Inductively Coupled Plasma Mass Spectroscopy Quantitation of Platinum-DNA Adducts in Peripheral Blood Leukocytes of Patients Receiving Cisplatin- or Carboplatin-based Chemotherapy

Andrea Bonetti, Piero Apostoli, Marta Zaninelli, Flavia Pavanel, Marco Colombatti, Gian Luigi Cetto, Tiziano Franceschi, Loris Sperotto, and Roberto Leone

Department of Medical Oncology, Azienda Ospedaliera and University of Verona, 37121 Verona, Italy [A. B., M. Z., F. P., G. L. C., T. F., L. S.]; Institute of Occupational Medicine, University of Brescia, 25121 Brescia, Italy [P. A.]; and Institutes of Pharmacology [R. L.] and Immunology [M. C.], University of Verona, 37121 Verona, Italy

ABSTRACT

Platinum-DNA adducts can be assayed in peripheral blood leukocytes by means of atomic absorption spectroscopy and ELISA, and high adduct levels have been correlated previously with favorable clinical response to platinum-based chemotherapy. Our purpose was to study adduct formation in peripheral blood leukocytes by means of a new method, inductively coupled plasma mass spectroscopy (ICP-MS), and to correlate adduct formation with clinical response and toxicity.

Platinum (Pt)-DNA adducts were measured by means of ICP-MS in leukocytes of 66 patients receiving a cisplatin- or carboplatin-based chemotherapy, collected either before the beginning of treatment and incubated in vitro with cisplatin or 1 and 24 h after the administration of drug to the patient.

The Pt-DNA adduct level in leukocytes from patients exposed to drug in vitro was $14.33 \pm 14.71$ fmol/µg DNA (mean ± SD), which was not significantly different from the value of $23.4 \pm 19.53$ fmol/µg DNA observed in leukocytes from nine healthy volunteers. In samples collected after the administration of chemotherapy, Pt-DNA adducts ranged from $1.91 \pm 3.59$ fmol/µg DNA (mean ± SD) at the 1-h time point to $2.61 \pm 3.35$ fmol/µg DNA at 24 h ($P > 0.05$). Adduct levels in leukocytes exposed in vitro did not correlate with adduct levels from patients treated with cisplatin-based chemotherapy ($r = 0.085$ and 0.011 at 1 and 24 h, respectively). At 24 h, adduct levels in patients receiving cisplatin ($3.15 \pm 3.64$ fmol/µg DNA, mean ± SD) were significantly higher ($P = 0.02$) than those observed in patients treated with standard dose carboplatin ($0.57 \pm 0.73$ fmol/µg DNA) and also higher than those in patients receiving high-dose carboplatin ($1.18 \pm 1.06$ fmol/µg DNA), although the latter difference did not reach statistical significance ($P = 0.071$).

No differences in adduct levels (mean ± SD) were evident between patients responsive ($3.23 \pm 3.51$ fmol/µg DNA) and nonresponsive ($2.34 \pm 3.01$ fmol/µg DNA) to chemotherapy. In the homogeneous group of patients treated with combination of cisplatin and 5FU, received dose intensity, hemoglobin decrease, and posttreatment creatinine could not be linked with the extent of leukocyte adduct formation.

The data presented here demonstrate that ICP-MS allows the detection of adducts in patients treated with cisplatin or carboplatin and suggest that adduct formation in leukocytes is not a major determinant of response or toxicity.

INTRODUCTION

Cisplatin and the analogue carboplatin are antineoplastic agents with demonstrated activity in different types of cancer, particularly testicular, ovarian, lung, head and neck, and bladder cancers (1). However, for the majority of these cancers, with the notable exception of germ cell tumors, the proportion of responding patients is usually small; therefore, the identification of a marker that would predict the response to chemotherapy could be useful.

After intracellular acquisition, cisplatin and carboplatin form intra- and interstrand adducts in DNA (2). Pt$^{3+}$-DNA adduct levels in normal tissues and in tumors can be determined by means of immunochemical methods (3–5) or by AAS (6).

