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A phase I and pharmacology study of an oral platinum complex, JM216: dose-dependent pharmacokinetics with single-dose administration

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Abstract JM216 [bis-acetato-ammine-dichloro-cyclohexylamine-platinum (IV)] is an oral platinum complex with in vivo activity against murine and human tumor models and a lack of nephro- and neurotoxicity in rodents. During a phase I study of a single-dose schedule, JM216 was given in dry-filled hard gelatin capsules by mouth without hydration or diuresis. In all, 37 patients were given a total of 88 courses at doses ranging from 60 to 700 mg/m^2. The study was stopped before the MTD was reached because of nonlinear pharmacokinetics. Myelosuppression was manifest by leucopenia or thrombocytopenia and showed marked variability at 420–700 mg/m^2. Vomiting was mild and controllable by antiemetics in approximately 50% of courses. The onset of vomiting was delayed to 4 h after during ingestion. There was no nephro-, oto- or neurotoxicity. A partial response was recorded in a patient with recurrent ovarian cancer, and significant falls in plasma tumour markers (CA125) were seen in two further cases. Plasma pharmacokinetics were linear and showed moderate interpatient variability at dose levels of ≤ 120 mg/m^2. At dose levels of ≥ 200 mg/m^2, C_{max} and AUC increased less than proportionally to dose. This was associated with greater interpatient pharmacokinetic variability and reduced urinary platinum recovery. A significant sigmoidal relationship existed between ultrafilterable plasma AUC and the percentage of reduction in platelet count ($r^2 = 0.78$). Nonlinear absorption was a limitation to this single-dose schedule of oral NM216; however, little non-haematological toxicity was seen at doses associated with myelosuppression and antitumour activity. Clinical studies of divided dose schedules using doses within the range of pharmacokinetic linearity (≤ 120 mg/m^2) are now being investigated.

Key words Phase I · Oral administration · Platinum · Dose-dependent pharmacokinetics · JM216

Abbreviations *AUC* Area under the plasma concentration versus time curve · C_{max} peak plasma concentration · *cxs* courses · *FAAS* flameless atomic absorption spectrophotometry · *Gd* CTC toxicity severity grade · *JM216* bis-acetato-ammine-dichloro-cyclohexylamine-platinum(IV) · *MRT* mean residence time · *MTD* maximally tolerable dose · *pts* patients · T_{max} time of peak plasma concentration

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Introduction

Cisplatin and its less toxic analogue carboplatin are the existing clinical platinum agents. Cisplatin causes severe gastrointestinal, renal and neurological toxicity. Carboplatin causes myelosuppression and less severe emesis than cisplatin. Both agents are given by the intravenous route. They display cross-resistance and similar susceptibility to multifocal resistance mechanisms [7]. Decreased uptake of drug through the cell membrane has been a consistent biochemical abnormality found in studies of cisplatin-resistant tumor cells [13]. The development of new platinum drugs that are (a) given orally, (b) lack the severe nonhaematological

toxicity of cisplatin, or (c) overcome transport-mediated platinum resistance to cisplatin and carboplatin is now an important goal. The diaminocyclohexane platinum complexes circumvent transport-mediated cisplatin resistance in murine leukaemia models [1]. Two examples (tetraplatin and oxaliplatin) have recently entered clinical trials; however, severe neurotoxicity has impeded their further clinical development [4, 19].

The ammine/amine platinum(IV) dicarboxylates were synthesised in the expectation of improving the limited gastrointestinal (GI) absorption of cisplatin and carboplatin [10]. The axial dicarboxylate groups and one of the ammine ligands carry lipophilic groups [5], and the platinum(IV) oxidation state confers stability within the GI tract [5]. These compounds are well absorbed from the GI tract in mice and exhibit antitumour activity superior to that of cisplatin in in vivo models [10]. They possess emetogenic properties comparable with or less potent than those of cisplatin [10]. They lack cross-resistance with cisplatin in vitro and susceptibility to transport-mediated resistance [11].

