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Preliminary observations of intraperitoneal carboplatin pharmacokinetics during a phase I study of the Northern California Oncology Group*

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Summary. The pharmacokinetic behavior of carboplatin administered by the i.p. route at a dose of 200 mg/m^2 was studied during five courses of therapy in four patients with ovarian cancer. A regional pharmacologic advantage was noted with carboplatin administered by this route, with (1) peak peritoneal fluid concentrations 18-fold those in plasma, and (2) area under the curve (AUC) for the peritoneum showing a 18-fold and 6-fold increase over plasma AUC at 4 and 24 h, respectively. The mean residence time of total platinum in the peritoneum was 4.7 h. Approximately 10% and 40% of plasma platinum was protein bound at 4 and 24 h after treatment, respectively, whereas peritoneal fluid platinum showed minimal protein binding. Peak plasma platinum levels were comparable to those recorded in previous studies with i.v. doses of carboplatin. Peritoneal clearance of carboplatin in these four patients appeared to be less than that previously reported for cisplatin. Further studies are in progress with higher doses of i.p. carboplatin.

Introduction

Recent studies have demonstrated that delivery of some anticancer drugs via the i.p. route is feasible and well tolerated, with drug concentrations achieved at the tumor site and enhanced tumor exposure [5–8, 11, 15]. Cisplatin has been studied following i.p. administration, demonstrating a substantial regional advantage over the i.v. route [5]. Carboplatin (*cis*-diammine-1, 1-cyclobutane dicarboxylate platinum II, CBDCA, JM8), an analogue of cisplatin, is of interest because of its lower toxicity and promising antitumor activity in early clinical studies compared with cisplatin [2, 16]. The plasma pharmacokinetics of carboplatin given i.v. appears to differ significantly from that cisplatin, in particular with respect to the triphasic elimination and much less protein binding [4, 14, 16, 17]. These antitumor and pharmacokinetic properties, and the chemical properties, such as a larger molecular weight and a higher aqueous solubility, suggest that carboplatin would be cleared more slowly than cisplatin from the peritoneum. These data provide a rationale for the study of i.p. carboplatin in ovarian carcinoma.

This is a preliminary report of the pharmacokinetic behavior of carboplatin given i.p. at the first dose escalation level of a phase I study by the Northern California Oncology Group.

Materials and Methods

Patient characteristics. Five courses of i.p.-administered carboplatin were studied in four patients with advanced carcinoma (stage III-VI) of the ovary. All patients had histologically documented malignancy, had failed primary chemotherapy, and were not eligible for radiation therapy. Patients were required at study entry to have a Karnofsky performance status of $>50\%$, and leukocyte and thrombocyte counts $>4000/mm^3$ and $>100000/mm^3$, respectively. Adequate renal function defined as a serum creatinine <1.5 mg% and a 24-h creatinine clearance >50 ml/min was required at study entry.

Method of drug delivery. Carboplatin (200 mg/m^2) was delivered through an indwelling peritoneal catheter connected to a Port-A-Cath (Pharmacia; Piscataway, NJ). The drug was reconstituted in 2 l warm (30–37 °C) 0.45% normal saline prior to instillation into the peritoneal cavity. Half-normal saline was used rather than normal saline to reduce the possibility of conversion of carboplatin to cisplatin in the presence of the higher chloride concentration. In patients with ascites, as much fluid was drained as possible prior to administration of the drug in a 1-l volume. In three of five courses, drug was infused over 16–20 min, while in two courses the duration was of approximately 2 h. No attempt was made to drain the fluid from the peritoneum at any time after infusion.

Biologic specimen handling and drug assay. Blood and peritoneal fluid samples were collected in pre-iced heparinized tubes at various time points after the cessation of carboplatin infusion. The exact time of sampling was recorded in each case, and this value was used for pharmacokinetic analyses. Plasma was separated from whole blood by centrifugation and was immediately frozen (−20 °C). In two

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patients, plasma and peritoneal free platinum samples were prepared by thawing previously frozen plasma samples and immediately performing ultracentrifugation (5000 *g* for 15 min) using Amicon CF-30 filters (Amicon Corp., Danvers, Mass.). Urine was collected for the 4- to 6-h period immediately after the infusion and for the remainder of the 24-h postinfusion period. Following each collection period, an aliquot of urine was removed for analysis. All biologic specimens were stored at −20 °C until analysis.

