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Pharmacokinetics of cis-Dichloro-Trans-Dihydroxy-bis-Isopropylamine Platinum IV (CHIP) in Patients with Advanced Cancer

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Summary. *The pharmacokinetics of a second-generation platinum (Pt) analog cis-dichloro-trans-dihydroxy-bis-isopropylamine platinum IV (CHIP) have been studied in 12 patients at doses from 20 to 350 mg/m². Three Pt species have been measured: total Pt and non-protein-bound Pt by atomic absorption spectrophotometry, and unchanged CHIP by separation on high-performance liquid chromatography followed by atomic absorption spectrophotometry. Plasma decay of total Pt was biexponential at all doses with a β-phase half-life of 32.1–124 h. Plasma decay of filterable Pt was monoexponential at low doses but biexponential at high doses, with a terminal-phase half-life of 17.8–54.6 h. Plasma decay of unchanged CHIP was monoexponential at all doses, with a half-life of 0.64–1.27 h. Excretion of Pt after CHIP was rapid up to 10 h after the end of infusion and then slow. The total recovery of Pt was 15%–61% of the dose at 24 h in 19 patients. The data indicated that essentially all plasma Pt after 12 h is in the form of metabolites, most of which are protein-bound. The most striking difference between CHIP and reported data for cisplatin is the biexponential decay of non-protein-bound Pt.*

Introduction

cis-Dichloro-*trans*-dihydroxy-bis-isopropylamine platinum IV (CHIP) is a quadrivalent platinum (Pt) complex recently introduced into clinical trial as a second-generation Pt antitumor agent. Cisplatin, the prototype antitumor Pt complex, is active against a number of human cancers, including carcinoma of the ovary, bladder, and head and neck, and in combination with vinblastine and bleomycin it can be curative against non-seminomatous testicular tumors. However, its use is limited by nephrotoxicity, which is often only partially reversible. In preclinical studies CHIP showed a wide spectrum of antitumor activity equivalent to that of cisplatin [2, 4, 5, 17, 23] and in rats and dogs had little or no renal toxicity, its dose-limiting toxicity in both species being myelosuppression [6, 17, 22]. Preclinical pharmacokinetics in the rat and the dog showed a biphasic plasma decay of total Pt after CHIP, similar to that of cisplatin but with a considerably shorter β-phase half-life in both species ($t_{1/2}\beta$ 39.4 h in the dog, 14 h in the rat) [6, 21, 22]. In the dog, unchanged CHIP showed a monoexponential plasma decay with a half-life of about 30 min as calculated from urinary excretion rates. The initial clinical trial revealed dose-limiting toxicity of myelosuppression, no renal toxicity, and maximum tolerated dose of 350 mg/m² every 3–4 weeks [7]. In this paper we report the pharmacokinetics of three Pt species, total Pt, filterable (non-protein-bound) Pt, and unchanged CHIP after IV administration of CHIP to patients entered into the phase I study.

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Materials and Methods

CHIP was formulated in 50-mg vials and kindly supplied by Bristol Laboratories, Syracuse, New York.

Patients, Protocol, and Sample Collection. Patients entering the phase I trial who gave written informed consent to the pharmacokinetic evaluation were studied if suitable samples could be obtained. Plasma levels in 12 patients, and urinary excretion in 19 patients receiving CHIP at doses of 20–350 mg/m² (the maximum tolerated dose) were analyzed. The drug was given by 2-h infusion in 250 ml of isotonic saline, preceded by hydration with 2 l of 0.5 *N* saline over 12 h, except in patient 20, who did not receive any prehydration. Blood (5–10 ml) was collected half-way through the infusion, at the end of the infusion, and at 0.08, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 h after the end of the infusion, and whenever possible also at 36, 48, and 72 h. Urine was collected at the end of the infusion, at 2, 4, 6, and 8 h after the infusion and as it was voided thereafter.

Blood was centrifuged immediately, 100–200 µl of plasma separated for total Pt estimations, and the remaining plasma ultrafiltered using Amicon CF-25A centrifugal ultrafilters at 4° C. Aliquots (100–150 µl) of plasma ultrafiltrate (PUF) were separated for the estimation of filterable (non-protein-bound) Pt species and the remaining PUF was used to determine the concentration of unchanged drug by high-performance liquid chromatography (HPLC) and flameless atomic absorption spectrophotometry (FAAS). It has been shown in an earlier in vitro study that CHIP does not bind to the ultrafiltration membrane [21].