Previous reports link the Pt-DNA adduct levels in peripheral blood leukocytes collected from patients receiving cisplatin- or carboplatin-based chemotherapy with the clinical activity of the two drugs, and the suggestion has been made that the level of Pt-DNA adduct formation in leukocytes could be a marker of chemosensitivity (3, 7–10). Furthermore, a correlation has been reported between adduct formation in leukocytes collected from treated patients and adduct formation in in vitro cisplatin-treated leukocytes, thus suggesting the possibility that the rate of adduct formation in vitro could help in predicting the response to chemotherapy (11, 12). A similar conclusion was reached when

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2 To whom requests for reprints should be addressed, at Department of Medical Oncology, Azienda Ospedaliera di Verona, P.le Stefani 1, 37121 Verona, Italy. Phone: 39 45 8072351; Fax: 39 45 8341277.

The abbreviations used are: Pt, platinum; AAS, atomic absorption spectroscopy; ICP-MS, inductively coupled plasma mass spectroscopy; 5FU, 5-fluorouracil; DI, dose intensity; AUC, area under the curve of concentrations over time; CI, confidence interval.
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the DNA damage in leukocytes was determined by the PCR-
stop assay (13).

In the present study, Pt-DNA adducts were measured in
leukocytes from treated patients and in leukocytes collected
before the administration of drugs, and incubated in vitro with
cisplatin to confirm in a large cohort of patients the hypothesis
that there is a correlation between leukocyte adduct formation in
vivo and in vitro and between leukocyte adduct formation and
response and toxicity.

A new method for the assay of Pt-DNA adducts was used:
ICP-MS. ICP-MS is a powerful analytical technique for the
determination of trace and ultra-trace amounts of elements in
biological samples (14). The instrumentation is comprised of an
inductively coupled plasma (normally an argon plasma) used as
an ion source and a quadrupole mass spectrometer for ion
detection and quantification. Because the inductively coupled
plasma works at atmospheric pressure and the mass spectrom-
ter requires a vacuum better than 10−5 millibars, an interface is
placed between the two components. The ICP-MS method of
measurement has several advantages for trace element determi-
nation: simultaneous multielement determinations; excellent de-
tection limits, in particular for elements such as platinum; wide
linear dynamic range; and high sample throughput.

MATERIALS AND METHODS

Patient Selection and Treatment Schedule. Forty-nine
men and seventeen women ranging in age from 22 to 72 years
(median age, 54) gave informed consent to participate in this
study between January 1, 1994, and December 31, 1995. Patient
characteristics are listed in Table 1. Clinical staging was based
on a complete history, physical examination, a routine biochem-
ical profile, a complete blood cell count, and the results of
imaging procedures for all patients before the beginning and
after three cycles of chemotherapy. Response and toxicity were
evaluated according to standard WHO criteria (15).

Entry criteria included a pathologically confirmed diagno-
sis of cancer; serum creatinine <1.14 μM, blood urea nitrogen
<14 mg/dL, leukocyte count >3,000 cells/μL, platelet count
>100,000/μL, hemoglobin >9 g/dL, and adequate hepatic func-
tion (total bilirubin <26 μM; transaminases less than two times
upper limit of normal); no evidence of cardiomegaly on chest
X-ray; clinically normal hearing; life expectancy >3 months;
and an Eastern Cooperative Oncology Group performance status
≤2. If patients had received cisplatin previously, they must
never have suffered cisplatin-induced nephrotoxicity (peak crea-
tinine >195 μM) or disabling neurotoxicity.

Cisplatin was administered at the dose of 100 mg/m² as a
single bolus (1-h infusion in 3% sodium chloride with pre- and
posthydration) in combination with: 5FU 1000 mg/m²/day as a
continuous infusion over 5 consecutive days (head and neck,
esophageal, and colon cancer patients); or vinblastine 6 mg/m²
and mitomycin C 10 mg/m² (non-small cell lung cancer pa-
tients); or cyclophosphamide 1000 mg/m² single agent, or cy-
clophosphamide 500 mg/m² and doxorubicin 50 mg/m² (ovarian
cancer patients). Patients with testicular cancer received cispla-
tin 20 mg/m² (1-h infusion in 3% sodium chloride with pre- and
posthydration) on days 1–5 in combination with weekly bleo-
mycin (30 units) for 12 weeks and etoposide 100 mg/m² on days
1–5.