Quantitation of elemental platinum was performed with a flameless atomic absorption spectrometry assay. A Perkin Elmer Model 2280 atomic absorption spectrometer with a HGA 400 graphite furnace was standardized daily ($r > 0.990$). Platinum absorption was monitored at 266.9 nm and was quantitated by determining the peak area of absorption for each sample and using a previously developed standard curve (peak area versus concentration).

Pharmacokinetic analysis. Pharmacokinetic analyses were performed using compartment- and model-independent estimations of pharmacokinetic parameters based on statistical moment theory derived from chemical engineering data analysis methods [3, 12]. The areas under the plasma and periotoneal time curves were calculated using linear and logarithmic trapezoidal methods [1, 18]. The elimination rate constant was estimated by fitting three or more data points to a monoexponential equation [12]. This was found to give comparable results to a computerized program used to obtain polyexponential parameter estimates [13]. For patients not having plasma or peritoneal sampling throughout a 24-h period, this elimination rate constant was used to calculate a 24-h plasma or peritoneal concentration for use in the area under the first moment curve and area under the curve analyses described below.

Mean residence time (MRT) was calculated from the following equation:

$$MRT = AUMC/AUC,$$

where AUC is the area under the concentration–time curve:

$$AUC = \int_0^T Cpdt$$

and where AUMC is the area under the first moment curve, which is the area under curve of the product of time (t) and plasma concentration (Cp):

$$AUMC = \int_0^T tCpdt.$$

Peritoneal (CL_{PE}) and renal (CL_R) clearances were calculated using the following equations:

$$CL_{PE} = Dose/AUC$$

$$CL_R = \text{Platinum in urine (0–24 h)}/AUC\ (0–24\ h).$$

In vitro plasma protein binding studies. The binding of platinum to plasma proteins was studied in vitro following the addition of carboplatin and cisplatin to human plasma at concentrations representative of those observed in patients receiving therapeutic doses of each agent. Samples were incubated at 37 °C for 2, 4, and 24 h, and aliquots were analyzed for total platinum and ultrafiltrate platinum following ultrafiltration using Amicon CF-30 filters as described above.

Results

Total plasma and peritoneal elemental platinum levels after i.p. administration are shown in Fig. 1. Peak concentrations of total platinum in the peritoneal fluid were between 0.267 and 0.416 μmol/ml immediately after completion of the infusion. Peak plasma concentrations of total platinum were achieved 1–2 h after the end of the i.p. infusion and were between 0.014 and 0.020 μmol/ml (Table 1). The ra-

Table 1. Peak peritoneal and plasma concentrations (μmol/ml) of i.p. carboplatin

Patient	Peritoneal conc.	Plasma conc.	Ratio
1	0.267	0.017	15.8
2	0.305	0.019	16.2
3	0.416	0.014	28.8
4	0.268	0.017	15.6
5	0.320	0.020	16.2
Mean	0.307	0.017	18.5
SD	0.071	0.002	5.8

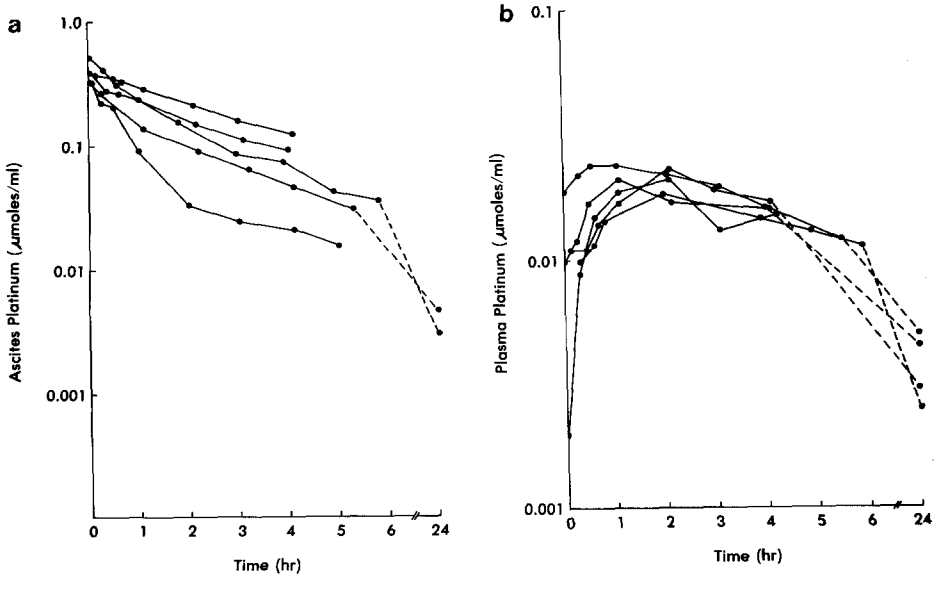

Fig. 1a, b. Total ascites and plasma platinum concentrations after five courses of carboplatin therapy. Each *point* represents the average of at least two platinum determinations