Pt Estimations. Total Pt in plasma, PUF, and urine was estimated by FAAS using either a Perkin-Elmer Model 403 atomic absorption spectrophotometer equipped with a 2100 graphite furnace or an Instrumentation Laboratories 457 atomic absorption spectrophotometer equipped with a 655 atomizer and a fastac 254 autosampler. The conditions for using the Perkin-Elmer AAS have been described previously [21]. For the Instrumentation Laboratories AAS a five-stage

temperature program, with atomization for 4 s at 2,400° C, was used. Argon was the purge gas. Plasma samples were digested with an equal volume of 70% HNO_3 and the residue redissolved in 0.5% HCl. Aliquots (10–50 µl) of this solution were injected into the furnace. PUF and urine (10–50 µl) were injected directly into the furnace without preprocessing.

Estimation of the Levels of Unchanged CHIP in Plasma. PUF containing the filterable Pt species was precleaned by passing it through Seppak C18 cartridges (Waters Associates) and eluting the cartridge with 30%, 70% and 100% MeOH. The void volume and the eluates for each sample were pooled, lyophilized, reconstituted in H_2O, and injected into the HPLC. Samples of PUF with low concentrations of Pt were concentrated by lyophilization, before analysis. Separation of unchanged CHIP from metabolites was carried out on a Waters Associates HPLC system using a µBondapak C18 column with H_2O (pH 4.0) to methanol gradient elution [21]. Fractions eluted from the column were collected and the Pt in each fraction was estimated by FAAS. By this procedure CHIP-Pt concentrations could be measured down to 7.5 ng/ml in the PUF. All values for unchanged CHIP in this paper are quoted in terms of Pt (CHIP-Pt). Recovery of Pt from PUF by this method is 95.5% ± 7.8%.

Analysis of Data. The plasma drug disposition data were fitted to either equation (1) or (2) by non-linear regression analysis using the program NONLIN [16] on a Univac 90/80 computer.[1]

$$C_P = \frac{A(1 - e^{-\alpha\tau})e^{-\alpha t}}{\alpha\tau} + \frac{B(1 - e^{-\beta\tau})e^{-\beta t}}{\beta\tau} \quad (1)$$

$$C_P = \frac{A(1 - e^{-\alpha\tau})e^{-\alpha t}}{\alpha\tau}. \quad (2)$$

The data for total Pt were fitted to Eq. (1), data for unchanged CHIP to Eq. (2), and data for filterable Pt to both equations. Data for total Pt in the urine were fitted to Eq. (3).

$$\frac{dXu}{dt} = \frac{A(1 - e^{-\alpha\tau})e^{-\alpha t}}{\alpha\tau} + \frac{B(1 - e^{-\beta\tau})e^{-\beta t}}{\beta\tau}. \quad (3)$$

Equations (1)–(3) have been adapted from the standard equations for one- and two-compartment models by the method of Loo and Riegelman [14] to account for the effect of the 2-h infusion. The renal clearance for total Pt as a function of time was calculated by dividing Eq. (3) by Eq. (1), after each equation had been fitted separately to real data, and parameters estimated. Other desired parameters $t_{1/2}\alpha$, $t_{1/2}\beta$, CL, Q, k_{12}, k_{21}, V_c, V_2 and AUC were calculated from the estimated parameters, A, α, B and β by standard pharmacokinetic equations [10]. Relationships among the desired parameters were explored using SPSS (Statistical Package for the Social Sciences) [18].

1 Symbols used in the paper are defined as follows: C_p is the concentration of drug in plasma, Xu is the amount of drug in urine, dXu/dt is the urinary excretion rate, t is the post infusion time, τ is the duration of the infusion; A, α, B, β are empirical parameters; $t_{1/2}\alpha$, $t_{1/2}\beta$ are half-lives for the α and β phases, respectively; CL is the plasma clearance, Q is the renal clearance, Vc is the volume of distribution of the central compartment, V_2 is the volume of the peripheral compartment; k_{21}, k_{12} are intercompartmental distribution rate constants; AUC is area under the drug disposition curve

Results

The peak plasma concentrations and the AUC for total Pt, filterable Pt, and unchanged CHIP-Pt are shown as a function of dose in Table 1. These data suggest a linear increase in both the peak plasma concentration and AUC for all three species with increase in dose.

