatment was 0.84 ± 0.03 mg/dl, while on day 8 post-treatment it was 1.4 ± 0.25 mg/dl with a significant increase from basal and day 1 levels (paired t test p < 0.05 and Wilcoxon test p < 0.02). A decrease in diuresis was also found on day 5 (paired t test p < 0.01 and Wilcoxon test p < 0.02) (Table 2).

A comparative analysis between the changes in pharmacokinetic and blood or urine chemistry values (Table 2) as recorded on the day 5 vs the day 1 of treatment in each patient showed the following correlations: a) the decrease in diuresis vs the decrease of Pt Cl total body (positive; r = 0.8090, p < 0.01; R = 0.7856, p < 0.02) and
Table 3. - Pharmacokinetic parameters of Pt on the days 1, 3 and 5 of therapy. Mean of 7 patients (SEM) (a)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (min) α</td>
<td>8.26</td>
<td>13.8</td>
<td>20.31</td>
</tr>
<tr>
<td></td>
<td>(1.44)</td>
<td>(5.67)</td>
<td>(4.11)**</td>
</tr>
<tr>
<td>Half-life (hours) β</td>
<td>8.22</td>
<td>5.53</td>
<td>7.04</td>
</tr>
<tr>
<td></td>
<td>(2.1)</td>
<td>(0.7)</td>
<td>(1.6)</td>
</tr>
<tr>
<td>AUC (µg/ml min)</td>
<td>15.47</td>
<td>12.16</td>
<td>31.41</td>
</tr>
<tr>
<td></td>
<td>(3.83)</td>
<td>(2.4)</td>
<td>(8.05)**</td>
</tr>
<tr>
<td>Renal clearance (l/h)</td>
<td>13.92</td>
<td>5.85</td>
<td>5.87</td>
</tr>
<tr>
<td></td>
<td>(1.81)</td>
<td>(0.99)</td>
<td>(1.33)**</td>
</tr>
<tr>
<td>Total clearance (l/h)</td>
<td>6.92</td>
<td>6.88</td>
<td>2.56</td>
</tr>
<tr>
<td></td>
<td>(2.8)</td>
<td>(1.7)</td>
<td>(0.41)**</td>
</tr>
<tr>
<td>Distribution volume (l)</td>
<td>55.79</td>
<td>30.48</td>
<td>22.71</td>
</tr>
<tr>
<td></td>
<td>(7.9)</td>
<td>(5.6)**(d)</td>
<td>(2.6)**</td>
</tr>
</tbody>
</table>

(a): statistical analysis vs day 1 was performed using the paired-t test (*) and Wilcoxon matched pairs signed rank test (\(\star\))
\(\star\) p < 0.05; \(\star\) p < 0.01; \(\star\) p < 0.05; \(\star\) p < 0.03; \(\star\) p < 0.02

vs the cumulative dose of CDDP (positive R = 0.9266, p < 0.003), b) the increase in creatinine serum level vs the decrease of Pt Cl₉ (positive; \(r = 0.6590, p < 0.05\); \(R = 0.6847, p < 0.05\)) and vs urine Pt peak concentration (negative; \(r = -0.6634, p < 0.05\)), and c) the urine Pt peak concentration vs the decrease in Pt Cl₉ (negative; \(R = -0.7945, p < 0.01\); \(R = -0.6786, p < 0.05\)).

All other parameters considered (BUN; sodium, potassium and chlorine levels in plasma and urine; fractionated excretion of sodium) were within the normal range and did not show significant variations during the five days of treatment.

There was an improvement of the patients' clinical condition 6 weeks after the treatment (Table 1; Wilcoxon test p < 0.05).

Discussion

The dose has been shown to be a critical factor in cancer chemotherapy [11] and retrospective studies have suggested the importance of dosage of CDDP for treatment outcome [12]. The aim of the present study was to assess the pharmacokinetics of a very high dose (200 mg/m²) of CDDP in patients previously treated with the drug at the conventional dose and to evaluate these data against laboratory procedures which are usually applied in the clinical monitoring of patients.

Some Authors [13-15] reported in humans and animals a triexponential decrease with \(α, β\) and \(γ\) phase of 1.4-3.0 min, 10-16 min and 40 h, respectively. In our study plasma concentrations of total Pt decreased biphasically.

Our failure to detect an early \(α\) phase may be ascribable to the experimental protocol used for sample collection. On the other hand, a different mechanism may be hypothesized which is dependent on a different clinical schedule, i.e., we did not administer CDDP in bolus, but

Fig. 1.- Mean (+ SEM) of Pt plasma concentration in the seven patients measured over a 180 min period after the infusion of CDDP on the days 1, 3 and 5 of treatment. The arrow indicates completion of infusion.
by slow infusion during 30 min, which may have yielded results different from those described in the literature. In any case, it is worth noting that the mathematical model we used gave the best fitted curve to experimental points. Our $t_{1/2} \alpha$ of 8.28 min (day 1) and 20.3 min (day 5) are in accordance with those reported by other authors [16, 17], while $t_{1/2} \beta$ values (8.22 h, 7.04 h) were shorter than those described in the same previous reports (58-96 h). Plasma levels of total Pt were still detectable in all patients 24 h post-infusion (0.85 μg/ml on day 3; 1.7 μg/ml on day 5), suggesting that $t_{1/2} \beta$ half-life may be longer than the one we determined. Our results may be attributable to the short interval we used (3 h). Therefore, further calculation was performed, i.e. simulated levels were added at 24 h between 0 and the baseline before the following treatment. Thus, $\beta$ half-life on the day 1 reached values of 55.25 h or 14.64 h according to reduced level at 2/3 or 1/3 of the day 3 baseline value, respectively. The analogous values with the same model applied to the day 3 were 221.85 h and 17.30 h, respectively.