Standard-dose carboplatin (300–400 mg/m²) was admin-
istered as a single dose in 5% dextrose in water over 1 h, either
alone or with cyclophosphamide 600 mg/m² (ovarian cancer
patients), or in combination with doxorubicin 50 mg/m² and
etoposide 100 mg/m² on days 1–3 (cancer of unknown primary).
High-dose carboplatin (300 mg/m² in 5% dextrose in water over
1 h on days 1–4) was given in combination with ifosfamide 12
mg/m² (with mesna as a uroprotector) and etoposide 1200 mg/m²
over 4 consecutive days.

Planned and received DIs were calculated by the method of
Hryniuk and Bush (16); received DI was expressed as percent-
age of the planned DI. The effectively received carboplatin
AUC was determined by dividing the administered carboplatin
dose by the carboplatin clearance, calculated according to Chat-
elut's (17) formula: 0.134 × weight × (1 −
0.00457 × age) × (1 − 0.314 × sex)/creatinine expressed in
micromolar concentration (with weight in kilograms, age in
years, and sex = 0 if male and sex = 1 if female).

The analysis of toxicity and of received DI was performed
for all the cisplatin-based cycles but will be reported here only
for the patients treated with the cisplatin–SFU combination.

Blood Sample Collection. Thirty ml of blood were col-
lected by venipuncture in syringes containing heparin sodium
before the beginning of treatment and at 1 and 24 h after the end
of infusion of cisplatin (or carboplatin), during the first cycle of
chemotherapy. Immediately after the collection, blood was lay-
ered in three 50-ml tubes containing 10 ml of hystopaque-1119
and 10 ml of hystopaque-1077 (10 ml of blood in each tube),
and then centrifuged at 700 × g for 30 min. Leukocytes were
collected and washed twice in PBS solution (pH 7.4); the
supernatant was removed, and the pellet was frozen at −20°C

Table 1 Characteristics of patients (n = 66)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>49</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td>Age (year) Median</td>
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<tr>
<td>Age (year) Range</td>
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<td>Diagnosis</td>
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<tr>
<td>Esophageal cancer-head and neck cancer</td>
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<tr>
<td>Lung cancer (NSCLC)</td>
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<tr>
<td>Ovarian cancer</td>
<td>8</td>
</tr>
<tr>
<td>Cancer of unknown primary</td>
<td>7</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>6</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
</tr>
<tr>
<td>Cisplatin-based chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Cisplatin-SFU</td>
<td>28</td>
</tr>
<tr>
<td>Cisplatin-vinblastine-mitomycin</td>
<td>7</td>
</tr>
<tr>
<td>Cisplatin-etoposide-bleomycin</td>
<td>5</td>
</tr>
<tr>
<td>Cisplatin-cyclophosphamide</td>
<td>3</td>
</tr>
<tr>
<td>Cisplatin-cyclophosphamide-adriamycin</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
</tr>
<tr>
<td>Carboplatin-based chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Low-dose (AUC 3–6 mg · min/mL)</td>
<td>10</td>
</tr>
<tr>
<td>High-dose (AUC 12–18 mg · min/mL)</td>
<td>6</td>
</tr>
</tbody>
</table>

* NSCLC, non-small cell lung cancer.
The lowest detection limit was 0.1 μg/liter for ICP-MS and 10 μg/liter for AAS.

**Determination of Pt-DNA Adducts.** DNA samples were analyzed for their Pt content by ICP-MS using an Elan 5000 Perkin-Elmer Sciex. Total Pt was determined by a quantitative method after dilution of the DNA samples in 2 ml of a 0.1% Triton solution in H₂O (Sigma). Standard curves were generated by using aqueous serial dilutions of a stock of H₂PtCl₄·H₂O in 10% hydrochloric acid (SPEX Industries, Inc., Edison, NJ). Measurements were made as the integrated value of ion number in an analysis time of 3 min. Pt-DNA adduct levels were calculated as femtomoles of elemental Pt per microgram of cellular DNA (fmol Pt/μg DNA). The lowest limit of detection of the assay was 10 pg of elemental Pt; the coefficients of variation ranged from 1 to 3% (intraassay) and from 5 to 10% (interassay). Fig. 1 compares standard curves for ICP-MS and atomic absorption spectroscopy.

