Persistence of Platinum-Ammine-DNA Adducts in Gonads and Kidneys of Rats and Multiple Tissues from Cancer Patients

Miriam C. Poirier,1 Eddie Reed, Charles L. Litterst, David Katz, and Shalina Gupta-Burt

ABSTRACT

The persistence of platinum-DNA adducts was investigated using normal rats as well as tissues from cancer patients receiving either cis-diamminedichloroplatinum(II) (cisplatin) or diaminocyclobutanedicarboxylatoplatinum(II) (carboplatin) for cancer chemotherapy. These studies used an enzyme-linked immunosorbent assay, established with a rabbit anti-cisplatin-DNA that is specific for intrastrand platinum-DNA adducts. The gonads and kidneys of male and female rats, sites for antitumor activity and toxicity, respectively, were monitored for cisplatin-DNA adduct formation after a single dose of drug and during multiple-dose exposures (once a wk for 3 wk). DNA adducts were measured by enzyme-linked immunosorbent assay 4 h and 2, 4, 7, and 14 days after administering a single i.v. injection of 8 mg/kg of cisplatin. Adduct profiles in renal tissues were similar in both males and females with adduct levels increasing between 4 h and 2 days, decreasing between Days 2 and 7, and stable between Days 7 and 14. In both sexes, levels of kidney DNA adduct measured 7 to 14 days after cisplatin injection comprised about 30% of the highest (Day 2) value. In testes and ovaries, adduct removal was complete by 4 days, and 40% to 50% of adducts present at Day 2 persisted until Days 7 and 14. A study of multiple dosing showed that adducts in renal and testicular DNA from rats given three weekly doses of 5 mg/kg of cisplatin had different accumulation profiles. In the testis there was a 2-fold accumulation of adduct after the third dose, while in the kidney adducts dropped with repeated dosing. In humans, the persistence of platinum-DNA adducts studied was in tissues from eight cancer patients who received their last dose of cisplatin or carboplatin chemotherapy between 1 day and 15 mo before autopsy. The patients had either ovarian cancer, breast cancer, or lymphoma, and the tissues studied included ovarian tumor, bone marrow, kidney, liver, spleen, lymph node, peripheral nerve, and brain. When samples were available from tumor tissues and from bone marrow within the same patient, adduct levels were similar in the two tissues. In addition, adducts were persistent for many months, since half of the individuals received their most recent platinum-drug therapy 7 to 15 mo before death. Overall, these studies demonstrate a widespread distribution and high degree of platinum-DNA adduct persistence in both animal and human tissues subsequent to cisplatin or carboplatin treatment.

INTRODUCTION

Cisplatin1 is one of the most effective drugs currently available for treatment of testicular, ovarian, and other cancers (1–3), but is also tumorigenic in rodents (4, 5). The possibility exists that the properties by which this drug kills tumor cells may also contribute to observed toxic effects and tumorigenicity. The primary toxicity of this compound in animals and in cancer patients is renal (6), and in cancer patients auditory and peripheral neuropathies have also been observed (2). The carcinogenicity of cisplatin in multiple organs of rats and mice has been well-documented (4, 5), and there are limited data to suggest that it may cause secondary tumors in cancer patients receiving chemotherapy (7–9). Because this drug is so effective clinically and is used extensively in combination therapies, the mechanisms underlying its effectiveness, toxicity, and tumorigenicity are of interest.

Cisplatin damages DNA, inducing the formation of chemically stable DNA adducts that have been studied in cell culture and animal models for some years (10–12). More recently, highly sensitive techniques have been developed that allow determination of these DNA adducts in tissues of rodents receiving multiple drug doses and human patients receiving chemotherapy. DNA modified with cisplatin has been used to elicit antisera specific for the intrastrand bidentate cis-diammineplatin adducts formed on the N7 positions of two adjacent deoxyguanines and of adjacent deoxyadenines and deoxyguanines, 5' → 3', with linkages at the N7 positions of the adenine and guanine bases (13, 14). These adducts comprise a major portion (approximately 80%) of platinum bound to DNA in biological samples (10). An ELISA developed with this antiserum underestimates the total amount of intrastrand adduct bound to DNA (14), but recognizes blood cell DNA damage that correlates with positive clinical outcome in ovarian and testicular cancer patients (15–17). Thus, the absence of measurable cisplatin-DNA ELISA-detectable DNA adducts is associated with poor disease response.

