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Phase I study of oral JM216 given twice daily

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Abstract JM216 [bis-acetato-ammine-dichloro-cyclohexylamine-platinum(IV)] is an oral platinum complex that is currently in phase II trials in ovarian cancer and lung cancer on a daily-times-5 schedule. This trial examined an alternative schedule of two doses given 12 h apart, which may be better tolerated by patients. A total of 19 patients were given 50 cycles of treatment at doses ranging from 150 to 350 mg/m^2 b.i.d. The study was stopped before the MTD was reached due to non-linear pharmacokinetics. Toxicity was similar to that encountered in previous phase I studies, with nausea, vomiting and diarrhoea being seen at all dose levels, although this was generally mild and short-lived, and grade 3 and 4 myelosuppression being seen at dose levels ranging from 250 to 350 mg/m^2. There was no nephro-, oto-, or neurotoxicity, but one patient had an allergic reaction at 300 mg/m^2 on the fifth and sixth cycles. No response was seen, but two patients with mesothelioma had stable disease and received six cycles. There was considerable interpatient variability in plasma pharmacokinetics at all dose levels. There was no relationship between dose and AUC (dose 1 and dose 2) or C_{max} after dose 1. In a limited number of patients the first dose was given in the morning rather than in the evening, apparently resulting in lower AUC, C_{max} and T_{max} values at the 250-mg/m^2 dose level, but this was not seen in one patient at 300 mg/m^2. This study confirms that the pharmacokinetics of JM216 is non-linear and highly variable due to saturable absorption and that the daily times 5 schedule is the optimal schedule for further phase II trials.

Key words Phase I study · Pharmacokinetics · JM216 · Oral administration · Platinum

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Abbreviations *AUC* Area under the plasma concentration versus time curve · C_{max} Peak plasma concentration · *FAAS* Flameless atomic absorption spectrophotometry · *MTD* Maximally tolerated dose · T_{max} Time of peak plasma concentration

Introduction

Platinum drugs are currently used in the treatment of many solid tumours in adults and children. The prognosis of advanced germ-cell tumours and ovarian cancer has improved since the introduction of cisplatin into the clinic 20 years ago [1, 2]. The toxicity profile of cisplatin includes neurotoxicity, ototoxicity, nephrotoxicity and nausea and vomiting and requires an admission to hospital for intravenous administration. Carboplatin may be given on an out-patient basis and myelosuppression is the dose-limiting toxicity.

JM216 is an ammine/amine platinum(IV) dicarboxylate (Fig. 1) that has increased lipophilicity and stability as compared with cisplatin and carboplatin [3]. It was shown to be well absorbed from the gastrointestinal tract in mice and exhibited oral antitumour activity against in vivo tumour models [4]. After oral administration, JM216 is metabolised into at least six different compounds, many of which retain activity [5, 6]. The initial phase I trial in humans using a single dose was incapable of defining an MTD due to absorption-limited non-linear pharmacokinetics [7]. A subsequent trial explored fractionated dosing using a daily-for-5 days regimen and determined the MTD to be 140 mg/m^2, with the dose-limiting toxicity being myelosuppression [8]. The dose and schedule recommended for phase II studies was 120 mg/m^2 given every 3 weeks for previously untreated patients, and these trials have commenced in ovarian cancer, non-small-cell (NSCLC) and small-cell lung cancer (SCLC), and prostate cancer [9–11]. The present study was initiated to determine whether two divided doses given 12 h apart

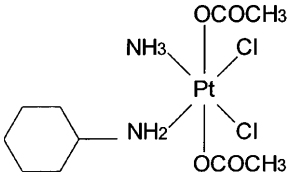

Fig. 1 Structure of JM216

would be an effective alternate schedule for administration of JM216.

