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Michael P. Gosland · Susan Goodin · Robert A. Yokel
Marietta Smith · William J. John

A phase I trial of 5-day continuous infusion cisplatin and interferon α

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Abstract Combination therapy of cisplatin with interferon α (IFN) has been shown in several in vitro as well as in vivo models to be synergistic. In order to decrease toxicity seen with cisplatin, 5-day continuous infusions, in place of bolus administration, have been introduced. This led us to investigate the combination of 5-day continuous infusion cisplatin with repeated IFN dosing in a phase I cisplatin dose escalation study. A group of 17 patients were enrolled in this trial . The maximum tolerated dose (MTD) of cisplatin was 20 mg/m^2 per day when combined with 3×10^6 units IFN given three times a week. The dose-limiting toxicities seen included thrombocytopenia, leukopenia, and nausea and vomiting. Pharmacokinetic analyses of free (unbound or ultrafilterable) platinum revealed that the decay curve fitted a monoexponential model. Pharmacokinetic parameters of cisplatin were found to correlate with toxicity. Both increases in the maximum concentration of cisplatin achieved (Cpmax) as well as the area-under-the-curve (AUC) for free platinum, correlated with the incidence of nausea and vomiting (both acute and delayed) and hematological toxicities (leukopenia and thrombocytopenia). None of the patients exhibited significant changes in renal function while on this study. The free platinum levels were higher than found in similar studies evaluating comparable cisplatin infusions alone. The enhanced toxicities seen in this trial may be explained by the results of an in vitro study using human plasma spiked with cisplatin and IFN that revealed decreased protein binding of cisplatin by 2.5–3.0-fold. Of the 17 patients treated, two non-small cell lung cancer patients obtained a partial response and one malignant melanoma patient obtained complete resolution of a malignant pleural effusion. Considering the acceptable toxicity seen in this trial, we recommend phase II trials be conducted with continuous infusion cisplatin with IFN in the treatment of non-small cell lung cancer.

Keywords Cisplatin · Interferon α · Continuous infusion therapy · Non-small cell lung cancer · Pharmacokinetics

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M.P. Gosland · R.A. Yokel
College of Pharmacy, University of Kentucky, Lexington, KY, USA

M.P. Gosland
Division of Hematology and Oncology, Department of Medicine, Lucille P. Markey Cancer Center, University of Kentucky, Lexington, KY, USA

M. Smith
Clinical Research Office, Lucille P. Markey Cancer Center, University of Kentucky, Lexington, KY, USA

S. Goodin
Cancer Institute of New Jersey, Rutgers University, New Brunswick, NJ, USA

W.J. John (✉)
Lucille P. Markey Cancer Center, University of Kentucky, 800 Rose Street, Rm. CC-405, Lexington, KY 40356-0093, USA

Introduction

Cisplatin has become a cornerstone in the treatment of many metastatic solid tumors including squamous cell carcinoma of the head and neck, small and non-small cell lung cancer, ovarian cancer, bladder cancer, and many germ cell tumors. The response rate of cisplatin as a single agent is up to 30%. However, with the exception of germ cell tumors, stage III ovarian cancer, and bladder cancer, the 5-year survival is no better than 1% in these advanced cancers [1–4]. The reason for the low response rates in these malignancies is most likely due to the presence of cell populations that are

intrinsically resistant to chemotherapy as a result of mutational changes. Along with the development of drug-resistant mutations, poor cell exposure to cisplatin and changes in growth kinetics among tumor cells reduce their vulnerability to chemotherapeutic agents [5]. Continuous intravenous (IV) infusion of chemotherapeutic agents allows for effective plasma concentrations for a prolonged period of time which results in better tumor exposure to cell-cycle phase-specific agents and those agents with a short half-life [6]. Following a rapid IV infusion of cisplatin, the mean terminal half-life of free (unbound or ultrafilterable) platinum is 20–50 min [7, 8]. In vitro experiments have revealed better response rates in certain tumors when cisplatin is administered as a low continuous exposure compared with short bolus treatments at higher concentrations. Human lymphoma cells treated in vitro with cisplatin by continuous exposure show the same cytotoxic effects as short exposure to concentrations ten-fold greater [9]. These data suggest that better therapeutic responses can be achieved with continuous infusion cisplatin. Several clinical studies in adults have supported this concept. Continuous infusion cisplatin (over 5 days) produces less gastrointestinal toxicity when compared to bolus administration [7, 8, 10–13]. Toxicites observed with cisplatin have also been shown to correlate with the maximum concentrations of free (unbound or ultrafilterable) platinum as well as pharmacokinetic parameters (e.g. clearance) of unbound cisplatin [14].