The accumulation of total plasma Pt in the five days regimen might be responsible for the significant increase of $\alpha$ half-life. On the other hand, we cannot exclude that sudden alterations in the mechanisms of CDDP excretion, either in glomerular filtration or in renal tubular secretion, may have determined such an increase.

AUC values of Pt were enhanced during the day of treatment, thus suggesting an increasing exposure of the patients to CDDP, which might mean a higher degree of efficacy and/or toxicity of the drug [18, 19]. No relationship was found between the peak of total Pt in plasma and AUC, which could be underestimated as a result of having measured Pt only at the end and not during the infusion.

Also other kinetic parameters showed significant variations from the day 1 to the day 5 of treatment. In particular, the CI and CIk of Pt were significantly reduced, suggesting that Pt is cleared more slowly at the end than at the beginning of this therapeutic schedule. Furthermore, during the last day of treatment the correlation between mean urinary Pt concentration and mean plasma level was not significant, suggesting a possible modification in the renal function. These observations support the assumption that CDDP-induced damage to the kidney occurs during the first hours after administration [20-22], because the drug may alter glomerular filtration, perhaps through vascular changes [23].

All pharmacokinetic parameters presented in this report were calculated on the basis of total Pt, while the biological activity and toxicity have usually been attributed to the free fractions of Pt. Recent data, however, suggest that protein-bound CDDP may be able to react with nucleophiles. Toxicity may also be enhanced by low levels of free Pt as a result of release from plasma proteins or tissue compartments [24, 25]. Anyway, kinetics of free Pt seems to be strictly related to bound Pt [26], and our data show also that bound Pt pharmacokinetics is related to renal function. These observations indirectly enforce the reliability of our results.

As far as nephrotoxicity of CDDP is concerned, some hypotheses can be forwarded on the renal alterations suffered by our patients. Although plasma creatinine and/or creatinine clearance cannot be considered reliable indicators of the glomerular function (particularly in patients with neoplasia to which malnutrition or muscular atrophy are sometimes associated), they are usually applied in the clinical practice and in most clinical studies concerning CDDP-induced nephrotoxicity. All patients but one showed serum creatinine levels within the normal range during the whole period of observation, but after the end of therapy (on the days 5 and 8) there was an overall significant increase (though still in the normal range) as compared with baseline and day 1 values (p < 0.05) (Table 2). Potential creatinine clearance variations were calculated using the Cockcroft and Gault’s formula [27], assuming that no muscular damage or changes in the nutritional status of patients occurred throughout the five day period of CDDP treatment. Results showed that a reduction in this “calculated” creatinine clearance occurred from days 1 and 3 (78.1 ± 7.8 and 71.0 ± 6.1 ml/min, respectively) to days 5 and 8 (63.5 ± 9.6 and 43.9 ± 9.1 ml/min, respectively). Wilcoxon test and paired t-test showed statistical significance only on the days 5 and 8 vs pretherapy values, both measured and calculated (p < 0.03), and vs day 1 values (p < 0.02). This has led us to speculate that at least on the day 5 of treatment renal damage due to treatment may occur, which lasts more than three days after CDDP withdrawal.

The second objective of this study was to evaluate the possible correlations of Pt pharmacokinetics and toxicity. A correlation between Pt pharmacokinetic data and some renal parameters (calculated as the difference between the values of the days 5 and 1 of treatment) was also found. The increase in creatinine was directly related to a reduction of Pt renal clearance and inversely related to Pt peak level in urine, and this latter parameter was inversely related to renal clearance of Pt. From these data it is therefore apparent that early (even if mild) symptoms denoting a trend towards kidney function damage are indicative of alterations in Pt kinetics in the same patient. This could suggest that simple laboratory evaluations might be useful indicators of the kidney function during Pt therapy.

We can conclude that: 1) a high dose CDDP (40 mg/ m²/day for 5 days) was well tolerated in our patients; 2) Pt kinetics showed slight though significant modifications from the day 1 to the day 5 of treatment; 3) the renal function apparently remained within clinically normal limits, but some parameters (creatinine, creatinine clearance and urine volume) worsened.
In any case we underline that our results justified the treatment, since only two out of seven patients showed a progression of disease, whereas in two there was a complete remission and in three the disease remained stable for at least six weeks (see Table 1). The clinical results and the relationship suggested in this study between pharmacokinetics and renal parameters require further investigation with a larger population and longer periods of follow-up, in order to assess whether a recovery of the baseline in the parameters of the renal function occurs. Other studies [28] have reported that a certain recovery may occur, especially if damage is not severe, as it was the case of our patients.

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