Patients and methods

Patients

The present study was approved by the Research Ethics Committee of the Royal Marsden NHS Trust, and written consent was provided by all patients. Patients with advanced cancer not amenable to curative therapy were recruited into the trial. Eligibility for the trial included an age of between 18 and 75 years, a treatment-free interval of 4 weeks (6 weeks for prior nitrosourea and mitomycin C), no large-field radiotherapy within the previous 8 weeks, adequate bone marrow function (leucocyte count $> 3.0 \times 10^9$/l, neutrophil count $> 2.0 \times 10^9$/l, platelet count $> 100 \times 10^9$/l), adequate liver function (bilirubin ≤ 25 μmol/l, ALT ≤ 100 IU/l, ALP ≤ 200 IU/l), a life expectancy of > 3 months and a WHO performance status of 0–2. Patients were ineligible if gastroenterological abnormalities were likely to compromise absorption and if severe toxicities from previous therapy had not yet resolved. The study was conducted under the auspices of the Cancer Research Campaign Phase I/II Committee.

Drug

JM216 was supplied by Johnson Matthey Technology Centre (Reading, Berkshire, UK). The drug was formulated as 10-, 50- and 100-mg hard gelatin capsules with excipients (microcrystalline cellulose, sodium starch glycolate, lactose anhydrous and magnesium stearate) by Bristol Myers Squibb (Syracuse, N.Y., USA). Patients were fasted prior to administration of the drug, which was given in two doses. In the first 17 patients the first dose was given in the evening and the second dose, in the morning of the following day. In the last two patients, dosing commenced in the morning, with the second dose being given 10–12 h later. The dosing interval was always > 10 h. The starting dose was 200 mg/m^2 for two doses and was escalated by 50 mg/m^2 on the basis of toxicity and pharmacokinetic data. Treatment was repeated every 3 weeks or more according to toxicity for up to a maximum of six courses. Antiemetics were used routinely; ondansetron at 8 mg and dexamethasone at 4 mg were given prior to each dose, followed by regular administration of dexamethasone and metoclopramide for 2–3 days post-dosing.

End points

The MTD was defined as grade ≥ 3 haematological or gastrointestinal toxicity or grade ≥ 2 renal, hepatic, cardiac, pulmonary or neurological toxicity in two of three patients. Toxicity was graded according to the Common Toxicity Criteria and patients were asked to complete a diary card of symptoms. Haematological, renal and liver toxicity were assessed weekly by blood and serum studies. Patients were also assessed by weekly examination for tumour evaluation and toxicity. A chest radiograph and an electrocardiogram were performed prior to each course, and response to treatment was evaluated every two courses. Tumour responses were measured according to WHO criteria. Toxic death was defined as any death to which drug toxicity was thought to have contributed. Early death was defined as death within 3 weeks of treatment.

Pharmacokinetics

Pharmacokinetics studies were attempted in all patients on the first treatment cycle except for one patient at the 300-mg/m^2 dose level. One patient had pharmacokinetics studies repeated on the third course, in which the drugs were given in a different time sequence (first dose in the morning and second dose in the evening).

Venous blood was collected at time 0, at 15 and 30 min as well as at 1, 2, 4, 8 and up to 12 h after each dose. Blood samples were centrifuged (2,000 *g* for 5 min at 4 °C) immediately after collection for preparation of plasma. Aliquots were placed into tubes for platinum analysis and stored in liquid nitrogen. Plasma ultrafiltrates were prepared using two Amicon Centifree Filters (30,000-MW cut-off) per sample. The filters were centrifuged at 2,000 *g* for 20 min at 4 °C and the ultrafiltrates were combined and stored as two aliquots in liquid nitrogen.

Platinum analysis was undertaken by flameless atomic absorption spectrometry (FAAS) using a Perkin Elmer Spectrometer (Perkin Elmer Models HGA 700, Ueberlingen, Germany). As performed in the daily-times-5 phase I study of JM216, pharmacokinetic analysis was performed using the PCNONLIN compartmental analysis model (models 4 and 12) using first-order-input one- and two-compartmental models for total and ultrafiltrable platinum, respectively. Due to the short sampling period, considerable variation was observed in the estimation of pharmacokinetic parameters such as $t½$ and AUC. Therefore, the AUC values presented herein were calculated (dose 1, 0–12 h; dose 2, 12–24 h) with the trapezoidal method. Where sampling times were not exactly 12 h post-dosing, AUC values were back-extrapolated to 12 h to allow for accurate comparison. No sample weighting was used.