Biologic response modifiers such as interferon (IFN) administered with certain chemotherapeutic agents have shown synergy in in vitro and in vivo models [15, 16]. IFN and cisplatin treatment in several human tumor cell models has shown enhanced tumor cytotoxicity [13–17]. Cisplatin and IFN also have been shown to be synergistic in mice with sarcoma implants [18]. As a result of the synergy noted between cisplatin and IFN and the non-overlapping toxicities of these two drugs, clinical trials have evaluated this combination. In initial trials cisplatin was administered as a bolus injection on day 1 followed by the IFN. The dose-limiting toxicities from these studies include myelosuppression and severe nausea and vomiting [19–26]. Subsequent to these studies, one trial examined continuous infusion cisplatin with IFN along with concomitant radiotherapy in the treatment of non-small cell lung cancer. In this study, 11 of 24 patients had either a complete or partial response and the dose-limiting toxicities included myelosuppression and nausea and vomiting. The nausea and vomiting was significant despite the fact that the cisplatin was given as a continuous infusion [27]. These studies provided the basis for our phase I study evaluating continuous infusion cisplatin with IFN to define the maximum tolerated dose of cisplatin while determining whether a correlation exists between the pharmacokinetic and pharmacodynamic parameters of cisplatin when administered in this manner with IFN.

Patients and methods

Patient eligibility

Patients with biopsy-proven cancer which was refractory to standard treatment or for which no effective treatment was available were eligible for this study. In tumors which were either measurable or evaluable, bidimensional measurements on chest X-radiographs, radionucleotide scans, CT scans, ultrasound, or physical examination were obtained to evaluate response. Eligible patients had a creatinine clearance of greater than 50.0 ml/min, a leukocyte count of greater than 4000/μl, an absolute neutrophil count greater than 1500/μl, a platelet count of greater than 100,000/μl, and a hemoglobin greater than 9.0 g/dl. Patients also had adequate hepatic function defined as a total bilirubin less than 3.0 mg%, an albumin greater than 2.0 g/dl, protime less than 16 s, and transaminases less than three times normal. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and all signed consents as approved by the Human Subjects Committee. Patients with concurrent irradiation, uncontrolled cerebral metastases, severe malnutrition and cachexia, cardiomyopathies or arrhythmias, or any other uncontrolled medical condition (e.g. diabetes mellitus or hypertension) were excluded from the study. Patients had to have had their last chemotherapy or radiotherapy treatment at least 1 month prior and surgery at least 2 weeks prior to the start of this protocol. The initial patient evaluation included a complete history and physical examination, a complete blood count with differential, chemistry panel with liver function tests, chest X-radiograph, electrocardiogram, a creatinine clearance, serum magnesium and appropriate computer tomographic scans, bone scans, or magnetic resonance imaging. All scans had to have been conducted within 2 weeks of treatment.

Treatment schema

All patients were started on cisplatin therapy at 11:00 a.m. From 3 h prior to the start of the cisplatin and continuing through its 5-day infusion period, patients received a maintenance fluid of 5% dextrose in 0.9% normal saline (USP; D5NS) alternating with 5% dextrose in 0.45% normal saline ($D5_{1/2}NS$) given at a rate of 100 ml/h. Hydration was continued for up to 12 h after chemotherapy was terminated. Each daily cisplatin dose was placed in 2.4 l of normal saline and given at 100 ml/h. Potassium and magnesium were added as needed. Furosemide was administered only when fluid overload developed. Antiemetics given included scheduled ondansetron (8-mg dose IV bolus and a 1–2 mg/h continuous infusion for the remaining 5 days while getting cisplatin) with droperidol, prochlorperazine, and metoclopramide administered as needed for nausea or vomiting not controlled with ondansetron. The initial cisplatin dose was 5 mg/m^2 per day given as a continuous infusion for 5 days. The first dose escalation was to 10 mg/m^2 per day with subsequent escalations at 10 mg/m^2 per day increments. At total of three fully evaluable patients were treated at each dosing interval prior to any dose escalations. Dose escalations to the next stratum were conducted only if the preceding dose was sufficiently nontoxic (defined as less than grade 3 toxicity). Therapy was repeated every 28 days for up to six cycles depending on the toxicity and evaluation of response. The maximum tolerated dose (MTD) was defined as the dose level at which two of six patients experienced grade 3 or 4 toxicity. If two of three patients or three of six patients developed grade 3 or 4 toxicity, the MTD would be the immediately lower dose level. A total of six patients were treated at the MTD. IFN α (Intron