We report a phase I clinical and pharmacology study of a platinum complex given by the oral route. Bis-acetato-ammine-dichloro-cyclohexylamine-platinum (IV) (JM216; Fig. 1) is the lead compound of the ammine/amine platinum(IV) dicarboxylate class. This compound has shown cytotoxicity similar to that of cisplatin against seven human ovarian carcinoma cells in vitro [12]. JM216 has exhibited non-cross-resistance in a panel of six pairs of acquired cisplatin-resistant and parent human tumour cell lines, particularly in examples of transport-mediated resistance [12]. Its antitumour activity and selectivity in vivo following oral administration to mice bearing murine ADJ/PC6 plasmacytomas was superior to that of parenteral cisplatin, carboplatin and tetraplatin [12]. Oral JM216 has shown activity that is broadly comparable with that of cisplatin and carboplatin but superior to that of tetraplatin against four human ovarian carcinoma xenografts [12]. In rodents the dose-limiting toxicity of this oral platinum complex is myelosuppression [15]. This agent has shown a lack of neurotoxicity [16] and nephrotoxicity [14] at maximally tolerable doses (MTDs) in rodents. JM216-induced decrements in jejunal mucosa maltase activity in mice have been lower than those produced by intravenous cisplatin and carboplatin [15]. Cytotoxic plasma platinum concentrations are achieved in mice after its oral administration [17]. Upon absorption the parent complex is rapidly and completely metabolised to at least six platinum species [20]. This agent's metabolism complicated the assessment of its oral bioavailability and precluded the use of pharmacokinetically guided dose-escalation strategies in this clinical study.

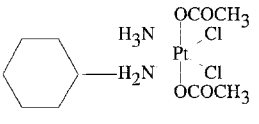

Fig. 1 Chemical structure of JM216

In this phase I trial, JM216 was given by mouth as a single dose once every 3–4 weeks without hydration or diuresis. Neurological and renal function were monitored by vibration sensation threshold and [^{51}Cr]-ethylenediaminetetraacetic acid ([^{51}Cr]-EDTA) clearance [2, 3]. We found nonlinear absorption, myelosuppression and a lack of nonhaematological toxicity with single-dose administration.

Patients and Methods

Patients

All patients were adults aged 18–75 years of either sex with pathologically (histologically or cytologically) proven cancer. Tumours were not amenable to conventional local or systemic therapy. There was a requirement for a treatment-free interval of at least 4 weeks, extended to 6 weeks for mitomycin C or nitrosourea and to 8 weeks for large-field radiotherapy. Patients were ineligible if GI abnormalities likely to compromise absorption, persisting toxicity from past therapy, or previously severe nonhaematological toxicity from platinum-based drugs were present. Adequate bone marrow (WBC, $\geq 3 \times 10^9$/l; neutrophils, $\geq 2 \times 10^9$/l; platelets, $\geq 100 \times 10^9$/l), liver (bilirubin, ≤ 25 μM; alanine aminotransferase, ≤ 100 IU/l; alkaline phosphatase, ≤ 200 IU/l) and renal function ([^{51}Cr]-EDTA clearance, ≥ 60 ml/min) were required. Eligible patients had a Zubrod performance status of 0–2 and a life expectancy of ≥ 3 months. This study was approved by the local ethics committee and written informed consent was obtained in all instances.

Drug

JM216 was supplied as a gift by the Johnson Matthey Technology Centre (Reading, Berkshire, UK). It was formulated by Bristol-Myers Squibb (Syracuse, N.Y., USA) as 10-, 50- and 200-mg hard gelatin capsules with excipients (microcrystalline cellulose, sodium starch glycolate, lactose anhydrous and magnesium stearate). The drug was stored in the light-resistant packaging and was stable at temperatures ranging from 30° to 50°C and at a humidity of 80% (37°C; personal communication, Dr. A. Crosswell). Prior to drug administration, patients fasted from midnight but had free access to fluids. JM216 was given by mouth at between 1000 and 1200 hours under direct supervision. The starting dose was one-tenth of the mouse MTD (60 mg/m^2) [15]. Dose escalation was undertaken according to a modified Fibonacci search (dose levels: 60, 120, 200, 300, 420, 540 and 700 mg/m^2). Three or more patients were treated at each dose level. Accrual to a new dose level proceeded after more than one patient had been observed for a ≥ 1 month at the previous dose level. Intra-patient dose escalation was not used. Treatment was given as a single dose repeated once every 3 weeks or more to a maximum of six treatment courses.