Total Pt in plasma decayed biexponentially and the data fitted well with a two-compartment open model at all doses. For making the decision between fitting to a one- or two-compartment model Akaike's information criteria [25] and an examination of the residuals were used. The initial rapid-decay (α) phase for total Pt had a short half-life ranging from 0.34 h to 2.23 h in the 12 patients studied, with a median value of 0.96 h (Table 2). The β-phase half-life ranged from 32.1 h to 124 h, with a median value of 64 h. Additional pharmacokinetic parameters, namely V_c, V_2, CL, and intercompartmental distribution rate constants k_{12} and k_{21}, derived from the plasma concentration data for total Pt, are also included in Table 2. Volume of the central compartment (V_c) for total Pt ranged from 8.2–18.8 l (median at 10.4 l), while that for the peripheral compartment (V_2) ranged between 21.9 and 107.8 l (median 44.2 l). Plasma clearance (CL) values ranged from 0.29 l · h^{-1} to 1.1 l · h^{-1}, with a median value of 0.77 l · h^{-1}. The calculated intercompartmental distribution rate constants indicated a larger k_{12} than k_{21} at all the doses.

The plasma decay of filterable Pt in patients receiving CHIP at 20–120 mg/m^2 conformed to a single-compartment model. In these patients the $t_{1/2}$ for filterable Pt in plasma ranged between 1.45 and 2.05 h, with a median value of 1.75 h (Table 3). In one patient (10) at 120 mg/m^2 and another at 180 mg/m^2 (14) the filterable Pt decay fitted a two-compartment open model. However, the β-phase was not well defined in these two patients, because of the limitations in detectability of Pt beyond 12 h. Therefore, the pharmacokinetic parameters were not calculated for these two patients. Above the dose of 180 mg/m^2 the filterable Pt in plasma showed a clearly biexponential decay, with the α-phase half-life ranging between 0.84 and 1.66 h (median at 1.08 h) and the β-phase half-life ranging between 17.8 and 54.6 h (median at 32.3 h). Thus, the β-phase half-life for filterable Pt is much shorter than that for the total Pt (Table 3). The volume of distribution for filterable Pt in patients with a one-compartment fit was 21.1–39.2 l (median 28.1 l). For the two-compartment fits, while the V_c ranged between 12.0 and 28.7 l (median 22.0 l) the volume of the peripheral compartment was 252.2–967.8 l (median 300.5 l). Plasma clearance of filterable Pt was similar for both one- and two-compartment fits, with median values of 11.6 and 9.0 l · h^{-1} respectively. The rate constants k_{12} and k_{21} for filterable Pt showed similarity to that for total Pt, in that k_{12} in general is larger than k_{21}.

The pharmacokinetics of unchanged CHIP showed a good fit to a single-compartment model at all doses studied. The $t_{1/2}$ values for unchanged CHIP in plasma ranged from 0.64 to 1.27 h (Table 4), with their median at 0.91 h. The V_c for CHIP ranged from 14.2–35.4 l with a median value of 23.4 l. Plasma clearance of CHIP-Pt ranged from 8.1 to 25.9 l · h^{-1} with a

Table 1. The peak plasma concentrations and areas under the curve (AUC) for total Pt, filterable Pt, and CHIP-Pt as a function of dose

Patient	Dose		Peak plasma level (μg/ml)			AUC (μg · h · ml^{-1})		
	mg/m^2	Total (mg)	Total Pt	Filterable Pt	CHIP-Pt	Total Pt[b]	Filterable Pt	CHIP-Pt[a]
1	20	32	1.77	0.57		49.1	2.07[a]	
3	20	40	0.80	0.33		28,0	1.21[a]	
4	40	60	1.38	0.82	0.65	70.7	2.44[a]	1.09
7	80	104	4.50	1.63		168.3	5.15[a]	
9	120	228	4.00	2.50	2.38	137.0	8.08[a]	6.18
10	120	180	3.70	1.57		112.0	6.04[b]	
14	180	270	7.69	3.98	3.22	120.0	15.70[b]	6.89
16	270	515	13.63	6.60	5.68	220.0	19.70[b]	12.60
17	270	540	11.00	8.70	7.90	402.0	47.90[b]	31.40
20	350	550	15.00	8.50	7.59	250.0	37.00[b]	16.10
21	350	600	17.50	6.50	6.17	282.0	25.70[b]	15.80
22	350	700	17.94	8.85	7.00	386.0	28.10[b]	17.10