The studies presented here have been designed to investigate cisplatin-DNA adduct persistence in rodent and human tissues. It is possible that adduct persistence may be related to the toxicity, tumorigenicity, and chemotherapeutic efficacy of the platinum-ammine complexes. Thus, interspecies comparisons of these chemotherapeutic agents may enhance our knowledge of both favorable and adverse effects.

MATERIALS AND METHODS

In Vivo Experiments in Rats. Sprague-Dawley rats (175 to 200 g) were given doses of cisplatin by i.v. or i.p. injection. Cisplatin was dissolved in 0.9% sterile saline at a concentration of 1 mg/ml and diluted with 0.9% saline so that all animals received the same total volume of fluid. Cisplatin was injected within 1 h of the time that drug was dissolved in the vehicle. Animals were sacrificed at designated times after cisplatin administration, and kidneys and gonadal tissues were harvested and frozen at −20°C until DNA isolation.

Two rat experiments were designed to assess adduct removal over time. In the first, 25 male and 25 female rats were given injections i.v. of cisplatin at 8 mg/kg of body weight. Four to six rats of each sex were killed at 4 h, 2 days, 4 days, 7 days, and 14 days after cisplatin dosing. In the second, 20 male rats were given injections i.v. of 8 mg/kg of cisplatin, and five animals were killed at 4 h, 2 days, 4 days, and 7 days.

Adduct accumulation with repeated cisplatin dosing was determined as follows. A cohort of 15 male rats was given injections i.p. of 5 mg/kg of cisplatin; 4 h later five animals were sacrificed and the tissues frozen. At Day 8, the 10 remaining animals were given i.p. injections of 5 mg/kg of cisplatin, and 4 h later five animals were killed and the...
tissues harvested. At Day 15, the last 5 animals were given injections of 5 mg/kg, and 4 h later these animals were sacrificed and the tissues frozen. At the time of the first injection, another 5 animals were given a single i.p. dose of 20 mg/kg of cisplatin and killed at 4 h. This experiment was performed twice, but data from only one experiment are shown; data from the second experiment were comparable.

Cancer Patient Specimens. The eight cancer patients studied were treated for ovarian or breast cancer or for lymphoma on approved experimental protocols in the Medicine Branch of the National Cancer Institute. Each patient had previously failed one or more cycles of therapy that contained cisplatin; however, the most recent platinum-based therapy was carboplatin. For the ovarian cancer patients this was given at either 400 or 800 mg/m² per cycle. The patient with breast cancer was given carboplatin in combination with 5-fluorouracil and leucovorin at a carboplatin dose of 300 mg/m² per cycle. The patient with lymphoma received a carboplatin dose of 200 mg/m² per cycle in combination with epidophyllotoxin.

Patients died at various times, ranging from 1 day to 15 mo after their most recent platinum dose. Autopsy was performed within 24 h of the time of death, and grossly normal tissues were taken, including bone marrow, lymph nodes, spleen, kidney, liver, peripheral nerve, and brain (gray and white matter). For ovarian cancer patients, samples of the ovarian tumor were obtained. Tissues were frozen at −20°C for 1 to 2 mo before DNA preparation.

DNA Isolation. As previously described (18, 19), tissues were homogenized and nuclei prepared by centrifugation in isotonic sucrose with detergent; DNA was isolated from rat and human nucleic on CsCl buoyant density gradients. The salt was removed by dialysis, and DNA content was determined by UV absorbance at 260 nm.

Cisplatin-DNA ELISA. All of the rat and human samples were assayed by the cisplatin-DNA ELISA. This assay was performed with a rabbit anti-cisplatin-DNA using 35 μg of DNA per well as previously described (14, 20, 21). For each assay, a standard curve was generated using calf thymus DNA modified in vitro to a level of 4.3 adducts per 100 nucleotides (determined by atomic absorbance spectrometry). The 50% inhibition for the standard curves averaged 12.9 ± 3.7 fmol/μg of DNA (mean ± SD, n = 14). DNA adduct levels for each of the biological samples were determined by comparison with the standard curve, and the lower limit of sensitivity was 8 amol/μg of DNA. This assay measures a subset of intrastrand cis-diammineplatinum adducts formed on the N7 positions of two adjacent deoxyguanines and of adjacent deoxyadenines and deoxyguanines that presumably have a conformation favorable for antibody recognition (14).

Clinical Data Obtained. The medical records of the eight individuals were reviewed to obtain the following information: age; sex; cause of death; the type and duration of response to the most recent platinum treatment regimen; time since most recent platinum dose; total cumulative drug dose; and number of courses of therapy prior to death.

