Cancer Chemother Pharmacol (1995) 37: 79–85

ORIGINAL ARTICLE

Ian N. Olver · Lorraine K. Webster
Michael J. Millward · Kerrie H. Stokes
James F. Bishop

A phase I and pharmacokinetics study of prolonged ambulatory-infusion carboplatin

Received: 3 November 1994/Accepted: 16 March 1995

Abstract A total of 18 patients received 6-week ambulatory infusions of carboplatin in groups at dose levels of 14, 28, 35 and 42 mg/m^2 per day. The dose-limiting toxicity was myelosuppression. At 42 mg/m^2, three of four patients had WHO grade 4 and one of four had grade 3 neutropenia, whereas two patients had grade 3 thrombocytopenia. At 35 mg/m^2, two of five patients had grade 3 neutropenia, whereas one had grade 4 and two had grade 3 thrombocytopenia. Non-hematological toxicities were predominantly gastrointestinal, with 3 of 18 patients experiencing grade 3 emesis. Total and ultrafiltrable platinum (UFPt) were assayed by flameless atomic absorption spectrometry in weekly and post-infusion plasma and urine samples. In plasma, levels of total platinum increased throughout the infusion, and the protein binding slowly increased from 60% platinum bound at week 1 to 90% bound by week 4. Although the UFPt level reached a steady state within 1 week, the concentration did not increase with the dose level, remaining at a mean value of 0.58 ± 0.24 μM. Renal excretion of platinum accounted for 70 ± 12% of the dose at steady state. There was a high inter-patient variability in both total body clearance of UFPt (range, 83–603 ml/min) and renal clearance (range, 67–390 ml/min). A terminal elemination half-life of 13–27 h was noted for post-infusion UFPt. Neutropenia was linearly related to the total daily carboplatin dose, but neither neutropenia nor thrombocytopenia could be related to steady-state UFPt or the UFPt area under the concentration-time curve (AUC). The recommended dose for phase II studies is 28 mg/m^2 per day.

Key words Phase I · Pharmacokinetics · Carboplatin · Ambulatory infusion

I.N. Olver · L.K. Webster · M.J. Millward · K.H. Stokes · J.F. Bishop
Division of Haematology and Medical Oncology, Peter MacCallum Cancer Institute, St. Andrews Place, East Melbourne, Victoria 3002, Australia

I.N. Olver (✉)
Royal Adelaide Hospital Cancer Service, North Terrace, Adelaide, South Australia, 5000, Australia

Introduction

Carboplatin is an analogue of cisplatin that has been shown to have similar efficacy in a range of malignancies [1, 5, 9, 24]. Its major advantage over cisplatin is reduced non-hematological toxicities, specifically less nephrotoxicity, ototoxicity, peripheral neuropathy and gastrointestinal toxicity [2, 5]. When it is given as a single-agent bolus, its dose-limiting toxicity is leucopenia and thrombocytopenia [14].

Initial attempts at optimising the dose of carboplatin were based on the observation of Egorin et al. [8] that the area under the plasma ultrafiltrable platinum concentration versus time curve (AUC) was related to the pre-treatment renal function and that this related to the percentage of fall in platelet counts. Calvert et al. [4] subsequently derived a formula based on the glomerular filtration rate, which would predict the dose required to produce a given AUC to allow consistent exposure to carboplatin.

Because myelosuppression is dose-limiting and there is preclinical evidence for a dose-response relationship, a strategy for improving the therapeutic ratio for carboplatin is high-dose therapy with hematological support. The preliminary studies have yielded high response rates, although randomised trials against conventional dosing will be required to establish a definite clinical dose-response relationship for carboplatin [3]. A further strategy is to increase the total dose delivered using prolonged infusions.

Little schedule dependency has been established for bolus dosing regimens when multiple frequent dosing schedules are compared with less frequent dosing.

Preclinical data suggest enhanced cytotoxicity with prolonged exposure [17]. Carboplatin has a longer half-life than cisplatin and is not cycle-specific. It is feasible to deliver it by prolonged infusion and explore the effect of increasing the dose intensity in this way. It has a lower chemical reactivity than cisplatin, and platinum-induced DNA inter-strand cross-links appear after incubation with cell suspensions at 6–12 h, which is later than that reported for cisplatin [6, 17]. The non-protein-bound ultrafiltrable platinum is responsible for the DNA lesions [11]. If cytotoxicity is related to the AUC, it may be enhanced by increasing the duration of exposure of the cells to ultrafiltrable platinum. Carboplatin given as a 24-h infusion demonstrated no advantage over bolus dosing in either efficacy or toxicity [13]. Carboplatin has been shown to be stable when stored for 14 days in a portable pump medication reservoir [20].