Endpoints

The MTD was defined as the dose producing $\geq$ Gd 3 haematological or GI toxicity or $\geq$ Gd 2 renal, hepatic, cardiac, pulmonary and

neurological toxicity in two of three patients. Toxicity was graded according to the Common Toxicity Criteria (CTC). Patients were asked to complete a diary card of symptoms. Patients were assessed weekly by clinical examination and by blood, serum and urinary studies to evaluate possible bone marrow, kidney and liver toxicity. Evaluations of [^{51}Cr]-EDTA clearance and vibration sensation threshold were undertaken prior to each course and after the final treatment course. Chest radiography, electrocardiography and audiometry were undertaken prior to treatment and thereafter as indicated. The response to treatment was assessed clinically and/or radiologically once every two to three treatment courses. Tumour responses were classified as complete responses (disappearance of all detectable disease), partial responses (decrease of $\geq$ 50% in the sum of the products of perpendicular diameters of all lesions), no change (decrease or increase falling short of a partial response or progressive disease without new lesions) or progressive disease (increase of $\geq$ 25% in one or more evaluable lesions or the appearance of a new lesion) and were scored on the basis of at least two observations spaced at least 4 weeks apart.

Supportive measures

No antiemetic was given prior to treatment at 60–300 mg/m^2 except to patients who had experienced nausea or vomiting on previous courses of JM216. All patients treated at 420–700 mg/m^2 received oral antiemetics prior to JM216. Intravenous antiemetics were used for the symptomatic management of emesis. Antiemetic protocols comprised intravenous or oral administration of (a) metoclopramide (20 mg given once every 4 h for 24 h) and dexamethasone (8 mg given pre-treatment and then 4 mg given once every 6 h for 24 h) or (b) ondansetron (8 mg given pre-treatment) and dexamethasone (8 mg given pre-treatment and then 4 mg given once every 6 h for 24 h). Ondansetron was used in patients with a history of dystonic reactions to metoclopramide or in those failing metoclopramide prophylaxis. No concurrent intravenous or oral hydration was used.

Pharmacokinetics

Pharmacokinetics were studied in all patients on the first treatment course except for one patient each treated at 300 and 540 mg/m^2, when studies were undertaken on the second treatment course, and one patient treated at 540 mg/m^2, who was not studied because of poor venous access. Venous blood (5 ml) was collected at 0, 10, 20, 30, 45 and 60 min and at 1.5, 2, 3, 4, 6, 8, 12, 24 h into tubes containing heparin for plasma total and ultrafiltrate platinum analysis. The clock-time of each sample acquisition was recorded. Blood samples were centrifuged (2000 *g* for 5 min at 4°C) immediately after collection to prepare plasma, and aliquots (2 × 300 µl) were placed in tubes for plasma total platinum analysis and stored in liquid nitrogen. Plasma ultrafiltrate samples were prepared immediately from the remaining plasma using two Amicon Centrifree filters (30,000-Da cutoff; Amicon Division, W.R. Grace Co., Beverly, Mass., USA) per sample. The filters were centrifuged at 2000 *g* for 40 min at 4°C and the ultrafiltrates were combined and stored as two aliquots (approximately 250 µl) in liquid nitrogen. Urine was collected from 0 to 8, 8 to 16 and 16 to 24 h after drug ingestion. The urine was chilled during the collection period and the total volume was recorded. Aliquots from each collection period were frozen for total platinum analysis.