RESULTS

Cisplatin-DNA Adduct Formation and Removal in Kidneys and Gonads of Rats Given a Single Dose of Drug. The formation and removal of cisplatin-DNA adducts in kidneys of male and female rats given injections of a single i.v. dose of 8 mg of cisplatin/kg of body weight were measured by cisplatin-DNA ELISA and are shown in Fig. 1. At 4 h after dosing, substantive levels of adduct were seen in kidney DNA from both males and females, but 2 days later, the adduct levels reached a peak, presumably due to the slow conversion of monoadducts to bidentate intranaduct adducts. Adducts decreased rapidly during the next 5 days, so that at Day 7 adduct levels were approximately 30% of those observed on Day 2. Due to a high level of toxicity in females, a 14-day point was not obtained for these rats; however, the data for male rats indicate no further adduct removal occurring between Days 7 and 14. The data for adduct formation and removal in male and female gonadal tissues are shown in Fig. 2. In DNA from testis, at 4 h after cisplatin injection, adduct levels were only about 20% of those observed in kidneys from the same animals. Considerably more adduct was present by 48 h after cisplatin exposure. Between Days 2 and 7, adduct levels decreased, and between Days 7 and 14, there was no further adduct removal. In DNA from ovaries, the highest adduct levels were seen 4 h after the cisplatin exposure. The adduct removal observed between Days 2 and 4 appeared to cease abruptly between Days 4 and 7, and the female rats were lost to toxicity at this point. Although the kinetics of adduct processing in gonadal tissues during the first 48 h may differ substantially between males and females, the kinetics after 48 h appears to be quite similar for the two sexes. As was observed in kidney tissues, a large fraction (40 to 50%) of the adducts present on Day 2 persisted in gonadal tissues for 7 (females) and 14 (males) days.

Cisplatin-DNA Adduct Accumulation in Rat Kidney and Testis following Multiple Cisplatin Dosing. Since most human chemotherapy protocols involve multiple drug exposures, we considered it of interest to compare the effect of multiple dosing versus single dosing on cisplatin-DNA adduct formation in kidney and gonads of male rats. Males were chosen for these experiments since, in these experiments, they survived longer than the females. The adduct values obtained after the three weekly i.p. drug injections are listed in Table 1. Following an initial dosing of 5 mg/kg of body weight, there was an average adduct level of 449 ± 89 amol/μg of DNA in kidney and of 80 ± 15 in testis. Four h after the second dose of 5 mg/kg (given on Day 8 of the experiment), adduct levels observed were 180 ± 45 amol/μg of DNA in kidney and 126 ± 37 amol/μg of DNA in gonadal tissues. Following the third weekly injection of 5 mg/kg of cisplatin (Day 15 of the experiment), there were 256 ± 64 amol/μg of DNA in kidney compared with 144 ± 14 amol/μg of DNA in testis. In a group of animals treated with a single
Fig. 2. Cisplatin-DNA (ELISA) profiles in testes and ovaries from male and female rats given one dose of cisplatin. Male and female rats were given injections i.v. of 8 mg of cisplatin/kg of body weight, and 4 to 6 animals per point were sacrificed at 4 h and at 2, 4, 7, and 14 days after drug exposure. Gonads were frozen at —20°C until DNA was isolated on CsCl2 buoyant density gradients.

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<th>Cisplatin dose (mg/kg)</th>
<th>Time (days)</th>
<th>Cisplatin-DNA adduct (amol/µg of DNA)</th>
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<tr>
<td></td>
<td></td>
<td>Kidney</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>449 ± 89 * (100)</td>
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<tr>
<td>5</td>
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<td>15</td>
<td>256 ± 64 (57)</td>
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<tr>
<td>20</td>
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<td>632 ± 128</td>
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* Mean ± SD (amol of adduct/µg of DNA).

Numbers in parentheses, percentage on Day 1.

Table 2 Summary of patient information

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<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Cancer</th>
<th>Total dose (mg/m2)</th>
<th>Time since last platinum therapy</th>
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dose of 20 mg/kg, adduct levels were 632 ± 128 amol/µg of DNA in kidney and 87 ± 12 amol/µg of DNA in testis.

A comparison of DNA adduct quantities formed after a single 5-mg/kg dose with those formed after a 20-mg/kg dose demonstrates that kidney and testicular DNA adduct levels were similar at the two doses. Furthermore, comparison of adducts induced by a single 20-mg/kg dose with adducts produced by a divided total dose of 15 mg/kg (5 mg/kg weekly for 3 wk) shows kidney adduct levels to be 2.5-fold higher in the 20-mg/kg dose group. In contrast, testicular DNA adduct levels were about 40% lower in the 20-mg/kg dose group than in the group that received three separate 5-mg/kg doses. In testes, an accumulation of adduct was apparent with each successive dose given 1 wk apart. In kidneys, adduct accumulation was not seen.