This study investigated prolonged ambulatory-infusion carboplatin given as a 6-week infusion. It explored a strategy for increasing the total dose and dose intensity of the drug. Since preclinical studies suggest that carboplatin is a radiosensitizer, it is also a potentially useful agent for administration throughout a course of radiation therapy [7]. The aim of this study was to establish a maximum tolerated dose for this schedule, identify the dose-limiting toxicities and recommend a dose suitable for phase II trials. The pharmacokinetics of carboplatin given in this schedule were also investigated.

Patients and methods

Eligibility

To be eligible for entry, patients were required to be adults (≥ 18 years) with a histologically confirmed malignancy, measurable or evaluable disease and a performance status (ECOG) of 0–2 and to have had prior radiotherapy to less than 50% of the bone marrow; an interval of at least 4 weeks since previous chemotherapy (6 weeks in the case of nitrosoureas); adequate bone marrow function (hemoglobin, $>$ 10 g/dl; total white cell count, $> 3 \times 10^9$/l; absolute neutrophil count, $> 1.5 \times 10^9$/l; platelet count, $> 100 \times 10^9$/l); a serum creatinine level of < 0.15 mmol/l; and serum bilirubin and aspartate transaminase values of less than twice the upper limit of the normal range. Exclusion cirteria were significant concomitant illness, other prior or concomitant malignancies (other than surgically treated basal-cell carcinoma of the skin or carcinoma in situ of the cervix), pregnancy or lactation, and the inability to manage a Hickman catheter with an ambulatory-infusion pump. Written informed consent was obtained from patients and the protocol was approved by the Institutional Ethics Committee.

Evaluation

Prior to entry, a full history and physical examination including height, weight and performance status were performed. Pre-treatment investigations included a full blood count (FBC); determination of serum electrolytes, urea and creatinine; liver-function tests; an electrocardiogram; determination of 24-h creatinine clearance; and radiological or other imaging as appropriate to document the extent of tumor. While on treatment, patients were evaluated weekly for toxicity and FBC; serum biochemistry and liver-function tests were repeated weekly. At the completion of treatment all pre-treatment investigations were repeated. Toxicity was assessed using WHO criteria.

Treatment plan

Carboplatin was delivered using portable infusion pumps (CORMED or CADD 1) via a Hickman catheter. Reservoir bags were changed weekly. The starting dose was 14 mg/m^2 per day, approximating the total dose per month delivered in initial phase II bolus studies that used 400 mg/m^2. Subsequent dose escalations were planned to 28 and 42 mg/m^2 per day. Cohorts of three to six patients were entered at each dose level. Intra-patient dose escalation was not permitted. The duration of the infusion was planned to be a maximum of 6 weeks, a duration favourable for future investigation in a radiosensitization program. The infusion reservoir was changed weekly. The infusion was discontinued if WHO grade 3/4 hematological toxicity or disease progression occurred during the 6 weeks. After 6 weeks, further ambulatory-infusion carboplatin could be given on recovery from myelosuppression if indicated. Prophylactic anti-emetics were not used.

Pharmacokinetic sampling

A 10-ml blood sample was taken prior to treatment and weekly to measure steady-state platinum concentrations, and post-infusion pharmacokinetics were measured in consenting patients with sampling at 0 (just prior to stopping the pump), 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 36 and 48 h post-infusion. In these patients, blood was collected via an indwelling cannula kept patent with heparinized saline. All blood samples were centrifuged immediately, and the plasma was separated and stored at -70°C. A weekly 24-h urine collection was obtained, the volume was recorded and an aliquot was frozen for later assay.