[a] Fitted to a one compartment model
[b] Fitted to a two compartment model

Table 2. Pharmacokinetic parameters of total Pt after administration of CHIP

Patient	Dose (mg/m^2)	$t_{1/2}\alpha$ (h)	$t_{1/2}\beta$ (h)	V_C (l)	V_2 (l)	CL (l · h^{-1})	K_{12} (h^{-1})	K_{21} (h^{-1})
1	20	2.23	121.0	9.3	44.2	0.31	0.23	0.05
3	20	0.34	49.9	9.0	39.2	0.66	1.61	0.38
4	40	0.79	78.8	12.8	32.5	0.40	0.61	0.25
7	80	1.33	73.3	8.8	21.9	0.29	0.35	0.15
9	120	0.94	111.0	18.1	107.8	0.78	0.59	0.11
10	120	1.01	48.1	15.7	36.8	0.76	0.45	0.21
14	180	0.68	34.3	8.2	44.1	1.06	0.75	0.16
16	270	0.81	55.0	10.9	76.5	1.10	0.66	0.11
17	270	2.11	124.0	18.8	94.3	0.61	0.25	0.06
20	350	0.86	44.7	9.5	57.3	1.03	0.60	0.11
21	350	0.98	32.1	9.8	36.4	1.00	0.48	0.15
22	350	1.05	77.0	12.5	82.16	0.85	0.52	0.09

Table 3. Pharmacokinetic parameters of filterable Pt after administration of CHIP

Patient	Dose (mg/m^2)	$t_{1/2}\alpha$ (h)	$t_{1/2}\beta$ (h)	V_C (l)	V_2 (l)	CL (l · h^{-1})	K_{12} (h^{-1})	K_{21} (h^{-1})
1	20	2.01[a]		21.1[2]		7.2		
3	20	1.75[a]		39.2[a]		15.5		
4	40	1.45[a]		24.1[a]		11.6		
7	80	2.05[a]		28.1[a]		9.5		
9	120	1.62[a]		30.9[a]		13.2		
16	270	1.05[b]	54.60	28,7[b]	967.8	12.3	0.22	0.02
17	270	1.66[b]	33.00	18.0[b]	252.2	5.3	0.11	0.03
20	350	0.84[b]	31.64	12.0[b]	318.8	7.0	0.23	0.03
21	350	1.10[b]	17.80	26.0[b]	282.2	11.0	0.19	0.06

[a] Fitted to a one compartment model
[b] Fitted to a two compartment model

median value at 18.1 l · h^{-1}. Plasma decay profiles of total Pt, filterable Pt, and CHIP-Pt are shown for two patients at doses 40 and 350 mg/m^2 in Figs. 1 and 2.

Urinary excretion of total Pt was rapid initially, but slowed by 10 h after the end of infusion. Although the pattern of urinary excretion is similar in all the patients studied the percentage of the administered dose excreted varied widely (15%–61% at 24 h; and 16.5%–63% at 48 h) (Table 5). Renal clearance of Pt was calculated for all the patients for whom both plasma and urinary concentrations of Pt were available (Fig. 3). Kidney clearance of Pt for every patient was higher initially but fell steadily with time except in one patient,

Table 4. Pharmacokinetic parameters of CHIP-PI[a]

Patient	Dose (mg/m^2)	$t_{1/2}$ (h)	V_C (l)	CL ($l \cdot h^{-1}$)
4	40	0.86	31.9	25.9
9	120	1.17	29.2	17.3
14	180	0.70	18.7	18.4
16	270	0.79	22.0	19.2
17	270	1.22	14.2	8.1
20	350	0.64	14.7	16.0
21	350	0.96	24.7	17.8
22	350	1.27	35.4	19.3