Measurement of DNA Adducts in Tissues of Cancer Patients Obtained at Autopsy. Clinical parameters for the eight patients studied are presented in Table 2. Patients 1, 2, and 4 did not respond to therapy and experienced the shortest posttherapy survival. Patients 5, 7, and 8 achieved partial responses (>50% reduction in tumor volume) and were in remission for 7, 4, and 6 mo, respectively. Patient 6 had no change in tumor status for 7 mo. Patient 3 died of fungal sepsis during her first cycle of therapy.

Platinum-DNA adducts were measured by cisplatin-DNA ELISA in from two to eight tissues obtained at autopsy from the eight individuals described above. The results are presented in Table 3. These data show that there was a widespread distribution of DNA adducts in many tissues of the same individual (note Patients 2, 3, and 4). It was possible to obtain ovarian tumor tissue from four of these patients, and the adducts measured in tumor were in the same range as those in bone marrow for three of these four individuals. In addition to tumor, adducts were measurable in kidney, bone marrow, brain, and nerve tissue, which are sites for platinum drug toxicity.

The data in Table 3 demonstrate that platinum-DNA adducts persisted in the tissues of these cancer patients for many months after chemotherapy. In the case of Patients 4 to 8, the time since last therapy (Table 2) varied between 4 and 15 mo, and it was still possible to measure adducts in tumor and several other tissues.

DISCUSSION

These investigations were designed to examine profiles of cisplatin-DNA adduct in processing target organs of rats and to investigate adduct persistence in tissues of cancer patients receiving platinum-drug therapy. Both the animal and human studies presented here demonstrated persistence of cisplatin-DNA adducts in tissue. In addition, the animal experiments showed an accumulation of adducts in testis during multiple dosing in the rat. If similar adduct processing occurs in the human testis, adduct persistence may be related to the particular susceptibility of this tissue to the chemotherapeutic effects of the drug. The human studies demonstrated that persistent platinum-DNA adducts can be found in many tissues, including ovarian tumor, at levels similar to those previously seen in blood. This may be important for clinical mechanism since, in ovarian cancer patients, the formation of blood cell DNA adducts has been shown to be highly correlated with a favorable disease response (15, 17).

The experiments with rats were complicated by the fact that adducts were not generally measurable at doses which gave significant survival. Because the dose of 8 mg/kg of body weight was lethal to approximately half of the animals within the first week, twice as many animals as necessary for statistical validity were exposed initially. The toxicities observed were similar to those previously reported (6, 22) with greater sensitivity exhibited by the females. The animals given single i.v. injections of cisplatin formed bidentate intrastrand adducts over a period of at least 48 h. Some of these adducts were removed during the first week postdosing; however, a substantial fraction remained persistent at 2 wk, when removal appeared to have ceased. In the kidney the persistent adducts comprised approximately 30% of the highest adduct levels observed at 2 days. In gonads, the
persistent adducts were 40 to 50% of the peak (Day 2) adduct levels. It was not possible to assess the influence of toxicity on cisplatin-DNA adduct formation in these animals.

Experiments in which drug was administered to rats at multiple times were designed to model human exposure. These studies demonstrated accumulation of platinum-DNA intrastrand adducts in testes of male rats (Table 1). It is possible that either circulating metabolites target the testis leading to enhanced DNA damage, or that DNA adduct removal is less efficient in testes. In the same multiple-dosing experiment, DNA adduct levels in kidney tissues dropped after the second cisplatin dose and remained low after the third dose. This might be due to compound-inducible repair mechanisms or a toxicity-mediated loss of cells, since kidney tubule cells can be readily sloughed into the urine following nephrotoxic drug exposures.

In the experiments presented here using the rat as a model, cisplatin-DNA adducts formed in kidney and gonads, which are biological targets for this drug (1, 2). Even though there is variability in the biology of adduct processing between organs, the most consistent finding of these experiments is a high degree of adduct persistence at a time when adduct removal appears to be complete. A similar pattern of DNA adduct removal has been observed in livers of rats chronically fed 2-acetylaminofluorene (23). However, in those experiments the persistent adduct levels, remaining after completion of the rapid phase of removal, were only about 18% of the peak adduct levels. In the cisplatin experiments the persistent adducts were a much larger fraction of the highest adduct levels, particularly in the testis.