Table 2. Peritoneal exposure as area under the concentration-time curve[a] AUC for i.p. carboplatin

Patient	AUC at 4 h			AUC at 24 h		
	Peritoneal	Plasma	Ratio	Peritoneal	Plasma	Ratio
1	0.399	0.054	7.4	0.631	0.188	3.4
2[b]	1.272	0.049	26.2	1.553	0.185	8.4
3	0.776	0.034	23.0	1.065	0.145	7.3
4	0.380	0.055	6.9	0.477	0.097	4.6
5[b]	1.612	0.059	27.3	1.841	0.248	7.4
Mean	0.908	0.050	18.2	1.107	0.173	6.2
SD	0.543	0.010	10.2	0.591	0.056	1.9

[a] AUC expressed as micromoles per milliliter per hour
[b] Infusions of approximately 2 h duration (all others were of 16–20 min)

Table 3. Other pharmacokinetic parameters of total platinum for patients treated with i.p. carboplatin

Patient	MRT (h)[b]	CL_{PE}[c] (mL/min)	Urinary excretion (% Dose/24 h)	CL_R[e] (ml/min/m^2
1	6.87	13.1	65	17.0
2[a]	5.83	6.3	65	13.4
3	4.23	8.1	62	16.7
4	2.95	21.8	–[d]	–[d]
5[a]	3.64	7.2	–[d]	–[d]
Mean	4.70	11.3	64	16.7
SD	1.60	6.4	1.7	3.2

[a] Infusions of approximately 2 h duration (all others were of 16–20 min duration)
[b] Mean residence time
[c] Peritoneal clearance
[d] Inadequate urine collection
[e] Renal clearance

tio of the peritoneal fluid to peak plasma concentrations averaged 18.5 (range 15.6–28.8). Peritoneal exposure, best expressed as AUC, is outlined in Table 2. The average AUC for total platinum in the plasma was 5.6% and 15.6% of the AUCs for the peritoneum at 4 h and 24 h, respectively. The ratio of the AUCs for peritoneal fluid to that for plasma illustrates the potential advantage of administration of carboplatin by the i.p. route. The exposure for the peritoneum averaged 18-fold higher at 4 h and 6-fold higher at 24 h than plasma exposure. The smaller ratio for total platinum AUC at 24 h is probably a reflection of carboplatin's longer half-life in the plasma (owing to protein-bound platinum) than in the peritoneum. Other pharmacokinetic data are outlined in Table 3. The mean residence time (MRT) for total platinum in the plasma averaged 4.7 h. Peritoneal clearance ranged from 7.2 to 21.8 ml/min. Approximately 64% of the administered dose was found to be eliminated by the kidneys in the first 24 h. The renal clearance of total platinum was found to be fairly consistent, ranging from 21 to 33 ml/min. The 24-h creatinine clearances for these patients ranged from 65 to 82 ml/min. In a single patient evaluated during two consecutive courses of therapy, platinum was still detected in the plasma 3 weeks after the previous dose, suggesting a prolonged elimination phase of approximately 140 h.

The plasma protein binding characteristics of carboplatin and cisplatin were compared after 2-, 4-, and 24-h incubations at 37 °C. Approximately zero, 6%, and 33% protein binding was noted for carboplatin, in contrast to 25%, 43%, and 89% binding for cisplatin, respectively. Consistent with these findings, very little protein binding was detected in vivo in plasma and peritoneal fluid up to 4 h after drug administration (Fig. 2). At 24 h after therapy, approximately 40% of plasma platinum was protein bound, with less than 10% protein binding of platinum in the peritoneal fluid at 24 h.

