Comparative Activity and Distribution Studies of Five Platinum Analogues in Nude Mice Bearing Human Ovarian Carcinoma Xenografts

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ABSTRACT

The antitumor activity of four new platinum analogues was compared at equitoxic doses to that of cisplatin in B10 LP/cpb nude mice bearing xenografts of human ovarian carcinomas. The two tumor lines used, MRI-H-207 and Pe, differ in histology, tumor doubling time, and sensitivity to cisplatin.

Complete remission of MRI-H-207 was observed with cisplatin, carboplatin, iproplatin, and JM-40, while spiroplatin only gave growth delay. Cisplatin and carboplatin caused some growth delay of Pe, while JM-40, spiroplatin, and iproplatin failed to affect tumor growth.

Platinum tissue distribution was also measured for each compound in groups of five to seven tumor-bearing mice. Platinum concentrations in the two tumors at 24 hr were similar for cisplatin and carboplatin, but differed for iproplatin, spiroplatin, and JM-40. Organ distribution was similar for each analogue, and concentrations were significantly higher in kidneys than in liver, except for iproplatin with comparable concentrations in these organs.

Our findings show a good correlation between analogue activity in ovarian cancer in the clinic and that in MRI-H-207. Platinum concentrations in tumor tissue did not predict antitumor activity.

INTRODUCTION

Cisplatin has proven to be effective in a variety of human cancers including ovarian cancer. However, toxic side effects may restrict its clinical use (16). Numerous analogues have been synthesized in a search for alternative active compounds with reduced toxicity. An additional criterion in analogue development is the lack of cross-resistance to cisplatin (2).

A number of transplantable rodent tumors has been used for selection of platinum analogues with a potentially improved therapeutic index (3, 18, 21, 18). Toxicity studies include myelosuppression and renal damage (8, 18, 19). These approaches have led to the introduction of several analogues into the clinic (1, 4–6, 15, 22, 26, 27). Screening of antitumor activity in nude (athymic) mice or artificially immune-deficient mice bearing human xenografts is potentially useful to obtain information on the activity of new drugs in specific tumor types (7, 20, 24).

We evaluated the activity of cisplatin and 4 platinum analogues, which were recently introduced in the clinic, in 2 human ovarian carcinoma tumor lines grown in nude mice in an attempt to assess the predictive value of these models. In a second experiment, we analyzed platinum concentrations in mouse serum and tissues to obtain information about distribution of the drugs to evaluate the predictive value of this parameter for experimental antitumor activity and clinical organ toxicity. The data suggest that MRI-H-207 is a good model for selection of platinum analogues for clinical evaluation in ovarian cancer. Organ platinum concentration does not predict either antitumor activity or organ toxicity.

MATERIALS AND METHODS

Animals. Female congenitally athymic nude mice, homozygous for the nu/nu allele, of the B10 LP/cpb strain (TNO, Zeist, The Netherlands), were maintained in isolation in cages with paper filter covers. Cages, covers, bedding, food, and water were changed and sterilized weekly. Animal handling was done in a laminar down-flow hood.

Tumor Lines. Tumor fragments with a diameter of 2 to 3 mm were transplanted s.c. into the flanks of 8- to 10-week-old nude mice. The 2 tumor lines, MRI-H-207 and Pe, used in these experiments originated from patients with advanced ovarian carcinoma. MRI-H-207 kindly provided by Dr. A. E. Bogden, Mason Research Institute, Worcester, MA, is an undifferentiated human (adenocarcinoma) carcinoma with a doubling time of 3 to 5 days which was studied in passages 22 to 26. A volume of 2x10^6 cells was reached within 16 to 20 days after transplantation. Pe is a moderately differentiated mucinous adenocarcinoma with a doubling time of 15 to 20 days. This tumor was xenografted in our laboratory and was used in passages 6 to 8. A volume of 5x10^6 cells was reached within 40 to 50 days after transplantation. During serial transplantation, the tumors maintained their original histological appearance, while the pattern of human lactase dehydrogenase isoenzymes persisted in tumor supernatants. Pe has consistently been producing carcinoembryonic antigen. MRI-H-207 is a cisplatin-sensitive tumor, while in Pe cisplatin causes some growth delay. Tumor take for both lines approaches 90 to 100%.