Results

Between October 1994 and July 1996, 19 patients were enrolled into the study whose characteristics are shown in Table 1. A total of 50 courses of JM216 were given and the median number per patient was 2 (range 1–6).

Table 1 Patients' characteristics

Total number	19
F/M	11/8
Age (years):	
Median	53
Range	30–72
Performance status:	
Median	1
Range	0–2
Prior treatment:	
None	2
Chemotherapy alone	12
Chemo/radiotherapy	5
Tumour type:	
Mesothelioma	5
NSCLC	4
Ovarian cancer	2
Sarcoma	3
Gastrointestinal cancer	4
Unknown primary	1

Table 2 Haematological toxicity: all courses

Dose level (mg/m^2)	Patients (*n*)	Courses (*n*)	Leucopenia		Neutrophils		Platelets		Haemoglobin	
			Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
150	1	2	0	0	0	0	0	0	0	0
200	3	8	6	0	5	0	3	0	4	0
250	5	9	4	0	1	0	2	1	3	0
300	6	16	3	0	3	0	1	1	5	1
350	6	15	1	2	2	1	3	1	3	1

The numbers of patients treated at each dose level are shown in Table 2. One patient had a dose reduction due to gastrointestinal toxicity (grade 1 vomiting and grade 3 abdominal pain). One patient had a dose escalation to a new dose level after three patients had tolerated the previous level without developing toxicity. Dose escalation ceased at 350 mg/m^2, before the MTD was reached, when it was clear that absorption was saturable in a fashion similar to that noted in the phase I trial using a single-dose schedule.

In all, 14 patients received more than 1 course and of these, 7 had a treatment delay due to toxicity or tumour-related problems. Two patients had grade 1 neutropenia at 3 weeks after the previous dosing and treatment was delayed by one week.

Haematological toxicity

As in the previous single-dose phase I study, leucopenia and thrombocytopenia were observed but in the main were mild (Table 2). Leucopenia developed in 16/50 (32%) courses but was of grade 3, 4 in only 2 (4%) courses. Grade 4 neutropenia occurred in one patient without infection. Thrombocytopenia was seen in 14/50 (28%) courses but was of grade 4 in only 3 (6%). This was seen in three patients at three different dose levels (250, 300, 350 mg/m^2), and one required a platelet transfusion. Mild anaemia was also a feature in almost all patients (44/50 courses), but grade 4 anaemia was seen in two patients, both of whom received a blood transfusion just prior to the beginning of the study. One had NSCLC and at the time of the anaemia, hypercalcaemia and brain metastases were diagnosed. This was seen on day 8 of the first treatment cycle. The second patient also had NSCLC and developed spinal cord compression and a chest infection due in part to his primary ling tumour. On day 10 of his first treatment cycle his Hb value dropped to 5.0 g/l. Both of these patients died of progressive disease and did not receive a subsequent dose of JM216.

Non-haematological toxicity

Nausea and vomiting were common side effects of JM216 but were almost always mild (grades 1,2) and short-lived (Table 3). One patient experienced grade 4 vomiting and one developed grade 3 nausea. All patients were given oral antiemetics consisting of ondansetron and dexamethasone prior to both doses of JM216.

Diarrhoea was noted in 24/50 (48%) courses, but in only 4 (8%) cases was it severe (grades 3,4). Five patients died while on study, all due to progressive disease. One patient had an allergic reaction during course 5 that occurred at 30–60 min after the JM216 dose and consisted of a rash, which responded to chlorpheniramine. In the following course the patient was observed in hospital after administration of the first dose and developed rigors, fever and rash, which responded to pethidine, hydrocortisone, and chlorpheniramine.

Antitumour activity

There was no response to JM216 in this study; 2 evaluable patients had stable disease after ≥ 2 courses of treatment, and 2 non-evaluable patients with mesothelioma had stable disease and completed 6 courses of therapy.