A, Schering Corporation) was administered subcutaneously at a dose of 3.0×10^6 U on days 2, 4 and 6 at 9:00 a.m.

Toxicities were graded using the Southwest Oncology Group (SWOG) criteria [28]. At day 15 of the cycle, patients underwent a physical examination (with special attention to neurological findings), complete blood counts, blood chemistries (including serum magnesium), and assessment of toxicities. Patients were followed every 2 months with tumor markers (if applicable), overall assessment of toxicities, and tumor measurements. Clinical response was evaluated after two, four, and six cycles of therapy.

Pharmacokinetic analyses

Free and total plasma platinum levels were determined before the chemotherapy and at 3,12, 24, 48, 72, 96 and 120 h after initiation of the infusion. Samples were also collected at 15, 30, 45, 60, and 120, and 180 min after completion of the infusion. Blood samples were collected by venipuncture into an iced syringe. Plasma was immediately obtained for ultrafiltration preparation. Plasma samples were filtered through Centriflo membrane cones (CF50A; Amicon, Danvers, Mass.) which retain material with a relative molecular mass of 30,000 Da or greater for measurement of free (unbound) platinum. Whole plasma was also retained for measurement of total platinum. All of these procedures were carried out at 4°C. Plasma platinum levels were determined using a flameless atomic absorption spectrophotometer (Perkin-Elmer model 460; Perkin-Elmer, Norwalk, Ct.) with a graphite furnace and a programmer (HGA-500). The matrix used was 0.045 *M* nitric acid and the inert gas was argon. Platinum absorption was monitored at a wavelength of 306.5 nm as has been previously described [14, 29]. Standard solutions were made daily and a standard curve was run daily with additional periodic checks performed during the day. Calibration of standard curves was done to a correlation coefficient (r) of 0.99. The daily regression equation describing the standard curve was used to determine the free and total platinum plasma concentrations.

The following pharmacokinetic parameters were determined: peak total and free plasma platinum levels, the terminal elimination rate constant (K_e) for free platinum, the half-life of free platinum, and the area-under-the-concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) for free platinum. The K_e was estimated by unweighted least squares linear regression analysis of the terminal phase of the free platinum log plasma concentration-time curve. The terminal half-life was estimated using the equation $T_{1/2} = 0.693/K_e$. The area under the concentration-time curve was calculated using the linear trapezoidal rule during the infusion and the logarithmic trapezoidal rule for decreasing plasma concentrations (MK Model; Biosoft, Cambridge, UK) [30]. Correlations between pharmacokinetic data and toxicity were performed. Patients were characterized as toxic or nontoxic on each separate toxicity based on the following criteria: acute nausea and vomiting (occurring during and up to 24 h after the cisplatin infusion and requiring therapy), delayed nausea and vomiting (occurring 24 h or longer after the end of the infusion and requiring therapy), leukopenia (nadir less than $2.0 \times 10^3/\mu l$), thrombocytopenia (nadir less than $75.0 \times 10^3/\mu l$), nephrotoxicity (increase in serum creatinine of 0.5 mg/dl over baseline and/or decrease in creatinine clearance by 25%), and peripheral neuropathy (any parathesisas causing a decrease in deep tendon reflexes). Pairwise analyses between toxic and nontoxic patients were performed using the Mann-Whitney U-test.

In vitro protein binding assay

An in vitro correlate of the clinical observation of alterations in protein binding of platinum in human plasma was performed. Human plasma from healthy volunteers was spiked with 2.5 μg/ml cisplatin and IFN at concentrations of 0, 50, 100, and 150 u/ml. The concentrations of both cisplatin and IFN used were comparable to those achieved in the clinical trial. Plasma samples were incubated at 37°C in a shaking water bath for 12 and 24 h to obtain maximum protein binding which was estimated according to a method previously reported [14]. Total and free (unbound) platinum were isolated and analyzed by atomic absorption spectometry as described above. Results were analyzed using a two-way analysis of variance followed by a multiple comparison test.