Treatment and Evaluation of Chemotherapeutic Effect. Besides cisplatin, the following platinum analogues were studied: carboplatin, JM-40, iproplatin, and spiroplatin (Chart 1). Cisplatin (Platinol; Bristol Myers, Weesp, The Netherlands) and JM-40 (Johnson Matthey, Reading, United Kingdom) were dissolved in H2O. Carboplatin and iproplatin (kindly provided by Dr. Ken Harrap, Institute of Cancer Research, Belmont, Sutton, United Kingdom) were dissolved in 0.9% NaCl. Spiroplatin (Bristol Myers, New York, NY) was diluted in 5% glucose. Equitoxic i.v. doses of the single agents were given weekly according to the maximum tolerated doses for this particular schedule.

At this maximum tolerated dose, the mice were allowed a weight loss of 5 to 10% in the first week. Mice bearing MRI-H-207 received 2 injections (except for spiroplatin), while Pe-bearing mice received a total of 3 injections. Dosages were as follows: 5 mg/kg for cisplatin, 60 mg/kg for carboplatin, 40 mg/kg for iproplatin and JM-40, and 3 mg/kg for spiroplatin (for spiroplatin, a dose reduction of 2 mg/kg was necessary in the second and third week of treatment).

In each experiment, groups of 10 to 12 mice were randomized into 6 to 7 animals for treatment and 4 to 5 animals for control. At the start of treatment, all tumors had a volume of 50 to 150 cu mm. Tumors were measured weekly for Pe and biweekly for MRI-H-207 in 3 dimensions by the same observer with a slide caliper. The volume was calculated by the equation abc/2, in which a represents tumor length; b, the width;
PLATINUM ANALOGUES IN HUMAN OVARIAN CARCINOMA XENOGRAFTS

\[
\begin{align*}
\text{cisplatin} & : \begin{array}{c}
\text{NH}_3 \\
\text{Cl}
\end{array} \\
\text{carboplatin} & : \begin{array}{c}
\text{NH}_3 \\
\text{Cl}
\end{array} \\
\text{JM - 40} & : \begin{array}{c}
\text{I - C}_3 \\
\text{OH} \\
\text{Cl}
\end{array} \\
\text{iproplatin} & : \begin{array}{c}
\text{I - C}_3 \\
\text{NH}_2
\end{array} \\
\text{spiropatin} & : \begin{array}{c}
\text{NH}_2 \\
\text{Cl} \\
\text{O}
\end{array}
\end{align*}
\]

Chart 1. Structures of 5 platinum analogues used in the experiments: cisplatin, cis-diaminedichloroplatinum(II); carboplatin, cis-diamine-1,1-cyclobutanedicarboxylateplatinum(II); JM-40, cis-ethylenediaminocarboxylatoplatinum(II)malonate; iproplatin, cis-dichlorobis(isopropylamine)-trans-dihydroxyplatinum(IV); spiropatin, cis-1,1-di(aminomethyl)cyclohexaneplatinum(II)sulphate.

and c, tumor thickness, expressed in mm. Because of the variety of tumor sizes at the initiation of treatment, tumor volumes were converted to values related to the initial tumor volume. The relative tumor volume was expressed by the formula \( V_1/V_0 \), where \( V_0 \) is the tumor volume at any given time, and \( V_1 \) the volume at the initiation of treatment (7). The ratio of the mean relative tumor volume in treated mice over that in control mice multiplied by 100 was calculated at each evaluation. For each experiment, the lowest value within 5 weeks after the last injection was considered the optimal ratio. Death occurring within 2 weeks after the final injection was considered as a toxic death. Complete remission was defined as the total disappearance of the tumor without regrowth within the next 2 months.

**Platinum Analysis in Serum and Tissues.** Randomized groups of 5 to 7 tumor-bearing mice with a tumor volume of 400 to 1200 cu mm in each flank were treated with a single i.v. injection at the maximum tolerated dose for each platinum analogue. At 24 hr, each animal was bled from the axillary vein under ether anesthesia. Thereafter, kidneys, liver, brain, and tumors were removed and weighed. Tissues and serum were stored at \(-30^\circ\text{C}\). For platinum analysis in tissue, samples of 250 mg were digested with 2.5 ml of concentrated nitric acid in a Teflon bomb at \(170^\circ\text{C}\) for 2 hr. After cooling, 5 mg of \(\text{NaCl} \) were added prior to evaporation under a stream of air. The residue was resolved in 1 ml of 0.9% \(\text{NaCl} \) in 0.2 N HCL and analyzed. Serum samples were diluted 1:1 with 0.9% \(\text{NaCl} \) in 0.4 N HCL. Platinum concentrations were analyzed in the pretreated samples by flameless atomic absorption spectrometry using a Perkin Elmer Model 5000. Briefly, conditions included 40-sec drying at 110\(^\circ\text{C}\), 30-sec ashing at 1400\(^\circ\text{C}\), and 3-sec atomizing at 2650\(^\circ\text{C}\) using maximum power. Ramps were used between the steps. The carbon rod was cleaned at 2550\(^\circ\text{C}\) for 5 to 7 sec before the next sample was introduced. Standards consisting of blank serum and tissues spiked with platinum were treated in the same way as the samples.