Table 3 Non-haematological toxicity: all courses

Dose level (mg/m^2)	Courses (*n*)	Patients (*n*)	Nausea		Vomiting		Diarrhoea		Other[a]	
			Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
150	2	1	0	0	0	0	0	1	0	0
200	8	3	4	0	4	1	2	0	0	0
250	9	5	3	0	1	0	0	2	1	0
300	16	6	6	0	7	0	7	0	0	0
350	15	6	4	0	7	0	11	1	0	0

[a] Allergic reaction

Table 4 PK parameters of platinum in plasma ultrafiltrate after dose 1 and dose 2 of JM216. Data represent mean values ± SD or individual values where $n < 3$

Dose (mg/m^2)	Patients (n)	C_{max} ($\mu g\ l^{-1}$)		T_{max}(h)		AUC_{0-T} ($\mu g\ h\ l^{-1}$)			$t_{1/2\beta}$ (h)	
		Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1 + 2	Dose 1	Dose 2
200	2	92, 124	109; 131	3.0; 3.3	2.8; 6.5	688; 965	1,099; 1,951	2,064; 2,639	3.7; 6.0	5.4; 8.7
250	4	157 ± 57	132 ± 53	4.1 ± 1.9	8.6 ± 1.4	1,223 ± 546	2,593 ± 1,586	3,816 ± 2,107	5.5 ± 2.7	13.2 ± 5.1
300	5	141 ± 71	155 ± 82	3.0 ± 1.3	9.2 ± 7.9	930 ± 485	2,939 ± 1,803	3,869 ± 2,237	4.7 ± 1.5	17.7 ± 9.5
350	3	171 ± 71	165 ± 105	1.9 ± 0.3	7.3 ± 4.7	1,401 ± 1,249	1,586 ± 388	2,987 ± 1,568	3.6 ± 2.2	11.3 ± 9.4

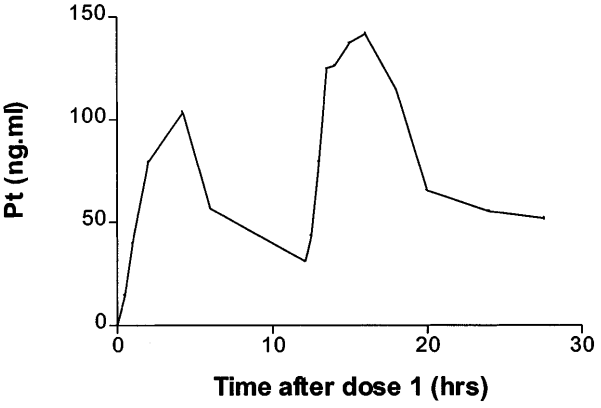

Fig. 2 PUF concentration-time curve generated for patient 1 (200 mg/m^2)

Pharmacokinetics

Pharmacokinetic (PK) sampling was done on 16 patients (in 2 patients, poor venous access did not allow adequate sampling). In one patient a repeat analysis was done after the drug had been given in the reverse order – morning before evening. In two patients there was insufficient sample for analysis of the ultrafiltrate platinum. The PK parameters for plasma ultrafiltrate (PUF) are detailed in Table 4. The time to peak ultrafilterable platinum (T_{max}) after the first dose was 3.1 h (range 1.6–6.3 h) and after the second dose, 7.9 h (range 1.2–20.2 h). The PUF AUC recorded for the second dose was higher than that noted for the first dose, reflecting that free platinum had not cleared from the plasma at 12 h post-dosing (Fig. 2). There was no correlation between the dose and the PUF AUC noted for the first dose, that recorded for the second dose or the sum of the two. Increasing the dose above 200 mg/m^2 did not result in an increase in the PUF AUC observed for dose 1 and 2, although there was a wide variation in values (Fig. 3). C_{max} was similar for both dose 1 and dose 2, but there