Treatment evaluation

Tumor response was measured in this phase I trial on all measurable disease and was judged using SWOG criteria [28]. All responses had to have persisted for a minimum duration of 4 weeks.

Results

A total of 17 patients were entered in this phase I trial and all were evaluable for toxicity and response. The pretreatment characteristics of the patients are summarized in Table 1. In all, 12 men and 5 women were treated, with a mean age of 54 years (range 26–69 years) and an average ECOG performance status of 1. A total of 7 patients (41%) had received prior chemotherapy, although none of the patients had received previous cisplatin, vinblastine, or vincristine. The initial daily doses of cisplatin that the 7 previously treated patients received were as follows: 5 mg/m^2 ($n = 2$), 10 mg/m^2 ($n = 2$), and 20 mg/m^2 ($n = 3$). The baseline (within 2 weeks prior to therapy) as well as post-therapy serum creatinine values (obtained on day 15 after their last cycle of chemotherapy) are summarized in Table 2.

Table 1 Patient characteristics

Number of patients	17
Sex	
M	12
F	5
Age (years)	
Mean	54
Median	52
Range	26–69
Performance status	
0	3
1	12
2	2
Prior therapy	
None	10
Chemotherapy	7
Radiotherapy	0
Primary tumor site	
Renal cell carcinoma	4
Adenocarcinoma, unknown primary	3
Non-small cell lung	2
Colorectal	3
Head and neck	1
Appendix	1
Melanoma	1
Hepatocellular	1
Pancreatic	1

Table 2 Renal function after therapy with cisplatin plus IFN. Values are means ± SD in mg/dl (*n* number of cycles)

	Cisplatin dose (mg/m²/day)			
	5 ($n = 4$)	10 ($n = 8$)	20 ($n = 19$)	30 ($n = 3$)
Pretreatment serum creatinine	0.6 ± 0.1	1.0 ± 0.35	0.86 ± 0.06	0.93 ± 0.06
Posttreatment serum creatinine	0.83 ± 0.15	1.1 ± 0.4	0.95 ± 0.2	1.2 ± 0.2

There were no patients who developed significant renal dysfunction while on therapy although a trend toward an increased serum creatinine was observed in those patients who received the 30 mg/m² per day dose of cisplatin.

The 34 courses of chemotherapy were delivered at the following doses: 5 mg/m² ($n = 4$), 10 mg/m² ($n = 8$), 20 mg/m² ($n = 19$), and 30 mg/m² ($n = 3$). Individual patients received one to four courses of therapy (average two cycles). Disease progression was the most common reason for discontinuation of therapy. The IFN toxicities were limited to a flu-like illness with some drowsiness, fatigue, and mild headaches. These were only seen during the first and second administration of the IFN and diminished upon each subsequent dose. Toxicities associated with the IFN did not cause any patients to be dropped from the study. Major toxicities seen during therapy were myelosuppression, and nausea and vomiting. These were evaluated by treatment cycle and dose and are summarized in Table 3. Significant leukopenia (less than $1.5 \times 10^3/\mu l$) was seen in five courses; however none of these episodes was associated with infection. Severe thrombocytopenia (less than $50 \times 10^3/\mu l$) was seen in three courses of therapy and all were at 30 mg/m² per day. The thrombocytopenia in each of these three patients required transfusions, but was not associated with significant bleeding. None of the patients became anemic during the therapy (hemoglobin less than 10 g/dl). Nausea and vomiting was characterized as acute (during and up to 24 h after therapy) and delayed (occurring more than 24 h after therapy). All patients had some degree of acute as well as delayed nausea and vomiting despite the use of a serotonin receptor antagonist (ondansetron) during therapy and adequate antiemetic therapy (e.g. metoclopramide, prochlorperazine, and droperidol) as needed after therapy. Grade 2 acute nausea and vomiting (one or two transient episodes of nausea and vomiting) was seen in 14 courses of therapy, while grade 3 acute nausea and vomiting (more than two episodes of vomiting during therapy that required antiemetic therapy) was seen in two courses of therapy. Delayed nausea and vomiting (defined as grade 2 or 3 or at least one or two episodes of vomiting) was also observed in five patients. One patient developed a grade 2 peripheral neuropathy (paresthesia and a decrease in deep tendon reflex) after the fourth cycle at 20 mg/m² and one patient developed grade 2 ototoxicity (20 dB loss of hearing) after the fourth cycle at a dose of 30 mg/m² per day. The results indicate that the maximum tolerated dose of cisplatin (when given as a 5-day infusion) with IFN was 20 mg/m² per day.