Drug analysis

Protein binding was estimated in plasma using Ultrafree (Millipore) ultrafiltration units with a molecular-weight cut-off of 30,000 Da. On the day of assay, 1.0 ml of plasma was centrifuged for 5 min at 11,000 *g* in a microfuge to remove fibrin clots, and 400 µl of supernatant plasma was ultrafiltered at 2,800 *g* at room temperature for 60 min. Platinum was measured in plasma, plasma ultrafiltrate and urine using flameless atomic absorption spectrophotometry. Standards (0.64–5.13 µM) were prepared by dilution of a platinum standard solution (BDH, Poole, UK) in HCl and, subsequently, in a matching matrix (plasma or urine). Samples were diluted as required with 0.1% (v/v) Triton X-100 (BDH, Kilsyth, Australia). All measurements were the mean values for triplicate analyses. Samples were analysed using a Perkin Elmer 3030 atomic absorption spectrophotometer with deuterium background correction, an AS-40 autosampler, an HGA-400 graphite furnace and a PR-100 printer. The furnace program was as follows: step 1 – 100°C, ramp 1s, hold 3s; step 2 – 110°C, ramp 40s, hold 1s; step 3 – 1,400°C, ramp 30s, hold 20s. Nitrogen was used as the inert gas. The platinum lamp (Photron, Narre Warren, Australia) was operated at 15 mA and the 265.9-nm platinum line was monitored using a slit bandwidth of 0.7 nm. Pyrolytically coated graphite tubes (Perkin Elmer) were used and the sample volume was 20 µl. The limit of detection was 0.1 µM.

Total and ultrafiltrable platinum (UFPt) were measured in the weekly plasma samples, and average steady-state concentrations

were calculated using data collected from week 2 to the end of the infusion. The AUC for the entire infusion was estimated by the trapezoidal rule. Total body clearance of UFPt was calculated as the infusion rate divided by the steady-state concentration. Although there were insufficient data for definitive determination of post-infusion pharmacokinetics, the terminal elimination half-life was calculated in several patients using linear regression of the linear portion of the semi-logarithmic plasma concentration versus time curve. The percentage of the platinum dose excreted in the urine in the 24-h samples was calculated and the weekly values were averaged. Renal clearance of platinum was estimated as the mean urinary excretion rate divided by the mean steady-state concentration of UFPt in plasma.

Pharmacodynamics

Myelosuppression was expressed as the percentage of fall in platelets and neutrophils from the pre-treatment to the nadir value. Linear regression was performed using the method of least squares to model myelosuppression to the total daily dose of carboplatin, the mean steady-state concentration of UFPt in plasma, and the free carboplatin AUC. The relationship between both the mean steady-state concentration of UFPt in plasma and the free carboplatin AUC and myelosuppression was also examined using a sigmoidal E_{max} model with a fixed lower point of zero and a fixed upper point of 100%.

Results

Clinical results

A total of 18 patients were entered onto the study at the Peter MacCallum Cancer Institute (Table 1). No response was observed. At 14 mg/m^2 per day all patients discontinued treatment prior to week 6 (at 29, 34 and 35 days respectively) because of progressive disease. One patient entered at 28 mg/m^2 per day stopped treatment after 5 days because of declining performance status. All other patients entered at this level completed 6 weeks of treatment and one patient continued to 11 weeks because no myelosuppression occurred. One patient entered at 42 mg/m^2 per day was taken off study after 10 days because of the development of spinal cord compression. The other patients entered at this dose level discontinued treatment at 36, 36, 21 and 26 days, respectively, because of myelosuppression. Because of the toxicity encountered at 42 mg/m^2 per day, the dose was de-escalated to 35 mg/m^2 per day for the next level. Two patients treated at that level discontinued therapy due to progressive disease at 14 and 34 days, respectively, one patient

Table 1 Characteristics of patients (*NSCLC* Non-small-cell lung cancer)

Patients (*n*)		18
Median age (years)		44 (range, 23–67)
Sex (M/F)		10/8
Performance status (ECOG):		
	0	1
	1	12
	2	5
Tumour type:		
	Melanoma	6
	Colorectal	4
	Renal	3
	NSCLC	2
	Mesothelioma	1
	Head and neck	1
	Unknown primary	1
Prior chematherapy:	Yes	12
	No	6
Dose Level Entered:		
	14 mg/m^2 per day	3
	28 mg/m^2 per day	4
	42 mg/m^2 per day	5
	35 mg/m^2 per day	6

Table 2 Numbers of patients exhibiting WHO grade toxicities

Total white cell count:

Dose level	Patients	WHO grade				
(mg/m^2 per day)	(*n*)	0	1	2	3	4
14	2	1	0	1	0	0
28	3	2	0	0	1	0
35	5	2	1	1	0	1
42	4	0	0	0	3	1