**Statistics.** Antitumor activity of platinum analogues and the differences in platinum concentration in tumor tissues were evaluated by Student's t test.

**RESULTS**

**Antitumor Activity of the Platinum Analogues.** The antitumor effect of each analogue for MRI-H-207 and Pe is shown in Chart 2, A to K, and Table 1. JM-40 was the only drug studied at 2 dosages. In MRI-H-207 complete remissions were achieved with cisplatin, carboplatin, iproplatin, and JM-40 (40 mg/kg). The tumors increased in size following treatment with spiropatin, while a complete remission could be achieved thereafter with 2 additional doses of cisplatin, 5 mg/kg i.v. (not indicated in Chart 2J). In some animals treated with iproplatin, there was a small remnant which repeatedly appeared to consist of fibrous tissue on histological examination. Comparison of the efficacy of the drugs in Pe-bearing mice showed moderate activity for cisplatin and carboplatin and minimal activity for iproplatin and JM-40 (40 mg/kg), while spiropatin was not active at all. Overall efficacy of the platinum analogues was more pronounced in MRI-H-207 (4 complete remissions) than in Pe (only 2 significant differences between treated and control animals; \(p \leq 0.05\)).

For each analogue, lower doses resulted in lower efficacy. At necropsy, the liver and kidneys of animals treated with the maximum tolerated dose of each analogue did not show specific histological changes.

**Platinum Organ and Tumor Distribution.** Total platinum concentrations in serum and tissues at 24 hr after a single i.v. injection of the maximum tolerated dose of each platinum analogue are shown in Table 2. Tumor platinum concentrations did not predict drug activity. This was illustrated in experiments with JM-40 (30 mg/kg) in which no complete remission of MRI-H-207 was achieved (Table 1) despite a higher tumor platinum concentration than those observed with the maximum tolerable dose of cisplatin and carboplatin (Table 2). Similarly, higher platinum concentrations in Pe following iproplatin and JM-40 as compared to those achieved with cisplatin and carboplatin did not relate to antitumor activity. Following iproplatin, JM-40, and spiropatin treatment, platinum concentrations in Pe tumors were significantly higher than in MRI-H-207 tumors, which actually related inversely to antitumor activity.

As expected, no differences were observed in platinum distribution in organs of MRI-H-207- and Pe-bearing mice. Highest platinum concentrations were observed in liver with iproplatin, and in kidneys with JM-40 (40 mg/kg) and iproplatin. A low platinum concentration was detected in the brain following all analogues except for spiropatin which was not detectable. Following 40-mg/kg JM-40, platinum concentrations in serum and tissues were relatively high as compared to those observed after JM-40, 30 mg/kg.

In order to obtain better understanding of analogue distribution, the ratios of tissue platinum and serum platinum concentrations were calculated (Table 3). The ratios for liver and kidneys appeared significantly higher (\(p < 0.001\)) than those for tumors. Except for iproplatin, where ratios were similar for liver and kidneys, all other drugs showed highest ratios for kidneys. Except for spiropatin and iproplatin, ratios for Pe were higher than for MRI-H-207 tumors, suggesting a higher platinum uptake or possibly a slower release from Pe. Retention of platinum per complete organ was calculated as percentage of the administered dose (Table 4). Retention was highest for spiropatin followed by cisplatin, iproplatin, JM-40 (40 mg/kg), and carboplatin. This sequence did not correlate with the corresponding serum
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Chart 2. Treatment results of platinum analogues at equitoxic doses i.v. x 2 to 3 in MRI-H-207 (n = 6 to 7) and Pe (n = 6 to 7), as compared to controls (n = 4 to 5). The relative tumor volume is the tumor volume at any given day Vt/the volume at the start of treatment V0, — —, mean of relative volumes of control mice; --- ---, mean of relative volumes of treated mice; bars, S.E.

concentrations (Table 2). No differences in retention of the individual analogues were observed between mice bearing MRI-H-207 and Pe.