Table 3 Myelosuppression and gastrointestinal toxicity with cisplatin and IFN (*n* number of cycles)

	Cisplatin dose (mg/m²/day)			
	5 ($n = 4$)	10 ($n = 8$)	20 ($n = 19$)	30 ($n = 3$)
Leukocytes				
$2.1–3.0 \times 10^3/\mu l$	1	–	4	–
$1.5–2.0 \times 10^3/\mu l$	–	1	2	1
$< 1.5 \times 10^3/\mu l$	–	1	2	2
Platelets				
$100–150 \times 10^3/\mu l$	–	1	2	–
$50–99 \times 10^3/\mu l$	–	–	2	1
$< 50 \times 10^3/\mu l$	–	–	–	3
Acute nausea and vomiting				
Grade 2	–	5	8	1
Grade 3	–	–	–	2
Delayed nausea and vomiting				
Grade 2	–	–	4	–
Grade 3	–	–	–	2

Total and free platinum levels were obtained in 14 of 17 patients and detailed pharmacokinetic data were generated from the free platinum levels. Only one of three patients at the 30-mg/m² per day dose of cisplatin had a complete set of cisplatin levels determined. The maximum concentration of both total and free (unbound) platinum occurred at least 72 h after the start of the infusion. The percentage of free platinum, averaged over all dosing levels, was high at 11.1 ± 0.8%. The AUC was dose dependent. All pharmacokinetic parameters are summarized in Table 4. The significant trends seen from the analysis of the pharmacokinetic parameters with regard to toxicity are summarized in Table 5. For acute nausea and vomiting, higher maximum concentrations of both total and free platinum ($Cpmax_{total}$ and $Cpmax_{free}$) corresponded to grade 2 and 3 toxicity. However, for delayed nausea and vomiting this association was only seen with the $Cpmax_{total}$. Patients with higher AUC of free platinum extrapolated to infinity (free $AUC_{0-\infty}$) also had a significantly higher incidence of delayed nausea and vomiting. Grade 2 and 3 leukopenia and thrombocytopenia were associated with higher cumulative doses of cisplatin.

Table 4 Pharmacokinetic data according to dose. Values are means ± SD (*n* number of cycles)

	Cisplatin dose (mg/m²/day)		
	5 ($n = 3$)	10 ($n = 3$)	20 ($n = 8$)
$AUC_{0-\infty}$ free platinum (mg/l h)	4.8 ± 1.6	11.7 ± 4.5	14.6 ± 1.8
K_e free platinum (h^{-1})	0.69 ± 0.21	0.411 ± 0.18	0.404 ± 0.23
Half-life of free platinum (h)	1.1 ± 0.4	1.7 ± 0.3	2.2 ± 0.8
Peak free platinum level (μg/ml)	0.032 ± 0.01	0.092 ± 0.02	0.183 ± 0.03
Peak total platinum level (μg/ml)	0.297 ± 0.04	0.77 ± 0.18	1.73 ± 0.55
Free (unbound) platinum (%)	11.0	11.9	10.1

Table 5 Relationships between cisplatin pharmacokinetic parameters and toxicity of therapy. Values are means ± SD (*n* number of patients, $Cpmax_{total}$ maximum total platinum concentration, $Cpmax_{free}$ maximum free platinum concentration, *Free* $AUC_{0-\infty}$ AUC of free platinum extrapolated to infinity)