**Statistical Analysis.** Unless stated otherwise, the significance of the differences between experimental data was tested with Student’s t test.

**RESULTS**

Two hundred-five cycles of chemotherapy were administered over the course of this study. Fifty patients received 156 cisplatin-based cycles; 10 patients received 40 carboplatin-based cycles, given at the standard target AUC of 3–6 mg-min/ml; the remaining six patients received nine high-dose regimens containing carboplatin given at the target AUC of 12–18 mg-min/ml.

Fig. 1 Standard curves for platinum determination by ICP-MS and by AAS. The lowest detection limit was 0.1 μg/liter for ICP-MS and 10 μg/liter for AAS.

In Vitro Cisplatin Treatment of Blood Samples. To study the in vitro formation of Pt-DNA adducts, leukocytes collected from 45 patients before the beginning of chemotherapy were incubated in vitro at 37°C for 2 h in RPMI 1640 containing cisplatin at a concentration of 15 μg/ml. After the incubation period, the cells were washed, and DNA was isolated, then treated following the steps described above. Pt-DNA adduct formation in vitro was also evaluated in leukocytes collected from nine healthy volunteers.

Leukocyte Pt-DNA adduct levels ranged from 1.91 ± 3.59 fmol Pt/μg DNA (mean ± SD; 95% CI = 0.81–3.01) at the 1-h time point after the first cycle of chemotherapy. Pt-DNA adducts were undetectable in 11 samples of the earlier time point (27%) and in 13 samples of the second time point (22%), giving a 24% overall incidence of samples below the detection limit of the method. The levels were undetectable at both time points in three patients treated with carboplatin and in three treated with cisplatin.

Leukocyte Pt-DNA adduct levels ranged from 1.91 ± 3.59 fmol/μg DNA (mean ± SD; 95% CI = 0.81–3.01) at the 1-h after chemotherapy time point to 2.61 ± 3.35 fmol/μg DNA (mean ± SD; 95% CI = 1.76–3.46) in samples collected at 24 h after chemotherapy (P > 0.05). With both drugs, plasma levels were higher, although not statistically different, at 24 h.

**Fig. 2** Pt-DNA adducts in leukocytes from patients (n = 66) treated with platinum-based chemotherapy. Dotted line represents the lowest limit of detection. Each data point represents a separate leukocyte sample (samples at 1 h = 41; samples at 24 h = 60). ———, median.
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were found in Pt-DNA adduct levels between leukocyte from
patients (mean SD = 14.33 14.71 fmol/μg DNA; 95% CI = 10.03–18.63) and healthy volunteers (mean SD = 23.4 ± 19.53 fmol/μg DNA; 95% CI = 7.12–31.94).

In patients receiving cisplatin-based chemotherapy, there was no correlation between adduct levels at 1 h (n = 29) or at 24 h (n = 29) and the level of adduct formation in vitro (r = 0.085 and 0.011, respectively).

Fig. 4 shows Pt-DNA adduct levels in leukocytes collected 24 h after chemotherapy as a function of the type of platinum analogue administered (cisplatin or carboplatin) and, in the case of carboplatin, with the effectively received AUC (4.6 ± 1.2 and 14.4 ± 2.3 mg·min/ml in the standard and in the high-dose groups, respectively). The value of adducts in patients treated with cisplatin (mean SD = 3.15 ± 3.64 fmol/μg DNA; 95% CI = 2.1–4.2) was significantly higher (P = 0.02) than that observed in patients treated with standard dose carboplatin (mean SD = 0.57 ± 0.73 fmol/μg DNA; 95% CI = 0.22–1.24), and was also higher than the adduct levels in the high-dose carboplatin group (mean SD = 1.18 ± 1.06 fmol/μg DNA; 95% CI = 0.21–1.91), although this latter difference did not reach statistical significance (P = 0.071). Furthermore, the increase in Pt-DNA adduct levels in the patients receiving high-dose carboplatin was not proportional to the increased AUC.