[a] Fitted to a one compartment model

Table 5. Urinary excretion of Pt after CHIP administration

Patient	Dose		% of the dose excreted	
	(mg/m^2	Total (mg)	24 h	48 h
1	20	32	45.5	47.0
2	20	38	42.0	
4	40	60	31.5	33.0
5	40	70	40.5	42.5
6	40	65	37.0	39.0
7	80	104	15.0	16.5
8	80	130	33.5	35.0
9	120	228	61.0	63.0
10	120	180	23.5	26.5
11	120	240	50.0	
12	180	340	41.0	44.0
13	180	300	26.0	
14	180	270	40.5	42.5
15	180	300	26.0	28.0
16	270	515	46.0	47.5
17	270	540	17.0	19.0
18	270	480	34.5	38.5
19	350	730	60.0	
20	350	550	45.5	47.0

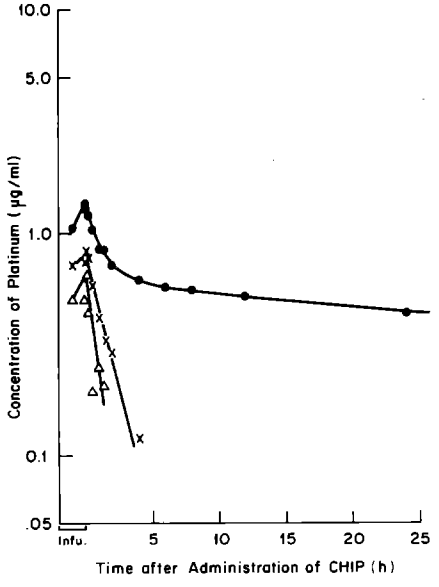

Fig. 1. Plasma decay of total Pt (●), filterable Pt (×), and CHIP-Pt (△) in a patient treated with 40 mg/m^2 of CHIP

who after an initial decline in the first 4 h showed an increase in clearance thereafter. No relationship between the dose of CHIP and the rate of decline in renal clearance was found.

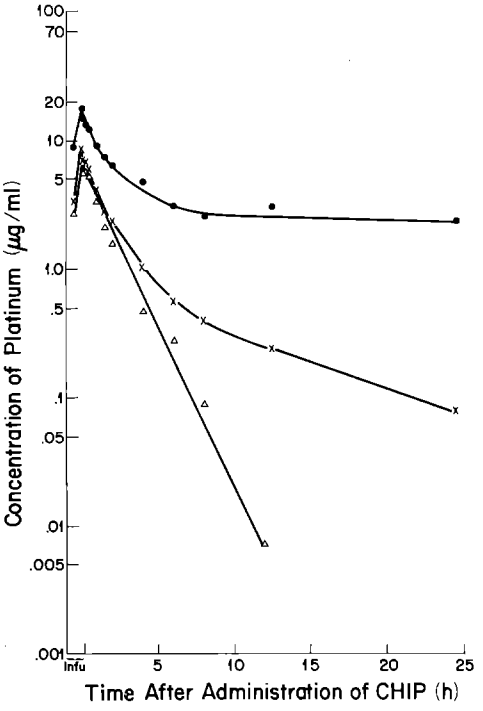

Fig. 2. Plasma decay of total Pt (●), filterable Pt (×), and CHIP-Pt (△) in a patient treated with 350 mg/m^2 of CHIP

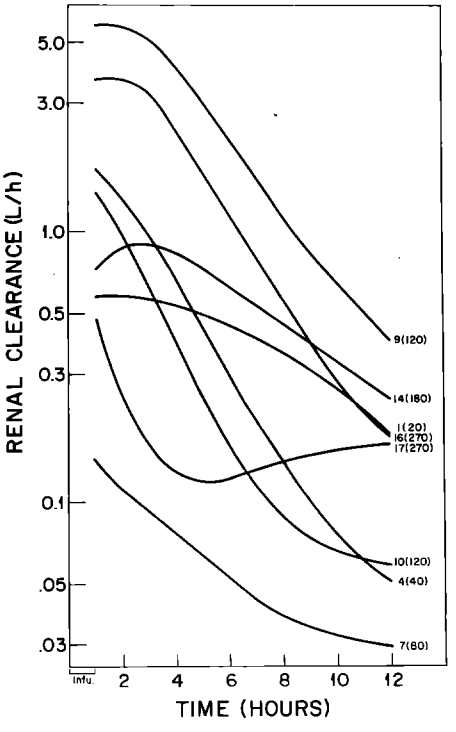

Fig. 3. Renal clearance of Pt. *Numbers* following each *curve* are patient numbers (see Table 5). *Numbers* in *parentheses* are doses in mg/m^2