Toxicity	Pharmacokinetic variable	Mean in nontoxic group	Mean in toxic group	*P*-value[a]
Acute nausea and vomiting, grade 2 and 3		($n = 5$)	($n = 9$)	
	$Cpmax_{total}$ (μg/ml)	0.59 ± 0.17[c]	1.8 ± 0.5	< 0.05
	$Cpmax_{free}$ (μg/ml)	0.136 ± 0.04	0.217 ± 0.06	< 0.05
	Free $AUC_{0-\infty}$ (μg/ml h)	9.0 ± 3.0	14.0 ± 5.0	0.17
Delayed nausea and vomiting, grade 2 and 3		($n = 9$)	($n = 5$)	
	$Cpmax_{total}$ (μg/ml)	0.83 ± 0.41	2.5 ± 0.9	< 0.05
	$Cpmax_{free}$ (μg/ml)	0.162 ± 0.09	0.220 ± 0.04	0.15
	Free $AUC_{0-\infty}$ (μg/ml h)	8.0 ± 2.2	18.0 ± 2.7	< 0.05
Leukopenia, grade 3		($n = 11$)	($n = 6$)	
	Cumulative dose (mg/m²)	72.7 ± 8.5	217.8 ± 36.5	< 0.05
Thrombocytopenia, grade 2 and 3		($n = 12$)	($n = 5$)	
	Cumulative dose (mg/m²)	79.2 ± 10.1	229 ± 41.0	< 0.05

[a] Mann-Whitney *U* test

The in vitro protein binding assay revealed that IFN influenced the percentage of cisplatin bound to protein (Fig. 1). After a 12-h incubation of cisplatin in human plasma, a significantly higher percentage of platinum was free in the presence of 100 and 150 U/ml IFN (13.2 ± 3.8% control versus 16.0 ± 2.5% with 100 U/ml and 19.0 ± 3.0% with 150 U/ml). A similar trend was also seen after a 24-h exposure to both agents.

Although this was a phase I dose-escalation trial, patients were evaluable for response. Of 17 patients enrolled in this trial, 3 responded. Two partial responses were seen in previously untreated patients with measurable stage IV and stage IIIB non-small cell lung cancer. In one of the non-small lung cancer patients the response was shortlived (4 months) while the other lung cancer patient had a response of more than 6 months in duration after receiving six cycles of therapy. A single patient with melanoma had complete resolution of a malignant pleural effusion as well as resolution of atelectasis secondary to malignant bronchial obstruction. Of note, this patient had been previously treated with IFN.

Discussion

We investigated the use of IFN with a 5-day continuous infusion of cisplatin and identified the MTD of cisplatin at 20 mg/m² per day when combined with 3×10^6 U/m² of IFN given three times weekly. These results are similar to other phase I studies combining cisplatin with IFN ($3–5 \times 10^6$ U/m²) in which the cisplatin was administered as a bolus dose. In the bolus studies, the MTD of cisplatin was 20–25 mg/m² weekly or 100 mg/m² every 21 days [19–21]. By administering the cisplatin by a continuous infusion, we were able to lower the incidence of some toxicities while increasing the incidence of other toxicities. Myelosuppression, predominantly manifested as leukopenia and thrombocytopenia, was one of the dose-limiting toxicities. The incidence of myelosuppression seen in our study was higher than prior experience with continuous infusion cisplatin [10–12, 31–33]. The incidence was also higher than in those studies with combined bolus cisplatin and IFN [19–26]. Along with myelosuppression, nausea and vomiting was a significant toxicity seen in our study despite the use of the serotonin receptor antagonist, ondansetron. Previous data with cisplatin alone as a continuous infusion have shown a lower incidence of grade 2 or greater nausea and vomiting (15%) than the 40% observed in the current study [10–12, 31–33]. Bolus cisplatin with IFN has resulted in a 40–70% incidence of grade 2 or greater nausea and vomiting [19–26]. One of the reasons for giving the cisplatin as a continuous infusion in our study was to