Platinum analysis was undertaken by flameless atomic absorption spectrometry (FAAS) using a Perkin Elmer Spectrometer (Perkin Elmer models 1100B and HGA700, Ueberlingen, Germany). Absorption was measured at 265.9 nm. All plasma and urine samples were diluted at least 10-fold or 20-fold, respectively, with water prior to analysis. Platinum concentrations were calculated by an external standard curve using platinum standards prepared in appropriate matrix. The correlation coefficients for all standard curves were > 0.997 and the detection limits for plasma total, ultrafilterable and urinary platinum were 50, 10 and 100 ng platinum/ml, respectively. The area under the platinum concentration versus time curve (AUC_{0-24h}) and the area under the first moment curve ($AUMC_{0-24h}$) were calculated by the trapezoid rule when successive values were increasing and by the logarithmic trapezoid rule when successive values were decreasing to 24 h. Renal clearance was estimated by dividing the amount of platinum excreted in urine in 24 h by the free plasma platinum AUC_{0-24h}. The mean residence time (MRT) was calculated by dividing the AUMC by the AUC and correcting for mean absorption time by subtracting the inverse of the absorption rate constant. The strength of relationships was assessed by linear regression, and the difference between means was assessed by unpaired and paired *t*-tests. The relationship between platinum exposure and myelosuppression was investigated by fitting a sigmoid Emax model to the data using nonlinear least-squares regression analysis (InPlot, GraphPad Software Inc.), where *y* was the percentage of reduction in platelet or white cell count and *x* was the ultrafilterable plasma platinum AUC.

Results

Patients

Between August 12, 1992, and June 22, 1993, 31 patients were enrolled whose details are shown in Table 1. Of 34 patients assessed, 3 were ineligible because of either poor renal function, poor performance status or severe anaphylaxis to previous platinum therapy. A total of 88 courses of oral JM216 were given. A median of 2 courses/patient were given (range, 1–6 courses/patient). The numbers of patients and courses at each dose level are shown in Table 2. Dose escalation stopped at 700 mg/m^2 and before the MTD was reached

Table 1 Patients' characteristics

Total number		31
F/M		17/14
Age (years):	Median	48
	Range	18–72
Performance status (Zubrod):	Median	1
	Range	0–2
Previous treatment:	None	1
	Chemotherapy	27
	Cisplatin/carboplatin	17
	Radiotherapy	10
	Chemo- + radiotherapy	8
Tumour type:	Ovary	10
	Soft-tissue sarcoma	6
	NSCLC	5
	Mesothelioma	3
	Colorectal	2
	Unknown primary	2
	Breast	1
	Lymphoma	1
	Head and neck	1

Table 2 Haematological toxicity

Dose level (mg/m^2)	Number of patients (courses)	Nadir count ($10^9/l$)[a]		Leukopenia grade (patients)					Thrombocytopenia grade (patients)				
		WBC	Platelets	0	1	2	3	4	0	1	2	3	4
60	3(16)	5.5 (3.7–7.3)	193 (122–407)	2	1				2	1			
120	4(11)	5.0 (2.3–17.7)	248 (162–457)	3		1			4				
200	5(13)	8.2 (5.3–13.1)	335 (117–384)	5					4	1			
300	5(17)	5.6 (3.1–8.7)	269 (141–474)	4	1				4	1			
420	5(10)	8.3 (2.3–9.7)	212 (17–347)	4	2				3	1			1
540	6(16)	4.1 (1.7–8.6)	154 (35–517)	1	4		1		2	3		1	
700	3(8)	4.8 (0.6–9.5)	128 (15–423)	1		1		1	1		1		1

[a] Median (range)

because of nonlinear pharmacokinetics and unpredictable myelosuppression.

Haematological toxicity

Myelosuppression was manifest by either leucopenia (35% of pts), thrombocytopenia (35% of pts), or both (25% of pts). The nadir counts and severity grades are shown in Table 2. The leucocyte nadir occurred at 14 days (range, 7–23 days), with recovery being observed at 22 days (range, 16–42 days). The platelet nadir occurred at 21 days (range, 2–43 days), with recovery being noted at 28 days (range, 8–42 days). There was considerable variability in the severity of haematological toxicity in the 420- to 700-mg/m^2 dose range that was not attributable to patient factors. There was no cumulative myelosuppression [treatment courses associated with most severe haematological toxicity: first course (25% of pts); intermediary course (40% of pts); last course (30% of pts)]. One patient required platelet support for thrombocytopenia complicated by menorrhagia and another required broad-spectrum antibiotics for neutropenic sepsis.