D I S C U S S I O N

In the present study, we used human ovarian carcinoma xenografts which grow in nude mice and differ in histology, tumor doubling time, and cisplatin sensitivity. The models were evaluated on their predictive value for antitumor activity of new platinum analogues in human ovarian cancer. Five platinum analogues which are being evaluated clinically have been studied. Antitumor activity of the analogues was analyzed with equitoxic doses of the drugs, using the ratio of relative tumor volume in treated and control mice as end points of the study. The data for MRI-H-207 show that carboplatin, iroplatin, and JM-40 had antitumor activity comparable to cisplatin, and that spiroplatin was less effective. This correlates well with recent findings in clinical studies of these drugs in advanced ovarian cancer (1, 6, 26, 27).

There is no information on the pharmacokinetics of platinum analogues in mice; however, the pharmacokinetic behavior has been studied extensively in humans, dogs, and rats. After an i.v. bolus injection of platinum analogues in the latter species, total platinum concentration in serum shows a biphasic decay with an initial half-life of several min to 1 hr and a terminal half-life of several days (4, 5, 12-14, 16, 22, 23, 25). A rapid increase of tissue platinum concentration has been observed followed by a plateau concentration for several days (9, 11, 12). These findings indicate that an equilibrium between the various compartments exists 24 hr after administration of the drugs, while only a small drop in concentration occurs thereafter. Therefore, organ distribution and serum concentrations were measured at that time.

With each analogue high platinum concentrations were observed in kidneys, the main organ of excretion. The platinum concentration in kidneys was similar or even higher after administration of the analogues than after cisplatin. Renal tissue concentrations do not appear to predict for human renal damage; clinical dose-limiting toxicity for both carboplatin and iroplatin has proven to be myelosuppression (4-6, 27).

Similarly, the high platinum concentrations in liver following iroplatin did not predict human hepatic toxicity (4). As unbound platinum species represent the active drug (10, 17), knowledge...
PLATINUM ANALOGUES IN HUMAN OVARIAN CARCINOMA XENOGRAFTS

Table 2

<table>
<thead>
<tr>
<th>Tumor line</th>
<th>Analogue</th>
<th>Dosea (mg/kg)</th>
<th>Liver</th>
<th>Kidneys</th>
<th>Brain</th>
<th>Tumors</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Cisplatin</td>
<td>5 7</td>
<td>3.29 ± 0.79b</td>
<td>5.45 ± 0.95</td>
<td>0.14 ± 0.04</td>
<td>0.68 ± 0.13</td>
<td>0.36 ± 0.06</td>
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<td>MRI</td>
<td>Carboplatin</td>
<td>60 7</td>
<td>2.34 ± 0.32</td>
<td>5.10 ± 1.16</td>
<td>0.25 ± 0.06</td>
<td>0.89 ± 0.18</td>
<td>0.37 ± 0.10</td>
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<tr>
<td>MRI</td>
<td>JM-40</td>
<td>30 6</td>
<td>1.79 ± 0.27</td>
<td>6.58 ± 1.72</td>
<td>0.11 ± 0.02</td>
<td>1.09 ± 0.14</td>
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<td>MRI</td>
<td>Iproplatin</td>
<td>40 6</td>
<td>3.90 ± 0.47</td>
<td>13.86 ± 1.74</td>
<td>0.28 ± 0.15</td>
<td>2.10 ± 0.37</td>
<td>1.23 ± 0.18</td>
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<td>Sproplatin</td>
<td>3 7</td>
<td>5.30 ± 1.06</td>
<td>14.31 ± 3.89</td>
<td>0.38 ± 0.16</td>
<td>3.42 ± 0.49d</td>
<td>1.37 ± 0.38</td>
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<td>13.03 ± 1.52</td>
<td>13.89 ± 1.49</td>
<td>0.20 ± 0.04</td>
<td>1.09 ± 0.44</td>
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<td>3 7</td>
<td>4.29 ± 0.56</td>
<td>7.74 ± 0.63</td>
<td>NDb</td>
<td>0.33 ± 0.05</td>
<td>1.26 ± 0.04</td>
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</table>

a Maximum tolerable dose, except JM-40, 30 mg/kg.
b Total number of animals.
c Mean ± S.D.
d Higher platinum concentration (p < 0.05) in Pe tumors than in MRI-H-207 tumors evaluated by Student's t test.
ND, not detectable (limit of detection 0.05 μg/ml).