Discussion

The second-generation Pt complex CHIP differs clinically from cisplatin in that its dose-limiting toxicity is myelosuppression (by standard criteria it produces no renal function impairment at its maximum tolerated dose) and its maximum tolerated dose is approximately three times that of the older drug. A detailed pharmacokinetic analysis of CHIP has been carried out during the phase I trial of single widely spaced doses of this agent to attempt to define pharmacokinetic differences between it and cisplatin which might explain these differences. Although cisplatin has been in clinical use for nearly a decade and there have been many reports of its pharmacokinetics, many of the older studies measured only total Pt [3, 9, 11, 15, 24] and/or filterable Pt in plasma [1, 8, 12, 19], the latter in some cases being equated with unchanged drug [8]. Recently, however, data on the human pharmacokinetics of cisplatin have been reported [13, 20], and these can form the basis of a comparison with the newer compound. However, in these reports filterable Pt and unchanged cisplatin could be followed for only 2–4 h after drug administration and this limits the extent to which a valid comparison can be made.

A number of authors have reported the pharmacokinetics of total Pt after administration of cisplatin. Most of these studies conclude that the plasma decay of cisplatin is biexponential [3, 8, 9, 11, 12, 15, 24] although triexponential plasma decay has also been reported [13]. All studies indicated a prolonged terminal-phase half-life, ranging from 30 h up to infinity in some studies. The data for CHIP reported here do not show any clear differences between this drug and cisplatin; the same biphasic decay and a prolonged β-phase half-life up to 124 h were seen.

The data on filterable Pt in the present study do, however, show marked differences between the pattern with this drug and that reported with cisplatin [13]. At doses up to 120 mg/m^2 plasma decay of filterable Pt was monoexponential, but at doses of 180 mg/m^2 and above the plasma decay of this species became clearly biexponential, with a β-phase half-life of up to 54.6 h. This pattern was not reported for cisplatin. Since this was seen at a dose of CHIP higher than that normally used for cisplatin, this may be an effect of dose rather than a real difference in the behavior of the two drugs. The pharmacokinetics of unchanged CHIP show a monoexponential plasma decay with a median half-life of 0.91 h. This value is approximately double that reported for cisplatin (0.3–0.5 h). This suggests that CHIP may have a longer $t_{1/2}$ than cisplatin, but further data will be necessary to confirm this as the present study involved a limited number of patients and followed unchanged drug levels up to 12 h post-infusion at the highest doses administered, whereas, as noted above, cisplatin has been followed for only 2 h.

Excretion of Pt after CHIP dosage shows marked variability from patient to patient not related to dose, with a range of recovery of 15%–61% at 24 h. With this variability it would be difficult to see any difference between the excretion of this drug and that of cisplatin.

When the pharmacokinetics of the three Pt species are compared, certain conclusions may be reached. We have previously shown that CHIP does not bind to plasma proteins so that the material responsible for the $t_{1/2}\beta$ of total Pt after CHIP must be entirely protein-bound metabolites. This fact, too, would account for the markedly lower plasma clearance of this material than of filterable Pt or unchanged CHIP noted in this study, and for the decrease in renal clearance of total Pt with time. The last appears to be related to the fact that with time more of the Pt in the plasma is represented by metabolites, most of which are protein-bound, and are cleared very slowly by the kidneys.

The difference in pharmacokinetics, particularly at high doses, between filterable Pt and unchanged CHIP indicates that in addition to protein-bound metabolites, nonprotein-bound metabolites of CHIP are formed. The pharmacokinetic parameters, particularly the very large volume of the peripheral compartment for this material, suggest that these species are highly localized in the tissue compartment, either because of a higher lipophilicity or because of binding to cellular components.

In this study with a small number of patients studied at each dose level, no clear relationship between any of the pharmacokinetic parameters measured and toxicity could be demonstrated. However, in more extensive phase II studies with a more uniform population of patients it may be possible to demonstrate such a relationship.

So far no major pharmacokinetic difference between CHIP and cisplatin has been elucidated that would be sufficient to explain the marked differences in clinical behavior of these two compounds. This would indicate either that the basis for these differences are at the cellular level or that more extensive pharmacokinetic evaluation must be carried out to reveal differences between these two compounds.

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