Nonhaematological toxicity

The incidence and severity of vomiting associated with oral JM216 are shown in Fig. 2. Vomiting in courses (dose levels, 60–300 mg/m^2) given without antiemetics prior to JM216 was (a) common (92% of cxs), (b) mild to moderately severe [grade 2 (range, grades 0–3)], (c) delayed in onset [4 h (range, 2.2–9.8 h)], (d) of short duration [1.5 h (range, 0.16–96 h)] and (e) frequently associated with mild nausea [83% of cxs; grade 1 (range, grades 0–1)] and mild diarrhoea [58% of cxs; median Gd 1 (range, Gd 0–2)]. These patients were given intravenous antiemetics before subsequent courses of JM216, and vomiting [48% of cxs, grade 1 (range, grades 0–3)], nausea [53% of cxs, grade 1 (range, grades 0–1)] and diarrhoea [24% of courses, grade 0 (range, grades 0–3)] were less severe and frequent. Oral antiemetics were given prior to JM216 for all courses at 420–700 mg/m^2. In these patients, GI toxicity was infrequent ($< 50\%$ of cxs) and mild ($\leq$ grade 2).

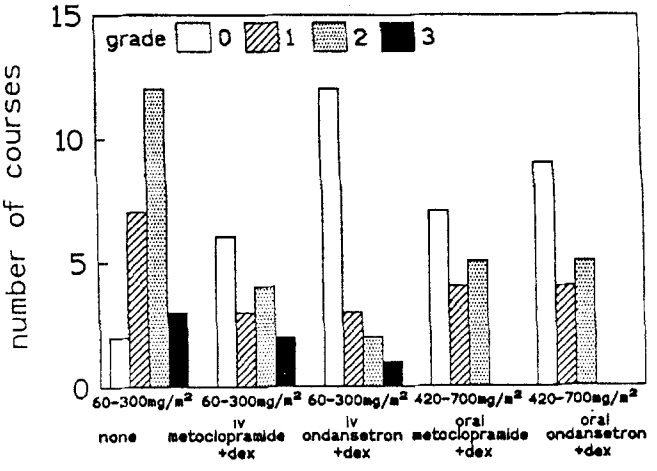

Fig. 2 Clinical grade of emesis related to dose level and use of prophylactic antiemetics (*dex* Dexamethasone)

[^{51}Cr]-EDTA clearance was measured prior to each treatment course (Fig. 3). Paired t-tests of [^{51}Cr]-EDTA clearence before and after treatment at each dose level showed no statistically significant change. Two patients had reductions is glomerular filtration rate attributable to obstructive uropathy. There was no clinical evidence of neurotoxicity. Serial vibration-sensation threshold determinations showed no evidence of subclinical neuropathy [vibration sensation threshold (μ): upper limb, pre-treatment, 0.51 $\pm$ 0.22, post-treatement, 0.47 $\pm$ 0.24, $P > 0.37$; lower limb, pre-treatment, 2.06 $\pm$ 2.0, post-treatment, 1.25 $\pm$ 1.14, $P > 0.05$). Tinnitus occurred in one patient only, but a repeat audiogram showed no change in comparison with the baseline. There were four early deaths as defined by death occurring within 3 weeks of treatment, three being attributable to progressive cancer and one, to thromboembolism. The latter patient died at home 9 days after the third treatment course and thrombotic occlusion of both pulmonary arteries was found post-mortem. There were further instances of deep venous thrombosis in three patients, two of which were complicated by pulmonary thrombo-embolism. Two of these three patients had a history of thrombo-embolic phenomena before study enrollment, and all received further JM216 while on anticoagulant therapy without experiencing further complications. Stomatitis was recorded on two treatment courses, each episode for lasting 7 days and being of Gd 1 and 2 severity, respectively.

Antitumour activity

Tumour responses to JM216 were partial (1 pt), no change (9 pts), progressive disease (16 pts) and not evaluable (3 pts). One patient aged 46 years had a > 50% regression in an ovarian carcinoma hepatic metastasis associated with a 20-fold fall in plasma tumour markers (CA125; from 4950 to 209 IU/ml) after two treatment cycles at 120 mg/m^2. She had previously received cisplatin, after which she experienced a 4-month progression-free interval. This patient received a total of six courses of JM216 treatment and the response duration was > 4 months. Two other women with recurrent ovarian carcinoma had falls in serum CA125 levels without objective changes in measurable tumour (from 5181 to 1198 IU/ml; from 1174 to 471 IU/ml).