Table 3

<table>
<thead>
<tr>
<th>Tumor line</th>
<th>Analogue</th>
<th>Dosea (mg/kg)</th>
<th>Liver</th>
<th>Kidneys</th>
<th>Brain</th>
<th>Tumors</th>
<th>Serum</th>
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<td>Cisplatin</td>
<td>5 7</td>
<td>9.16 ± 1.08b</td>
<td>15.24 ± 1.13</td>
<td>0.40 ± 0.11</td>
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<td>0.75 ± 0.47</td>
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<td>MRI</td>
<td>JM-40</td>
<td>30 6</td>
<td>10.94 ± 1.68</td>
<td>17.61 ± 1.91</td>
<td>1.23 ± 0.28</td>
<td>4.25 ± 0.85</td>
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<td>40 6</td>
<td>3.19 ± 0.15</td>
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<td>3.18 ± 0.29</td>
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<td>40 6</td>
<td>4.96 ± 0.73</td>
<td>10.52 ± 1.50</td>
<td>0.29 ± 0.15</td>
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<td>Sproplatin</td>
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<td>17.98 ± 2.64</td>
<td>NDb</td>
<td>1.33 ± 0.17</td>
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</table>

a Maximum tolerable dose, except JM-40, 30 mg/kg.
b Mean ± S.D.
c Higher tissue:serum ratio (p < 0.05) in Pe tumors than in MRI-H-207 tumors evaluated by Student's t test.
d ND, not detectable.

Table 4

<table>
<thead>
<tr>
<th>Tumor line</th>
<th>Analogue</th>
<th>Dosea (mg/kg)</th>
<th>Dose Ptb (mg/kg i.v.)</th>
<th>Liver</th>
<th>Kidneys</th>
<th>Brain</th>
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<td>3.25</td>
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<td>9.72 ± 2.40</td>
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<td>Carboplatin</td>
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<td>3.25</td>
<td>5.11 ± 0.79</td>
<td>1.62 ± 0.17</td>
<td>0.08 ± 0.02</td>
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<td>16.39</td>
<td>0.65 ± 0.10</td>
<td>0.52 ± 0.12</td>
<td>0.01</td>
<td>0.34 ± 0.24</td>
<td>1.52 ± 0.43</td>
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<td>Iproplatin</td>
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<td>16.39</td>
<td>0.77 ± 0.05</td>
<td>0.48 ± 0.06</td>
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<td>21.85</td>
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<td>NDb</td>
<td>0.99 ± 0.42</td>
<td>28.28 ± 2.27</td>
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a Maximum tolerable dose, except JM-40, 30 mg/kg.
b Amount administered per analogue.
c Total percentage of platinum retained in liver, kidneys, brain, and tumors.
d Mean ± S.D.
ND, not detectable.

CANCER RESEARCH VOL. 45 JANUARY 1985
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on the kinetics of this fraction might correlate better with antitumor
activity or toxicity than total platinum. In a pharmacokinetic study
in humans, Curt et al. (5) observed longer half-lives of free
platinum following carboplatin than following cisplatin. Little dif-
ference has been observed in total platinum kinetics of ioproplatin
and cisplatin in humans (4), but again protein binding and kinetics of
free platinum appear to differ (14). The increase in half-life of
the free platinum species is related to a reduced binding to
plasma proteins. These differences in reactivity may also be
responsible for the difference in retention of platinum in organs
after administration of the analogues. Interestingly, these same
analyses showed a similar organ distribution of platinum at 6
weeks after administration in dogs (23) as our 24-hr distribution
findings in mice.

While cisplatin appears to penetrate poorly into the mouse
brain, equitoxic doses of carboplatin, ioproplatin, and JM-40 re-
sulted in higher platinum concentrations, an observation which
may warrant the inclusion of patients with cerebral metastases
of platinum-sensitive cancers in future phase II studies.

The differences in platinum distribution observed in MHI-207
and Pe for JM-40, ioproplatin, and spiran platinum may be related
to a difference in biological characteristics and vascularity of
the tumors. Despite the fact that highest platinum concentrations
were detected in Pe tumors, the overall sensitivity was much
lower than in MHI-207. Four platinum analogues gave a com-
plete remission of MHI-207, while cisplatin and carboplatin
were the only analogues to cause minimal growth delay at best,
with the other analogues being essentially inactive in Pe. Ob-
viously, sensitivity is not related to platinum concentrations in
these ovarian xenografts. It is of interest to know that Pe
originated from a patient who showed resistance to cisplatin as
a second-line treatment, while MHI-207 was obtained from a
patient who showed a complete remission on cyclophosphamide
and never received cisplatin therapy.

It can be concluded from our data that the MHI-207 human
ovarian xenograft in the nude mouse is a model which seems to
predict antitumor activity of new platinum analogues in ovarian
cancer, while Pe may be of interest to study cross-resistance to
platinum analogues. Total platinum tissue concentration in our
models did not predict antitumor activity or organ-specific toxicity
in humans.

ACKNOWLEDGMENTS

I. Klein is gratefully acknowledged for the skilful analysis of platinum in serum and
tissue samples.

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