Absolute neutrophil count:

Dose level	Patients	WHO grade				
(mg/m^2 per day)	(*n*)	0	1	2	3	4
14	2	1	1	0	0	0
28	3	2	0	0	1	0
35	5	3	0	0	2	0
42	4	0	0	0	1	3

Platelets:

Dose level	Patients	WHO grade				
(mg/m^2 per day)	(*n*)	0	1	2	3	4
14	2	1	0	1	0	0
28	3	2	0	0	1	0
35	5	0	1	1	2	1
42	4	1	1	0	0	2

Haemoglobin:

Dose level	Patients	WHO grade				
(mg/m^2 per day)	(*n*)	0	1	2	3	4
14	2	1	0	1	0	0
28	3	0	2	0	1	0
35	5	2	2	0	1	0
42	4	0	0	3	1	0

Nausea/vomiting:

Dose level	Patients	WHO grade				
(mg/m^2 per day)	(*n*)	0	1	2	3	4
14	2	2	0	0	1	0
28	3	2	0	1	0	0
35	5	4	0	1	0	0
42	4	2	0	0	2	0

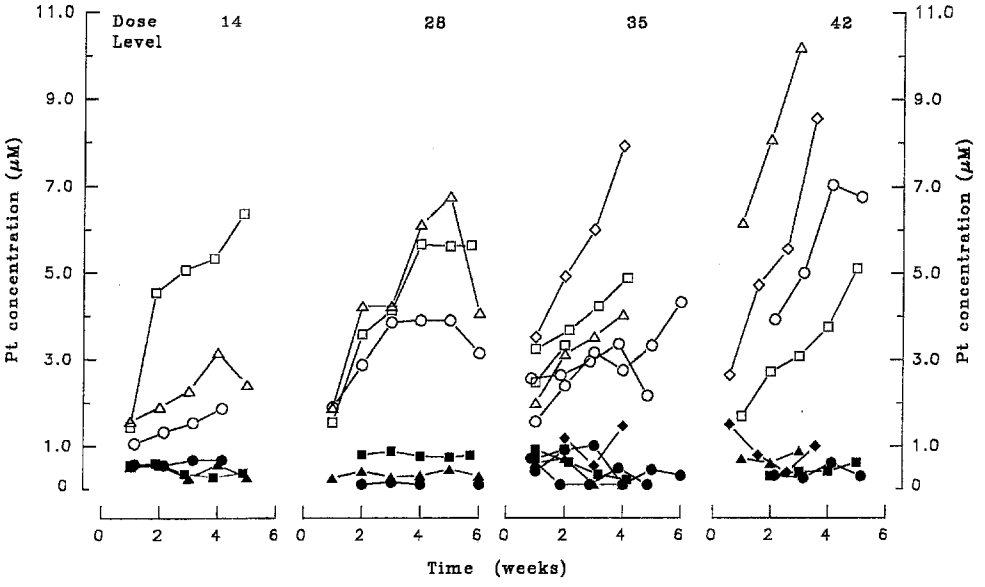

Fig. 1 Linear plots of weekly plasma concentration of total (*open symbols*) and ultrafiltrable (*corresponding closed symbols*) platinum measured in individual patients receiving prolonged ambulatory-infusion carboplatin at the four carboplatin dose levels of 14, 28, 35 and 42 mg/m^2 per day

Table 3 Plantinum pharmacokinetics determined in plasma and urine continuous infusion of carboplatin

Patient	Dose level (mg/m²/d)	Infusion duration (d)	Total dose[a] (mg)	Peak Total Pt (μM)	Plasma UFPt (mean)[b] (μM)	Plasma UFPt (range)[c] (μM)	AUC free drug[d] (mg min/ml)	Total body Clearance UFPt (ml/min)	Urinary Excretion (% Dose)	Renal Clearance (ml/min)
1	14	29	780	1.86	0.61	0.57-0.67	8.1	83	---	--
2	14	34	920	6.36	0.33	0.27-0.37	7.0	153	60	92
3	14	35	980	3.16	0.43	0.25-0.57	7.6	120	63	75
4	28	42	1760	3.90	0.13	0.11-0.16	2.5	603	65	390
5	28	78	3510	6.32	0.83	0.33-0.98	26.8	101	66	67
7	28	42	2100	6.76	0.34	0.26-0.46	7.1	276	73	200
13	35	34	2040	3.36	0.60	0.00-0.70	7.9	188	83	156
14	35	14	910	3.32	0.80	0.70-0.92	4.3	153	--	--
15	35	28	1960	4.04	0.70	0.00-0.70-	3.6	188	71	134
16	35	28	1620	7.92	1.00	0.00-1.44	11.4	109	79	86
17	35	42	3280	4.32	0.54	0.10-1.01	11.4	270	59	158
18	35	29	1680	4.88	0.53	0.22-0.92	7.9	204	69	141
8	42	36	2880	7.04	0.37	0.26-0.60	5.7	405	--	--
10	42	35	2940	5.12	0.44	0.30-0.62	5.9	356	81	289
11	42	21	1680	10.25	0.73	0.60-0.88	6.5	205	49	201
12	42	26	1750	8.56	0.92	0.38-1.50	10.6	143	92	131