Pharmacokinetics

Plasma ultrafiltrate and total platinum time-course profiles obtained in three patients on their first treatment course at the first dose level are shown in Fig. 4. The lag time in appearance of platinum in plasma after oral ingestion of JM216 was 10–20 min. At the first dose level there was modest interpatient variability in the pharmacokinetic parameters of total platinum [percentage of coefficient of variation (%CV): C_{max}, 5.8%; AUC, 7.6%] and ultrafilterable platinum (%CV: C_{max}, 28%; AUC, 42%). At the first dose escalation, C_{max} and AUC increased in proportion to dose (Table 3, Fig. 5). With further dose escalation, C_{max} and AUC increased less than proportionally to dose and reached a plateau after 200 mg/m^2. Greater interpatient pharmacokinetic variability was seen at higher doses (%CV: total plasma C_{max}, 21%–63%); total plasma AUC, 26%–63%; ultrafiltrate C_{max}, 35%–83%; ultrafiltrate AUC, (51%–103%). T_{max} showed no dose-related trend. Urinary platinum recovery accounted for 8.3% of the dose at the first dose level. With dose escalation, urinary recovery fell and accounted for only 1.6% of the dose at 700 mg/m^2.

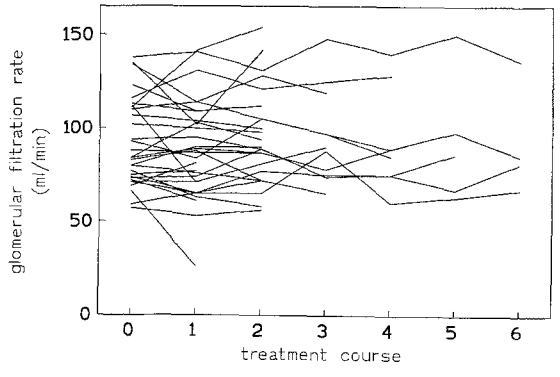

Fig. 3. Renal function during treatment with oral JM216

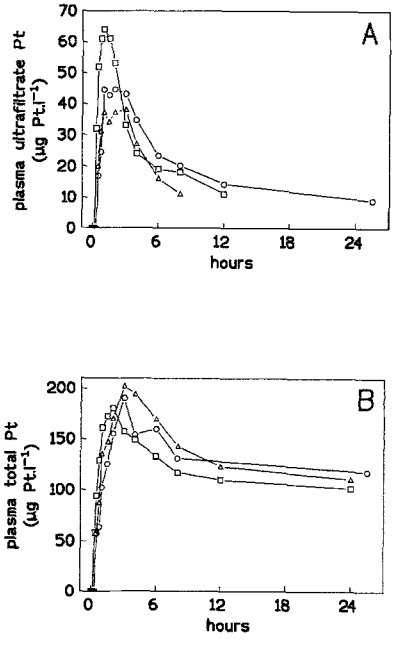

Fig. 4. Time course of ultrafilterable (**A**) and total (**B**) platinum in the plasma of three patients on their first treatment course at the first dose level (60 mg/m^2)

Table 3 Pharmacokinetic parameters (*PUF* plasma ultrafiltrate)

Dose level (mg/m^2)	n	C_{max} ($\mu g\ Pt\ l^{-1}$)[a]		AUC ($\mu g\ Pt\ l^{-1}$)[a]		T_{max} (h)[b]		Urinary recovery (% of dose)	Renal clearance[b] ($ml\ min^{-1}$)	MRT–PUF (h)
		Total	PUF	Total	PUF	Total	PUF			
60	3	191 ± 11	49 ± 14	3057 ± 232	365 ± 155	2.7	1.0	8.4	221	5.8
120	4	320 ± 21	79 ± 32	5529 ± 553	627 ± 507	8.8	4.0	4.5	98.3	7.9
200	5	384 ± 223	101 ± 35	6460 ± 3230	648 ± 330	3.6	2.0	2.2	108	7.9
300	5	407 ± 98	104 ± 55	7325 ± 1905	1187 ± 1175	5.3	2.1	2.6	85	8.0
420	5	509 ± 143	99 ± 37	9198 ± 3403	978 ± 878	6.1	2.0	4.7	95	8.5
540	5	420 ± 88	104 ± 38	6825 ± 2389	1384 ± 1426	4.3	2.1	1.6	166	7.1
700	3	487 ± 307	113 ± 94	8840 ± 5569	958 ± 814	4.0	2.0	1.6	174	7.5