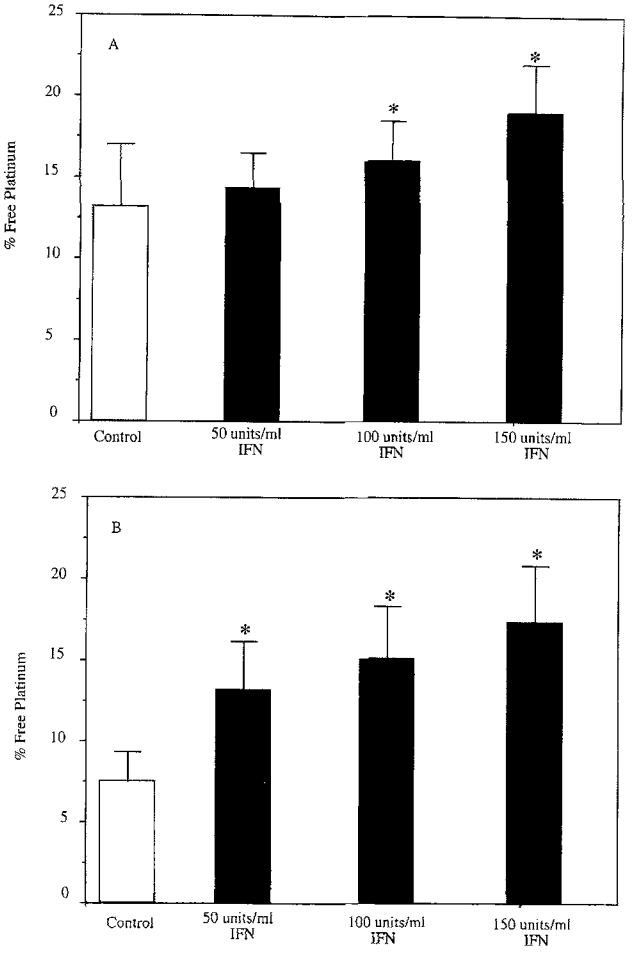

Fig. 1A,B Percentage of free platinum in human plasma after 12 h (**A**) and 24 h (**B**) in vitro incubation in the presence and absence of IFN. The values shown are the results of six separate experiments. $^*P < 0.05$, control versus IFN exposure

try to lower the incidence of nausea and vomiting, which we were unable to achieve. Finally, renal function did not change from baseline in our study (mean of two cycles), which is in agreement with other studies where prolonged infusion cisplatin was utilized (10–12, 31–33). In those studies that gave cisplatin as a bolus with IFN, the incidence of nephrotoxicity (grade 1 to 3) was 7–18% after two or three cycles. This result was higher than in our study and had little impact on defining the MTD of cisplatin with IFN since it occurred at the highest cisplatin dose (which also caused dose-limiting myelosuppression).

The pharmacokinetic data may offer insight into the etiology of the toxicities experienced in this trial. Free (unbound) platinum levels in the present study showed a similar trend as has been observed in other studies where the free $AUC_{0-\infty}$ increased with the dose [13, 31–33]. However, $AUC_{0-\infty}$ was higher than in other studies of continuous infusion cisplatin without IFN. In a study in which 30 mg/m^2 per day cisplatin was given alone for 5 days, the free $AUC_{0-\infty}$ was 9.2 ± 0.3 mg/l h as compared to our data at 20 mg/m^2 per day for 5 days where the free $AUC_{0-\infty}$ was 14.6 ± 1.8 mg/l h [32]. In both studies the free platinum levels were analyzed in a similar manner and a similar population of patients was studied. The elimination of free platinum in the present study was best represented by a monoexponential model. This is similar to what has been observed in other studies which have evaluated the pharmacokinetics of cisplatin when given as a 5 day continuous infusion. Studies which have evaluated the pharmacokinetics of cisplatin following short infusions, have consistently observed an elimination rate of free platinum which fits a biexponential model [8, 33]. We also observed a trend toward an increase in the terminal half-life of free platinum at higher doses. At 5 mg/m^2 per day the half-life was 1.1 h versus 2.2 h at the 20 mg/m^2 per day dose. This trend is interesting and is being further evaluated in a subsequent phase II study. The half-life in the present study was longer than found in studies looking at bolus infusions of cisplatin and has been observed in other 5-day continuous infusion studies utilizing cisplatin alone [7, 8, 32]. The differences seen in the pharmacokinetic parameters between bolus and continuous infusion cisplatin may be explained by renal reabsorption of filterable platinum. Renal clearance of cisplatin involves tubular secretion and reabsorption. Data from bolus administration of cisplatin (50–140 mg/m^2) have shown that tubular reabsorption of the drug reaches saturation at the end of the bolus when plasma and urinary platinum levels are elevated. Once the platinum levels start to decline, more reabsorption occurs proportional to a reduction in the renal clearance. When giving cisplatin as a continuous infusion, saturation of this transport process in the kidney is avoided. The end result is increased reabsorption of platinum that produces prolonged plasma levels, a longer half-life, and a monoexponential decay of platinum [32–35]. In one study an infusion of 40 mg/m^2 per day cisplatin was given for 5 days as a single agent and showed a terminal elimination half-life of free platinum of 81.2 ± 34.9 h in four pediatric patients. In this study it was possible to measure free platinum levels for up to 14 days after the therapy. This observation of a prolonged terminal elimination half-life has only been reported in one pediatric study [36]. This effect has not been observed in any studies with continuous infusion cisplatin in adults.