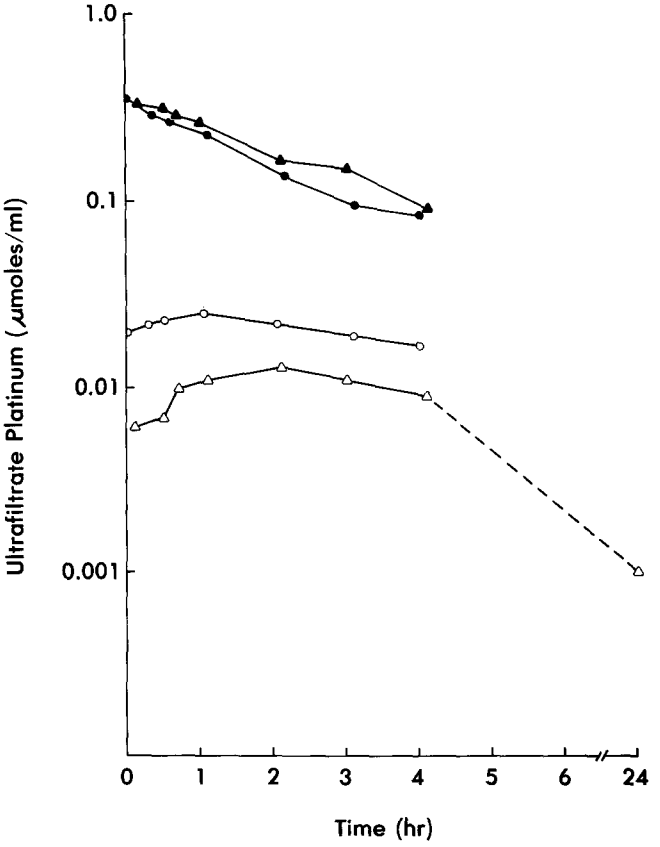

Fig. 2. Ultrafiltrate peritoneal fluid *(closed symbols)* and plasma *(open symvols)* platinum levels in two patients. Each *point* represents the average of at least three platinum determinations

Discussion

Ovarian carcinoma, even in its advanced stages, tends to remain localized in the abdomen, thus making it an ideal tumor for i.p. chemotherapy. Preclinical data, pharmacokinetic modelling, and recent clinical investigations have demonstrated a greater tumor exposure for a number of antineoplastic agents such as cisplatin, cytarabine, doxorubicin, 5-flourouracil, melphalan, and methotrexate when administered by the i.p. route as opposed to the i.v. route [5–8, 11. 15]. Our preliminary data for the pharmacokinetics of i.p. carboplatin, administered at the starting dose of 200 mg/m^2 in four patients during a phase I evaluation, demonstrates a pharmacologic advantage for this route of administration. The peak peritoneal fluid concentrations in these patients were 18-fold higher than those in plasma. If potential pharmacologic advantage for local versus systemic drug exposure is best expressed as the AUC or concentration per unit time, then peritoneal AUCs are 18-fold and 6-fold the corresponding plasma AUCs at 4 h and 24 h after infusion, respectively. Our results are consistent with the pharmacokinetic data reported by McVie et al. [10] in two patients receiving carboplatin i.p. early in a phase I study at a similar dose to that given to our own patients.

Our limited protein binding studies in vitro and in vivo suggest that virtually all the platinum present in the peritoneal fluid at times up to 24 h after drug administration is present as the non-protein-bound form and confirm that there is considerably less plasma protein binding of carboplatin than of cisplatin [4, 16, 17].

The higher molecular weight (371 vs 299) and higher aqueous solubility (17 mg/ml vs 1 mg/ml) of carboplatin than of cisplatin are predictive of slower peritoneal clearance. Howell et al. [5] reported that peritoneal clearance for non-protein-bound reactive platinum averaged 2.6 l/m^2 per h; we found the peritoneal clearance of carboplatin to be 0.42 l/m^2 per h, approximately a 6-fold difference. This correlates with the peritoneal half-life of 0.85 h for cisplatin reported by Howell et al. [5] and with our findings of a mean residence time of 4.7 h for carboplatin.

Administration of carboplatin by the i.p. route did not appear to dramatically change plasma pharmacokinetics. The peak plasma concentrations achieved in our study correspond with those achieved with i.v. administration in fractionated doses over 5 days as reported by Van Echo et al. [16], even when adjustment is made for dose differences. Thus, plasma levels achieved with i.p. carboplatin may provide therapeutic levels to tumor via capillary flow, as well as by direct surface exposure. In addition, our determinations of percent renal elimination and renal clearance are in agreement with those reported by other investigators [10, 14, 16].

We are presently continuing to escalate the doses of i.p. carboplatin in our phase I study, in anticipation of phase II and III clinical trials in patients with ovarian cancer. Further studies examining the pharmacokinetics of carboplatin at higher doses are in progress.

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