[a] Mean ± SD
[b] Median value

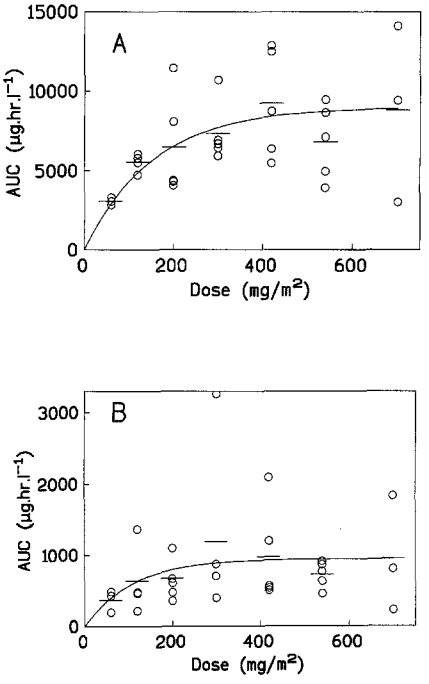

Fig. 5. AUC of total (**A**) and ultrafilterable (**B**) platinum in plasma versus dose (n = 3–5; the *horizontal line* represents the mean)

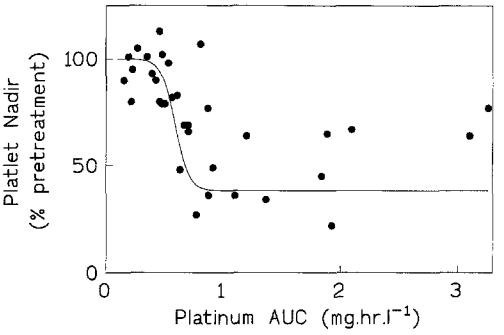

Fig. 6. Relationship between the percentage of reduction in platelet count versus the AUC of ultrafilterable plasma platinum. The curve represents a fit to a sigmoid E_{max} model with the following parameters: E_{max}, 38.1%; EC_{50}, 0.59 mg h l^{-1}; Hill constant, − 7.36; and $R^2 = 0.78$

Most urinary platinum was excreted in the first 8 h (0–8 h, 49% ± 12%; 8–16 h, 30% ± 7.1%; 16–24 h, 17% ± 3.8%). Renal clearance showed no dose dependency and was higher than the glomerular filtration rate (GFR). Renal clearance did not correlate with the GFR ($r = 0.4410$). A significant sigmoidal relationship was found between the ultrafilterable plasma AUC and the percentage of reduction in platelet count ($r^2 = 0.78$; Fig. 6). There was no relationship between the ultrafilterable plasma AUC and the percentage of reduction in leucocytes.

Discussion

We undertook a phase I and pharmacology study of a novel antitumour tetrahedral platinum complex (JM216) given by the oral route. The MTD of a single-dose schedule (every 3 weeks) was not reached because of nonlinear pharmacokinetics. At initial dose levels the plasma pharmacokinetics were dose-independent and showed modest interpatient variability. With further dose escalation, plasma platinum concentrations and AUC increased less than proportionally to dose and became highly variable. Urinary recovery fell from 8.0% to 1.5% of the dose within the dose range studied. These findings are consistent with nonlinearity of GI absorption of JM216. Such a pattern has been shown for oral drugs that (a) are absorbed via saturable active transport mechanisms or (b) have limited dissolution and poor aqueous solubility [21]. In the former case, saturation of active transport mechanisms is associated with zero-order input kinetics and dose-dependent changes in related parameters (T_{max}, K_a). No dose-dependent change in the T_{max} of JM216 was observed. However, JM216 has poor aqueous solubility (≦ 300 mg/l) [5], and pharmacokinetic nonlinearity occurred as the total dose exceeded 300 mg. This suggests that the nonlinear pharmacokinetics of oral JM216 are due to its poor aqueous solubility limiting its dissolution and availability for GI absorption. Etoposide, another poorly soluble oral anticancer agent, has shown

a similar pattern of nonlinear pharmacokinetics [8]. Absorption of JM216 was predictable and linear at doses of $\leq 120\ mg/m^2$. We have tested the hypothesis that schedules using individual doses within the range of pharmacokinetic linearity could overcome the unpredictability of JM216 absorption and toxicity. We found optimal antitumour activity, tolerance and pharmacokinetics with daily × 5 dosing in nude mice bearing xenografted tumours [17]. These results have prompted the clinical evaluation of a daily × 5 schedule [18].