[a]Total dose of carboplatin
[b]Mean of 3–6 measurements
[c]Range of all weekly measurements
[d]AUC of UFPt converted to AUC of carboplatin

completed 6 weeks of treatment and the remaining three discontinued therapy because of myelosuppression at 29, 29 and 30 days, respectively.

Patients were considered evaluable for hematological toxicity if they either completed 6 weeks of infusion, stopped prior to 6 weeks because of myelosuppression or completed at least 4 weeks of therapy (Table 2). One patient entered at 14 mg/m^2 per day could not be evaluated for hematological toxicity due to a lack of end-of-infusion blood counts. Neutropenia and thrombocytopenia were dose-related. At 42 mg/m^2 per day, two of four patients had WHO grade 4 thrombocytopenia and three of four had grade 4 neutropenia. At 35 mg/m^2 per day, one of five patients had grade 4 thrombocytopenia and no patient had grade 4 neutropenia. Anemia was not obviously dose-related. Neutrophil nadirs were late, occurring at day 34 or later. Usually the timing coincided with the platelet nadir but sporadically the platelet nadir occurred earlier in the 5th week of the infusion.

The only important non-hematological toxicity was gastrointestinal. No severe renal or neurological toxicity occurred. WHO grade 3 nausea/vomiting occurred in one of three patients at 14 mg/m^2 per day and in two of four patients at 42 mg/m^2 per day (Table 2). Diarrhoea (grade 3) was experienced by one patient at 14 mg/m^2 per day and two patients had stomatitis (grade 2, 28 mg/m^2 per day; grade 1, 35 mg/m^2 per day).

Pharmacokinetics

The steady-state plasma pharmacokinetics of total platinum and UFPt were evaluated in 16 patients, and urinary data were available for 13 patients. The weekly plasma concentrations of total platinum and UFPt for all dose levels are illustrated in Fig. 1. Total platinum concentrations increased with increasing dose and usually did not achieve a steady state. In contrast, UFPt reached a steady state within 1 week, but the concentrations did not increase with increasing dose. The mean UFPt plasma concentration was 0.58 ± 0.24 μM. Individual pharmacokinetic parameters are given in Table 3. Although inter-patient variability was high, the mean (± SD) values recorded for total body clearance of UFPt at three carboplatin dose levels (14, 35 and 42 mg/m^2 per day) were 119 ± 35 (n = 3), 185 ± 54 (n = 6) and 277 ± 123 (n = 4) ml/min, respectively. Plasma protein binding of platinum progressively increased each week, usually ranging from 60–70% bound at the end of week 1 and 80–90% bound by week 4 (Table 4). The post-infusion plasma concentrations measured in two patients treated on the 42-mg/m^2 daily dose level are given in Fig. 2. The terminal elimination half-lives ranged from 24 to 163 (n = 8) for total platinum and from 13 to 27 h (n = 3) for free platinum.

Renal excretion of platinum was consistent, with 70 ± 12% (range, 49–92%; Table 3) of the dose being excreted in urine over 24 h at steady state. However, renal clearance was highly variable and often exceeded the normal glomerular filtration rate (range, 67–390 ml/min; Table 3). The mean urinary excretion rate did tend to increase with the dose level. Values obtained at 14, 28, 35 and 42 mg/m^2 per day were 46 (n = 2), 84 ± 13 (n = 3), 125 ± 11 (n = 5) and 154 ± 42 (n = 3) μmol Pt/day.