The association between response to chemotherapy and adduct levels at 24 h was investigated in 48 patients. From the analysis were excluded the six patients treated with high-dose carboplatin, six with germ cell tumors, and six patients who were inevaluable because the treatment was administered in an adjuvant setting (n = 2) or because of early loss to follow-up (n = 4). Overall, 20 responses were observed (42%; complete response, 5; partial response, 15). Although responsive patients showed a higher adduct level than patients showing disease stabilization or progression, the difference was not significant (Table 2).

Finally, the toxicity of treatment (hemoglobin decrease, peak creatinine) and the received DI were evaluated for the homogeneous group of patients treated with the combination cisplatin-5-FU, the majority of whom (25 of 28; administered cycles, 76) had evaluable adduct levels at 24 h. In this subset of patients, the median adduct level at 24 h (1.97 fmol/μg DNA) was chosen as a cutoff to separate two groups with low and high adduct formation. As shown in Fig. 5, no differences were observed between the two groups in terms of received DI, posttreatment creatinine, and hemoglobin decrease.

**DISCUSSION**

In this study, the quantitation of Pt-DNA adducts in peripheral blood leukocytes of patients receiving a cisplatin or carboplatin-based chemotherapy was performed by ICP-MS. This method gave a good reproducibility and was about 100 times more sensitive than standard AAS in detecting Pt-DNA adducts (Fig. 1). This is in agreement with two published papers focusing on the use of ICP-MS for the determination of Pt in biological samples such as blood (18), urine, and tissue specimens (19). The sensitivity of the ICP-MS allowed the detection of adducts in 76% of the samples. The percentage of samples below the detection limits of the different methods is rarely reported in the literature; we found this important information only in a paper by Reed et al. (3), who used a very sensitive ELISA method and found detectable Pt-DNA adduct levels in 37% only of the samples.

In previous studies, Pt-DNA adducts in peripheral blood leukocytes have been determined by ELISA (3, 5, 7), AAS
Fig. 5  Mean of received DI, posttreatment creatinine, and hemoglobin decrease in patients treated with the combination cisplatin-5FU. □, patients (n = 12) with Pt-DNA adducts =1.97 fmol Pt/µg DNA; ■, patients (n = 13) with Pt-DNA adducts >1.97 fmol Pt/µg DNA. Bars, SD.

Table 3  Published studies evaluating platinum-DNA adducts formation in leukocytes and tumor response to platinum-based chemotherapy

<table>
<thead>
<tr>
<th>First author (reference)</th>
<th>Tumor type</th>
<th>No. of patients</th>
<th>Method of assay</th>
<th>Correlation Adducts/Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed et al. (3)</td>
<td>Testis and ovary</td>
<td>45</td>
<td>ELISA</td>
<td>Positive</td>
</tr>
<tr>
<td>Reed et al. (7)</td>
<td>Ovary</td>
<td>55</td>
<td>ELISA</td>
<td>Positive</td>
</tr>
<tr>
<td>Parker et al. (8)</td>
<td>Different types</td>
<td>21</td>
<td>AAS</td>
<td>Positive</td>
</tr>
<tr>
<td>Reed et al. (9)</td>
<td>Different types</td>
<td>49</td>
<td>AAS</td>
<td>Positive</td>
</tr>
<tr>
<td>Schellens et al. (10)</td>
<td>Different types</td>
<td>45</td>
<td>AAS</td>
<td>Positive</td>
</tr>
<tr>
<td>Motzer et al. (22)</td>
<td>Testis</td>
<td>36</td>
<td>ELISA</td>
<td>Negative</td>
</tr>
<tr>
<td>Gupta-Burt et al. (23)</td>
<td>Ovary and breast</td>
<td>52</td>
<td>ELISA</td>
<td>Positive*</td>
</tr>
</tbody>
</table>

* Only in patients with ovarian cancer.