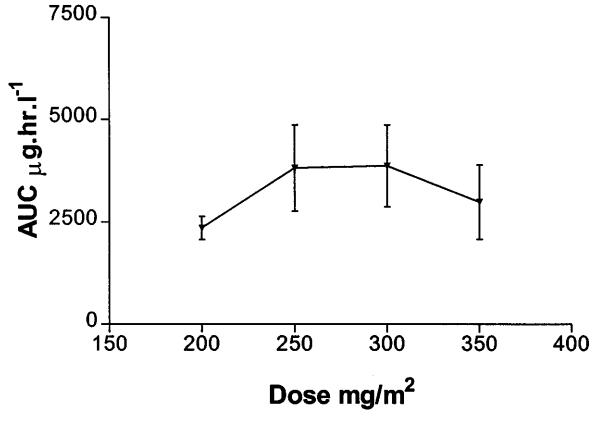

Fig. 3 PUF AUC recorded for dose 1 and 2 versus the JM216 dose (mg/m^2)

Table 5 PK parameters of platinum in plasma after dose 1 and dose 2 of JM216. Data represent mean values ± SD or individual values where $n < 3$

Dose (mg/m^2)	Patients (n)	C_{max} (μg l^{-1})		T_{max}(h)		AUC_{0-T} (μg h l^{-1})			$t_{1/2\alpha}$ (h)	
		Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1 + 2	Dose 1	Dose 2
200	2	479; 805	1,261; 1,293	5.8; 7.4	6.9; 9.3	4,586; 8,041	11,850; 29,070	19,890; 33,650	21.9; 38.0	8.7; 27.9
250	5	747 ± 400	1,192 ± 630	7.0 ± 3.4	9.5 ± 2.9	6,233 ± 3,181	23,480 ± 18,840	29,710 ± 21,980	27.3 ± 8.9	18.7 ± 19.3
300	5	563 ± 110	1,655 ± 419	9.5 ± 3.9	7.5 ± 3.2	5,441 ± 1,425	39,650 ± 11,190	45,090 ± 11,210	36.5	21.7 ± 9.1
350	4	777 ± 297	1,595 ± 1,334	6.5 ± 4.2	6.0 ± 3.9	7,209 ± 2,430	31,220 ± 24,210	38,430 ± 25,950	18.8 ± 3.7	14.1 ± 8.1

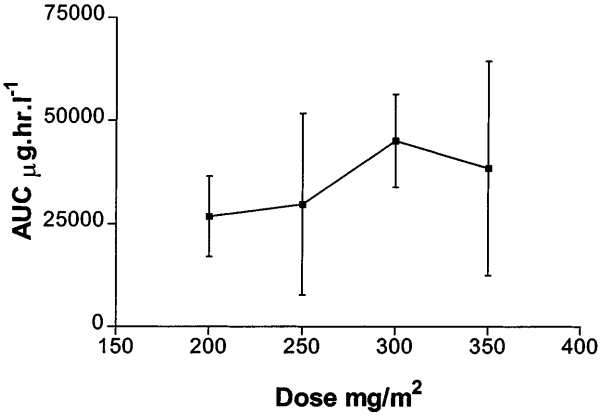

Fig. 4 Plasma AUC recorded for dose 1 and 2 versus the JM216 dose

was no increase at dose levels above 200 mg/m^2. Levels of drug were detectable in plasma prior to the second dose but did not appear to be significant.

There was no correlation between PUF AUC (dose 1 and 2) and pre-treatment albumin or creatinine clearance as measured by the Cockcroft and Gault formula. Similarly, there was no relationship between AUC or C_{max} and the development of grade 3–4 haematological toxicity. At the 250-mg/m^2 dose level, two patients were treated in the reverse order (dose 1 in the morning and dose 2 in the evening). Although the number of patients was small, the AUC dose 1 was lower when the first dose was given in the morning (774 versus 1,671 μg h l^{-1}), as was the AUC dose 2 (1,269.5 versus 3,916.5 μg h l^{-1}; (Table 6). T_{max} was shorter when dose 1 was given in the morning as compared with the evening (2.7 versus 5.6 h), and C_{max} was lower when dose 1 was given in the morning (118.5 versus 196.4 μg/l). However, in the one patient who had repeat pharmacokinetics studies done at 300 mg/m^2, there was no change in the dose 1 AUC, T_{max} or C_{max}.