Pharmacodynamics

No relationship was found between neutrophil or platelet toxicity and the free carboplatin steady-state level or AUC. For the linear model the correlation coefficients (r) were less than 0.1. According to the sigmoidal E_{max} model for neutrophil toxicity the coefficients of determination (r^2) were 0.076 for the AUC and 0.212 for the steady-state level. For platelet toxicity the r^2 was 0.016 for the AUC and 0.035 for the steady-state level. There was a linear relationship between the daily carboplatin dose and neutrophil toxicity (r = 0.73, P = 0.003) . However, there was no such relationship between the carboplatin dose and platelet toxicity.

Table 4 Plasma protein binding determined during prolonged ambulatory infusion of carboplatin (*NA* Data not available)

Patient	Dose level (mg/m^2)	% Platinum bound in plasma			
		Week 1	Week 2	Week 3	Week 4
1	14	46	58	56	64
2	14	62	87	93	95
3	14	67	71	89	82
4	28	95	96	96	97
5	28	NA	78	79	87
7	28	86	90	93	95
13	35	72	NA	NA	86
14	35	72	72	NA	NA
15	35	70	78	NA	NA
16	35	NA	76	91	82
17	35	73	62	68	96
18	35	72	83	92	96
8	42	NA	92	95	92
10	42	NA	89	87	89
11	42	89	93	91	NA
12	42	43	84	93	88
Mean		71	81	86	88
SD		15	11	12	9

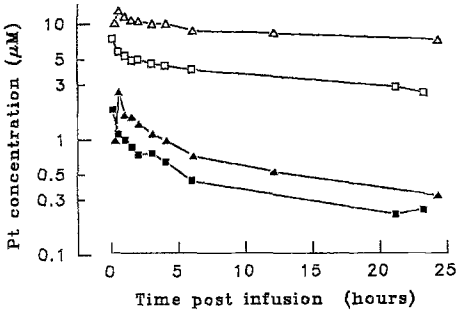

Fig. 2 Semi-logarithmic plot of plasma concentration of total (*open symbols*) and ultrafiltrable (*corresponding closed symbols*) platinum measured in two patients following the end of ambulatory infusion of carboplatin at 42 mg/m^2 per day

Discussion

For carboplatin delivered by a prolonged infusion over 6 weeks, our recommended dose for phase II trials is 28 mg/m^2 per day, which results in a cumulative dose of 1,176 mg/m^2. The dose-limiting toxicity is myelosuppression. Both neutropenia and thrombocytopenia occur and the toxicity is dose-related. In general, non-hematological toxicities were mild, with gastrointestinal toxicity dominating. No nephrotoxicity

was recorded, but platinum-induced renal impairment may not show as a decrease in creatinine clearance [21, 22]. Bolus dosing reported at similar total dose intensities yields greater gastrointestinal toxicity and myelosuppression [25]. Leyvraz et al. [13] reported no advantage in the severity of toxicities for a short-term infusion (24 h) as compared with bolus dosing.

For a 21-day infusion, Smit et al. [23] recommended 30 mg/m^2 per day, giving a total cumulative dose of 630 mg/m^2. Myelosuppression was the dose-limiting toxicity and no nephrotoxicity was recorded [23]. Lokich et al. [14] found myelosuppression to be dose-limiting in a phase I trial in advanced cancer, where the optimal dose rate was 25 mg/m^2 per day over 14 days, giving a cumulative dose of 350 mg/m^2. A dose of 2,100 mg/m^2 over 5 days was reached in a phase I study of a 5-day continuous infusion for refractory acute leukemia [16]. The extramedullary toxicity was mild. Responses were seen but phase II results have not been reported. A phase II trial in acute non-lymphoblastic leukaemia reported that 300 mg/m^2 per day for 5 days produced some responses and minimal toxicity [15]. Drugs for leukaemia, however, are given with the intention of marrow ablation. There is a great variation in reported doses over these phase I studies. The patient population for such trials is small, and some of the differences may simply reflect the different patient populations selected for each trial.