(8–10, 20, 21), or both (22, 23). Mean adduct values determined by AAS are usually in the range 5–500 fmol/µg DNA, about one to two orders of magnitude higher than in the present study. However, because the patients studied differ in terms of several variables, such as the type of administered chemotherapy, the doses of cisplatin, and the procedures followed for DNA isolation, it is impossible to make a direct comparison with the already published adduct values. Particularly, it has been demonstrated that the isolation of leukocytes done immediately after the blood collection (procedure followed in this study) leads to the determination of significantly lower adduct levels than the isolation of leukocytes done after thawing frozen whole-blood samples (21).

It is well known that the kinetic of reaction of carboplatin with DNA is slower than that of cisplatin (2, 24), and this observation can explain the lower level of adducts observed at 24 h in patients who received carboplatin compared with cisplatin-treated patients. In carboplatin-treated patients, the difference in adduct levels did not parallel the difference in the target AUC. Although this observation needs to be confirmed in a larger group of patients, it might suggest the utility of studying the formation of Pt-DNA adducts in the high-dose setting to help adjust the dose based on drug-DNA interactions rather than on plasma AUC.

A correlation between Pt-DNA adduct formation in leukocytes incubated in vitro with cisplatin and in leukocytes collected from treated patients, measured by an ELISA method, has been reported previously (11, 12), but is not confirmed in the present study, which involves a larger group of patients. This discrepancy could be due to several factors, such as the procedure of in vitro treatment (i.e., incubation of whole blood instead of isolated leukocytes), the different assay method, or the selection of the patients.

No differences in adduct levels were evident between patients responsive and nonresponsive to chemotherapy. The correlation between adduct levels in leukocytes and response to chemotherapy has been reported either as positive (3, 7–10), as lacking (22), or as limited only to patients with ovarian cancer who had adducts assayed by ELISA (23) by previous investigators (Table 3). These discrepancies could be due to the different types of tumors studied (which are likely to show different degrees of sensitivity to the platinum drugs with conceivably different thresholds of response), to the confounding factor of the other drugs used in the combinations, or to the fact that leukocyte adduct formation simply does not parallel adduct formation in tumors. Regarding this last aspect, data linking adduct formation in tumor samples and in normal tissues come only from autopsy studies (6, 25, 26), and it was these studies that raised the question of whether there were pharmacogenetic properties shared by tumors and normal tissues of a given...
individual. However, this point of view is not generally accepted, and data from different clinical situations (e.g., the lack of correlation between the distribution of O6-alkylguanine alkyltransferase in tumor samples and in leukocytes) argue against this hypothesis (27). Furthermore, no data are available regarding the possible correlation between adduct formation in tumor samples from Pt-treated patients and the response to chemotherapy. Surprisingly, Pt-DNA adduct levels in blast leukocytes, collected from patients with acute nonlymphocytic leukemia and incubated in vitro with cisplatin, were inversely correlated to the remission rate, regardless of whether the patients received carboplatin as a component of the treatment (28).

In patients treated with the cisplatin-5FU combination, no differences in renal toxicity, hemoglobin decrease, and received dose intensity were observed in the two groups of patients having either a high or low level of adduct formation. This fact might be due to the well-known differences in tissue distribution of cisplatin (29, 30), with leukocytes giving only a very limited representation of cisplatin action. In the present study, WBC nadirs were not regularly evaluated, and, therefore, it was not possible to assess differences in the degree of myelosuppression as a function of adduct formation. Furthermore, the adducts’ removal during the treatment, rather than the adduct levels measured on the first cycle, may be more closely linked to leukocyte toxicity (31).

In conclusion, in this paper we have shown that ICP-MS allows the determination of Pt-DNA adducts in leukocytes of patients treated according different doses and schedules of cisplatin and carboplatin combination chemotherapy. The lack of correlation of adduct levels with response and toxicity in this consistent group of patients supports the view that the handling of Pt drugs in leukocytes is very much different from that observed in other normal tissues and in tumors. Therefore, the determination of adduct levels in leukocytes does not enable one to predict the response and the toxicity to Pt-based chemotherapy.

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