A significant relationship was found between the ultrafilterable platinum AUC and the severity of thrombocytopenia. This suggests that the unpredictable toxic effects of this oral agent may be due to its pharmacokinetic variability and that strategies lessening the pharmacokinetic variability could lead to more predictable toxicity. The pharmacokinetic variability of other platinum agents have been attributed to interpatient variability in renal clearance. In the case of carboplatin, renal clearance is equivalent to the GFR [9]. Renal platinum clearance of oral JM216, however, correlated poorly with the GFR and was higher than the GFR in most patients. This suggests that dose individualisation using GRF estimations may not be feasible with this oral agent and that renal tubular platinum secretion may be an elimination mechanism for JM216. The pharmacokinetic variability of this agent may be due to variability absorption rather than to interpatient variability in renal clearance. The interpatient variability in plasma levels was lower at doses within the range of linear absorption. Moreover, more information is required on the effect of food and antiemetics on JM216 pharmacokinetic variability.

Pharmacokinetic analyses of oral agents often involve a comparison of oral and intravenous data for the derivation of bioavailability. This study of oral JM216 was limited in this regard, several factors having precluded intravenous/oral pharmacokinetic comparisons to date. Firstly, the limited solubility of JM216 has impeded the development of suitable parenteral formulations for clinical studies. Secondly, preclinical studies have shown the parenteral administration of JM216 to be more toxic than dosing by the oral route, a concern for its intravenous use in patients [12]. Thirdly, JM216 is a pro-drug and is metabolised completely upon first pass to several platinum-containing species. These metabolites are presently being characterised and their pharmacokinetic properties are under study [20]. Intravenous/oral bioavailability assessment using the parent compound is therefore not feasible at present and could be potentially hazardous to patients.

Significant toxicity was observed in this study, although the MTD was not reached. Seven patients experienced moderate or severe leucopenia or thrombocytopenia ($\geq$ grade 2), which in two instances was complicated by bleeding or sepsis. Myelosuppression had usually recovered by 4 weeks after treatment and was not cumulative. The only significant nonhaematological toxicity was vomiting. Without the use of antiemetics before JM216 this was very common. The onset of vomiting was delayed to after the time of peak ultrafilterable platinum levels. This suggests that vomiting of ingested drug did not contribute to the variability in JM216 absorption. The severity and incidence of vomiting was reduced by intravenous antiemetics before JM216 ingestion. Oral antiemetic protocols were also effective in controlling emesis in most courses. These simple oral antiemetic protocols will be suitable for use in outpatients. Overall, the GI toxicity of JM216 appears to be less severe than that associated with cisplatin and similar to that of the less toxic analogue carboplatin. Hydration and diuresis were not used, but there was no evidence of nephrotoxicity on repeated determinations of GFR. Peripheral nerve function was monitored clinically and by serial vibration sensation threshold and neither showed changes indicative of neurotoxicity. Thrombo-embolic events occurred in four subjects, but patients with advanced cancer are at high risk of de novo thrombosis [6]. An objective partial response was recorded in a woman with ovarian adenocarcinoma recurrent after cisplatin treatment, and significant falls in CA125 levels were recorded in two other patients with recurrent ovarian cancer. In summary, oral JM216 caused no nephro-oto- or neurotoxicity and emesis was controllable by simple oral antiemetic protocols at JM216 doses associated with significant myelosuppression and antitumour activity.

In conclusion, nonlinear absorption associated with pharmacokinetic variability and unpredictable myelosuppression were encountered in this phase I study of oral JM216 given on a single-dose schedule. The study was abandoned before the MTD was reached. Clinical studies of divided dose schedules using doses within the range of pharmacokinetic linearity ($\leq 120\ mg/m^2$) are now being investigated.

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