The plasma protein binding of carboplatin-derived platinum is known to be time-dependent [10, 12, 18], reaching approximately 80–90% of platinum bound to plasma proteins by 24 h following a short infusion. We also observed this slow rate of binding, as did Smit et al. [23] during their 21-day ambulatory-infusion study, which may account for the continual increase in total platinum plasma levels observed throughout the infusion. However, there is little explanation for the observation that in both of these prolonged-infusion studies the UFPt reached a similar steady-state plasma concentration, regardless of the dose level. Our mean steady state UFPt level of 0.58 μM was comparable with that found by Smit et al. (0.82 μM) at doses of 20–32 mg/m^2 per day. Although the post-infusion terminal elimination half-life for total platinum is comparable with previously published data [10, 18, 23], the UFPt terminal half-life (13–27 h) is much longer than that observed after bolus dosing of carboplatin (2–6 h) [10, 12, 19] or following 3 consecutive daily bolus doses (6–16 h) [18]. This may be a reflection of the slow protein binding causing differences in the distribution equilibrium of UFPt between steady-state and bolus dosing. Whereas following a bolus dose the true distribution equilibrium is not reached during the period of the pharmacokinetics study, the plasma UFPt concentrations measured following prolonged infusion are high enough above the assay detection limit to enable determination of a true terminal elimination half-life. In fact, Smit et al. [23] did detect a triphasic elimination profile for UFPt with a terminal elimination half-life of 23 h.

The mean urinary excretion rate did tend to increase with dose level, resulting in values for the percentage of dose excreted in urine that were consistent with those reported in the literature [10, 12, 18]. However, the calculated renal clearance was highly variable and often exceeded the normal glomerular filtration rate (GFR). Renal clearance of platinum after bolus dose carboplatin is generally 70–80 ml/min [10, 12], but this is known to be correlated with the GFR, which was not measured in the present study. The total body clearance of UFPt also exhibited a large inter-patient variability and was usually higher than that seen following bolus doses (100–130 ml/min) [10]. In line with the dose-independent steady-state levels of UFPt, we found that the total body clearance of UFPt tended to increase with increasing dose level.

Egorin et al. [8] found after bolus dosing of carboplatin that thrombocytopenia was linearly related to the AUC of UFPt in plasma. We could not confirm this relationship when carboplatin was given as a prolonged infusion. The degree of neutrophil, but not platelet, toxicity was related to the total daily carboplatin dose. Further investigation of carboplatin pharmacodynamics in this schedule should be performed in phase II studies, where the study population will be more homogeneous with respect to tumour type and prior therapy.

We conclude from this study that continuous ambulatory infusion of carboplatin allows dose-intense delivery of the drug with less toxicity than that produced by bolus schedules. As compared with a bolus schedule of 400 mg/m^2 every 4 weeks, the dose intensity of the prolonged infusional therapy is doubled. Although the overall elimination of UFPt does not appear to be compromised during prolonged ambulatory infusion of carboplatin, there are unusual pharmacokinetics that require further explanation, especially dose-independent steady-state plasma levels of UFPt and increased total body and renal clearances. Phase II studies are required to test the anti-tumour activity of this schedule. A 6-week infusion may also be usefully tested in combination with radiation therapy given with curative intent in diseases such as head and neck cancer, bladder cancer and lung cancer.

Acknowledgements We acknowledge the contributions of Heather Baxter as data manager and Julie McGirr as nurse coordinating the pharmacokinetic sampling for this study. This work was supported by a grant from the National Health and Medical Research Council.

References

1. Adams M, Kerby IJ, Rocker I, et al (1989) A comparison of the toxicity and efficacy of cisplatin and carboplatin in advanced ovarian cancer. Acta Oncol 28: 57
2. Alberts DS, Green S, Hannigan EV, et al (1992) Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: final report