We also evaluated the possible correlations between the pharmacokinetic data and toxicities experienced in our patients. The cumulative cisplatin dose corresponded to the incidence of grade 3 leukopenia and grade 2 and 3 thrombocytopenia. These results are consistent with the results of previous studies evaluating 24-h infusions of cisplatin [13]. Acute and delayed nausea and vomiting correlated with both the Cpmax of total and free platinum. This appeared to be predictive and occurred despite aggressive antiemetic therapy with serotonin receptor antagonists. Delayed nausea and

vomiting was associated with higher Cpmax total platinum levels as well as the $AUC_{0-\infty}$ of free platinum. Since delayed nausea and vomiting may be associated with total (protein bound) platinum, it would be expected that the Cpmax of total platinum levels would be predictive of delayed nausea and vomiting. In contrast, acute nausea and vomiting, which is associated more with free (unbound) platinum, should correlate better with the Cpmax of free platinum. Patients with higher $AUC_{0-\infty}$ free platinum also showed a higher incidence of delayed nausea and vomiting, suggesting that prolonged exposure of free drug levels may play a role as well. Although no single pharmacokinetic parameter in our study was shown to be most important in predicting toxicity, the $AUC_{0-\infty}$ of free platinum after the first cycle of therapy may be of use in selecting the dose of subsequent cycles. Finally, it was noted early in the present study that the percentage of drug that was free at the Cpmax concentration (seen at 72 h after the start of the therapy) was higher than in other studies evaluating cisplatin as a 5-day continuous infusion alone. In our study the percentage of free platinum at the Cpmax concentrations was $11.1 \pm 0.8\%$. This is twofold higher than the percentage of free drug seen in two studies looking at cisplatin alone (5.3% free and 5.6% free). In each of these studies a similar dosing range and methods of isolating and detecting free platinum were used [7, 32].

The increased percentage of free platinum with concurrent IFN dosing prompted the in vitro study using human plasma. IFN levels used (50–150 U/ml) were in the range of those obtained in the clinical trial. The results showed that after 12 and 24 h exposure to both drugs, the protein binding of cisplatin in human plasma decreased two-fold with the addition of IFN. This may explain the high free platinum $AUC_{0-\infty}$ seen in the present study and the increased incidence of acute nausea and vomiting when compared to other 5-day infusions of cisplatin without IFN.

The response rates were low, as would be predicted in a phase I trial. Of 17 patients treated in this study, 3 achieved significant responses. Two of the patients had previously untreated stage IIIB and IV non-small cell lung cancer while one patient had stage IV malignant melanoma. The latter patient had received prior IFN therapy. Two of the three responders had definite improvement in functional status correlating with response. One responder had no improvement in performance status and a short duration of response. The response rate seen in these tumors was encouraging but not unexpected in view of the results of a phase II study which evaluated IFN with bolus cisplatin. In this study, an overall response rate seen in previously untreated non-small cell lung cancer was 46% [21]. The preliminary results from our study have encouraged us to evaluate this combination therapy in a phase II study to treat non-small cell lung cancer in a crossover design in which patients will receive cisplatin alone and cisplatin with IFN. Detailed cisplatin pharmacokinetic analyses will be performed in the presence and absence of IFN and patients will serve as their own controls in order to further evaluate the potential interaction between cisplatin and IFN. This will be used to design more individualized therapy with respect to toxicity. Protein binding changes of platinum with IFN may also explain these toxicities and allow for lower cisplatin doses to be given since the free platinum level is the active form of the drug. Although the administration of cisplatin as a continuous infusion with IFN did not allow for higher doses of cisplatin to be administered when compared to the bolus administration, the results from the pharmacokinetic analyses may allow for more rational approaches to dosing cisplatin with IFN in the future.

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