In attempting to apply observations from animal models to humans, it can be postulated from the above experiments that platinum-drug-DNA adducts might also be persistent in human tissues. We have previously reported the results of a small pilot study involving 4 individuals, in which cisplatin-DNA adducts were measured in kidney, liver, and spleen obtained at autopsy from patients receiving cisplatin chemotherapy (24). In that study, kidney DNA adduct persistence was demonstrated for up to 22 mo in one individual, but tumor tissue was not available. In the present study, multiple tissues, including ovarian tumor, were obtained at autopsy from eight individuals who had received either cisplatin or carboplatin chemotherapy. Platinum-DNA adducts were detected in a wide variety of tissues (Table 3) and were present as late as 15 mo following the most recent drug exposure (Table 2). Interestingly, DNA adduct levels were roughly similar in most tissues of the same individual whether the tissue was rapidly dividing, such as bone marrow, or relatively quiescent, such as liver. In the case of the bone marrow, this suggests that significant adduct formation occurs in stromal cells and/or immature bone marrow precursor cells. In addition, since carboplatin exhibits hematological toxicity, the bone marrow replication rate may have been decreased as a result of treatment, thus reducing the rate of cell turnover and concomitant adduct dilution.

It is possible that DNA damage might influence drug-related biological effects such as toxicity or antitumor activity. One of the major platinum-drug-related toxicities is peripheral neuropathy (2). The presence of adduct in peripheral nerve cell DNA was demonstrated in two individuals with clinically significant peripheral neuropathy, determined by loss of sensation and not histopathologically. Since no attempt was made to separate sensory and motor material when these samples were obtained and since neurological cells contain so little DNA, it is not possible to postulate the adduct-containing cell type. The peripheral neuropathies reported in these patients were primarily the result of cisplatin administration early in the course of the disease, and patients were later given carboplatin to avoid the continuing loss of neurological function.

A second major toxicity related to platinum-drug administration is renal toxicity. In order to compare renal toxicity with DNA adducts, values for 24-h creatinine clearance were obtained from medical records. In general, there was an inverse correlation with total cumulative platinum dose (data not shown), but DNA adduct levels in kidney did not correlate with either creatinine clearance or dose.

As regards chemotherapeutic efficacy, there is not enough evidence to prove that platinum-DNA adduction formation in tumor tissue correlates with disease response because it is so difficult to obtain tumor tissue for adduct analyses. However, in two studies involving a total of 82 ovarian cancer patients, blood cell DNA adducts (measured by the cisplatin-DNA ELISA) showed a highly significant correlation with disease response (15, 17). That is, individuals who did not respond clinically were more likely to have little or no measurable adduct (even when several samples were averaged from each patient), and those who responded were more likely to have measurable cisplatin-DNA adducts. This suggests that the DNA adducts detected by the cisplatin-DNA ELISA are at least correlated with platinum-drug efficacy. Thus, data from the cisplatin-DNA ELISA may be used to predict a lack of response, thereby allowing some patients to be spared from multiple drug administrations.

Previous studies by Stewart et al. (25, 26) have demonstrated long-term persistence of platinum, using X-ray fluorescence spectrometry, in tissues obtained at autopsy from cancer patients receiving therapy up to 6 mo antemortem. The data show a widespread distribution of persistent platinum in many organs. Interestingly, a correlation was observed (26) between positive clinical response and high tumor (tissue) platinum.

![Table 3](https://cancerres.aacrjournals.org/FIGURES/Table3.png)

Table 3 Platinum-DNA adducts (amol/μg of DNA) determined by ELISA

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* a, no sample assayed.
* b, ND, levels below 8 amol/μg of DNA, the lower limit of sensitivity.
concentrations in 27 patients who received cisplatin up to 7 mo before autopsy. Overall the relative concentrations of total tissue platinum are not similar to relative concentrations of DNA adducts in the different tissues. For example, levels of platinum in brain tissue were low (25), but studies presented here show brain DNA-adduct levels to be similar to those in other organs. It is possible that the factors that are likely to regulate platinum accumulation in tissue (e.g., diffusion, transport, binding to and turnover of proteins) are different from those probably influencing adduct accumulation on DNA (e.g., glutathione, metallothioneins, DNA repair). To a large extent DNA adduct removal processes may be primarily responsible for the observed adduct patterns in patients receiving their last therapy several months prior to death.

The overall conclusions from both the human and animal studies presented here are that intrastrand platinum-DNA adducts form in a variety of animal and human tissues and that a major fraction of the total DNA adducts recognized by the cisplatin-DNA ELISA persist for weeks and months subsequent to exposure.

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REFERENCES


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