by the Southwest Oncology Group of a phase II randomized trial in stages III and IV ovarian cancer. J Clin Oncol 10: 706
3. Bishop JF (1992) Current experience with high-dose carboplatin therapy. Semin Oncol 19: 150
4. Calvert AH, Newell DR, Gumbrell LA, et al (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7: 1748
5. Canetta R, Rozencweig M, Carter SK (1985) Carboplatin: the clinical spectrum to date. Cancer Treat Rev 12: 125
6. Cleare MJ (1983) Development of new platinum coordination complexes: overview. In: Hacker MP, Krakoff IH (eds) Platinum coordination complexes in cancer chemotherapy. Martinus Nijhoff, Boston, p 213
7. Double EB, Richmod RC, O'Hara JA, Coughlin CT (1985) Carboplatin as a potentiator of radiation therapy. Cancer Treat Rev 12: 111
8. Egorin MJ, Van Echo DA, Tipping SJ, et al (1984) Pharmacokinetics and dose reduction of *cis*-diammine(1,1-cyclobutanedicarboxylato)platinum in patients with impaired renal function. Cancer Res 44: 5432
9. Eisenberg M, Hornedo J, Silva H, et al (1986) Carboplatin (NSC 241240): an active platinum analogue for the treatment of squamous cell carcinoma of the head and neck. J Clin Oncol 4: 1506
10. Elferink F, Vijgh WJF van der, Klein I, Vermorken JB, Gall HE, Pinedo HM (1987) Pharmacokinetics of carboplatin after iv administration. Cancer Treat Rep 71: 1231
11. Gormly PE, Bull JM, LeRoy AF, et al (1979) Kinetics of *cis*-dichlorodiamine platinum. Clin Pharmacol Ther 25: 351
12. Harland SJ, Newell DR, Siddik ZH, Chadwick R, Calvert AH, Harrap KR (1984) Pharmacokinetics of *cis*-diammine-1,1,-cyclobutane dicarboxylate platinum (II) in patients with normal and impaired renal function. Cancer Res 44: 1693
13. Leyvraz S, Ohnuma T, Lassus M, Holland JF (1985) Phase I study of carboplatin in patients with advanced cancer, intermittent intravenous bolus, and 24-hour infusion. J Clin Oncol 3: 1385
14. Lokich J, Anderson N, Bern M, Zipli T, Gonsalves L, Moore C (1991) Infusional carboplatin, phase I studies of 5-day and 14-day infusions. Cancer 68: 68
15. Martinez JA, Martin G, Sanz GF, Sempere A, Jarque I, Rubia J de la, Sanz MA (1991) A phase II clinical trial of carboplatin infusion in high-risk acute nonlymphoblastic leukemia. J Clin Oncol 9: 39
16. Meyers FJ, Welborn J, Lewis JP, Flynn N (1989) Infusion carboplatin treatment of relapsed and refractory acute leukaemia: evidence of efficacy with minimal extramedullary toxicity at intermediate doses. J Clin Oncol 7: 173
17. Micetich KC, Barnes D, Erickson LC (1985) A comparative study of the cytotoxicity and DNA-damaging effects of *cis*-(diammino)(1,1-cyclobutanedicarboxylato)-plaltinum(II) and *cis*-diamminedichloroplatinum(II) on L1210 cells. Cancer Res 45: 4043
18. Mulder POM, Vries EGE de, Uges DRA, Scaf AHJ, Sleijfer DT, Mulder NH (1990) Pharmacokinetics of carboplatin at a dose of 750 $mg\,m^{-2}$ divided over three consecutive days. Br J Cancer 61: 460
19. Newell DR, Siddik ZH, Gumbrell LA, Bozall FE, Gore ME, Smith IE, Calvert AH (1987) Plasma free platinum pharmacokinetics in patients treated with high dose carboplatin. Eur J Cancer Clin Oncol 23: 1399
20. Northcott M, Allsopp MA, Powell H, Sewell GJ (1991) The stability of carboplatin, diamorphine, 5-fluorouracil and mitozantrone infusions in an ambulatory pump under storage and prolonged "in use" conditions. J Clin Pharm Ther 16: 123
21. Offerman JJG, Meijer S, Sleijfer DT, et al (1984) Acute effects of *cis*-diammine-dichloroplatinum (CDDP) on renal function. Cancer Chemother Pharmacol 12: 36
22. Sleijfer DT, Smit EF, Meijer S, et al (1989) Acute and cumulative effects of carboplatin on renal function. Br J Cancer 60: 116
23. Smit EF, Willemse PHB, Sleijfer DT, Uges DRA, Postmus PE, Meijer S, Terheggen PMAB, Mulder NH, Vries EGE de (1991) Continuous infusion carboplatin on a 21-day schedule: a phase I and pharmacokinetic study. J Clin Oncol 9: 100
24. Smith IE, Harland SJ, Robinson BA, et al (1985) Carboplatin (JM8) : a very active new cisplatin analogue in the treatment of small cell lung cancer: Cancer Treat Rep 69: 4325
25. Van Glabbeke M, Renard J, Pinedo HM, et al (1988) Iproplatin and carboplatin induced toxicites: overview of phase II clinical trials conducted by the EORTC Early Clinical Trials Cooperative Group (ECTG). Eur J Cancer Clin Oncol 24: 255