Total plasma pharmacokinetics were performed on 16 patients; blood was unobtainable from 2 patients and the data could not be fitted to the PK model in 1 patient (Table 5). Once again, there was no correlation between dose and the AUC for the first or second dose or the sum of the two (Fig. 4). Patients given the first dose in the morning at 250 mg/m^2 had lower AUC dose 1, dose 2, and C_{max} values, but T_{max} values were similar. Interestingly, in four patients the T_{max} was not reached after dose 1 (i.e. >12 h), but after the second dose the T_{max} was reached well before 12 h post-dosing (2.6–10.2 h).

Discussion

This study set out to explore an alternate schedule for the oral platinum analogue JM216, which is currently being tested in phase II trials using a daily-times-5 regimen. The original phase I trial using a single dose did

Table 6 PUF PK data – morning versus evening first dose

Dose level (mg/m^2)	Patients (*n*)	Dose 1	PUF AUC 1 ($\mu g\ h\ l^{-1}$)	PUF AUC 2 ($\mu g\ h\ l^{-1}$)	C_{max}($\mu g/l$) Dose 1	T_{max} (h) Dose 1
250	2	Morning	774	1,269.5	118.5	2.7
250	2	Evening	1,671	3,916.5	196.4	5.6
300	1	Morning	701	3,045	114	2.6
300	1	Evening	621	743	90.6	1.9

not achieve an MTD due to saturation of the absorption, leading to non-linear pharmacokinetics. In a subsequent trial a daily-times-5 schedule reached an MTD with a dose-limiting toxicity of myelosuppression and established the dose for further trials. The present study evaluated the alternative schedule of two doses given 12 h apart. A less than proportional increase in AUC and C_{max} was observed with increasing doses and, as a result, the MTD was not reached. There was no correlation between the AUC recorded for the first dose, the second dose or the sum of the two AUCs and the dose in milligrams per square meter of body surface area. Accepting the limited extent of the comparison, the T_{max} was longer, the C_{max} was higher and the AUC was greater in patients treated at 250 mg/m^2 when the first dose was given in the evening. However, the number of patients tested was small and this finding was not confirmed at 300 mg/m^2 in a single patient. The reasons for this may be altered active metabolic processes or bowel motility in the evening as compared with the morning. An alternative explanation could be interpatient variability in absorption or modification of clearance. However, there was no correlation of AUC with creatinine clearance (data not shown). In addition, there was no correlation of PUF AUC with serum albumin, although this is not surprising, given the tight binding of the species identified as a JM216 metabolite [6].

The site of maximal absorption of JM216, the energy requirements and the effect of GI tract (GIT) motility on the absorptive process are not known. In the single-dose phase I study there was significant interpatient variability in the AUC and saturability of absorption, and this was also observed in the current study. In the rat, absorption of carboplatin and cisplatin is maximal in the upper small intestine, but both of these drugs have a low oral bioavailability [12, 13]. With carboplatin, the addition of loperamide, which slows GIT motility, increased absorption, but this did not occur with cisplatin. At doses where the absorption of JM216 is saturated, changes in GIT motility may contribute significantly to the wide variability seen in the AUC. Slower motility may allow greater exposure to the upper small intestine, where absorption might be maximal and, therefore, allow additional absorption to occur. This suggests that GIT motility may be an important factor in the absorption of oral platinum drugs, but this is not easily measured in patients and such data were not collected on the patients during this study.

The toxicity of the drug given on the present schedule was similar to that seen in previous phase I trials. Nausea and vomiting are common but mild and short-lived. No nephrotoxicity or neurotoxicity was observed. Grade 3–4 neutropenia, thrombocytopenia and anaemia were observed at three different dose levels. There was one observed case of an allergic reaction to the drug, which was confirmed on retesting.

As found in the single-dose phase I trial, this trial establishes that the absorption from the GI tract is saturated and doses not allow increasing drug exposure for the dose given. Currently, the daily-times-5 schedule remains the recommended regimen for future trials with JM216.

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