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Original article

Phase I clinical and pharmacokinetic study of the oral platinum analogue JM216 given daily for 14 days

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Summary

Background: The oral bis (acetate) ammine dichloro cyclohexylamine platinum (IV) analogue (BMS-182751) was brought into clinical development because it was shown to be cytotoxic against some human tumour cell lines and to have an antitumor activity in murine tumours at least comparable to that of parenteral cisplatin and carboplatin. In early clinical studies in which the optimal schedule of treatment was daily for five consecutive days, dose-dependent nausea and vomiting occurred in about two-thirds of patients.

Patients and methods: To evaluate if the use of lower daily doses for longer periods of time could result in a better tolerability, JM216 was given once daily for 14 consecutive days every four to five weeks to adult patients with solid tumors. Oral antiemetics were given prophylactically only at the highest doses. The pharmacokinetics of total and ultrafiltrable platinum were studied on days 1 and 14 of the first cycle by Inductively Coupled-Mass-Spectrometry (ICP-MS).

Results: Forty-six patients were treated at doses ranging from 10 mg/m^2/d to 50 mg/m^2/d and 39 were evaluable for hematologic toxicity over 74 cycles. MTDs were reached at 45 mg/m^2/d and 50 mg/m^2/d × 14 repeated every five weeks in patients with extensive, or limited/no prior treatment, respectively. The dose-limiting toxicity was neutropenia which was delayed and variable among patients. Other non-hematological toxicities were severe vomiting (22% of cycles), diarrhea (28% of cycles) and drug-associated fever (32% of patients), controlled with paracetamol. Subjective improvement with disappearance of tumour-related pain was observed in one patient with chemotherapy-resistant metastatic prostate cancer and in one previously untreated patient with malignant mesothelioma. C_{max} and AUC values of both total and ultrafiltrable platinum on days 1 and 14 were highly variable among patients. Only C_{max} on day 1 was linearly related to the dose. Total and ultrafiltrable platinum were still detectable two weeks after the last dose. No relationship could be established between AUC values and toxicities.

Conclusions: Daily doses of JM216 of 40 mg/m^2 and 45 mg/m^2 for 14 consecutive days every five weeks with oral antiemetic prophylaxis are selected for phase II evaluation of single agent in patients with extensive or limited/no prior treatment, respectively. The administration of JM216 on a day × 14 schedule produced nausea and vomiting comparable to that observed with the day × 5 regimen but of longer duration. The variability of pharmacokinetics and pharmacodynamics, even though limited at the doses proposed for phase II evaluation of JM216 as single agent, recommend a careful monitoring of the patients.

Key words: oral chemotherapy, oral platinum analogue, phase I

Introduction

A variety of oral analogues of known antitumour agents has been developed in the past few years for economic, pharmacological and practical reasons. To merit further clinical development the oral analogue should have a preclinical antitumour activity and toxicity comparable to those of the parent compound, no or only limited gastrointestinal (GI) toxicity, acceptable bioavailability, safe and reproducible pharmacokinetic profile.

A series of ammine/amine platinum (IV) dicarboxylates of higher lipophilicity and stability than cisplatin and carboplatin has been developed in an effort to improve absorption and to decrease the metabolic activation through processes in the GI tract. The oral bis (acetate) ammine dichloro cyclohexylamine platinum (IV) analogue (BMS-182751, JM216; Figure 1) was introduced into clinical development because it was shown *in vitro* to be toxic to some human tumour cell lines [1] and to have an antitumour activity in rodent tumours at least comparable to that of parenterally administered cisplatin and carboplatin.

In one murine and one human tumor model, a schedule dependency of the antitumor activity was shown, the daily × 5 administration producing tumor growth delay and tumor regression superior to those observed after single intermittent or chronic indefinitely dosing [2].

Myelosuppression, mainly neutropenia and thrombocytopenia, was dose-limiting in mice, while nephrotoxicity was comparable to that of i.v. carboplatin in mice

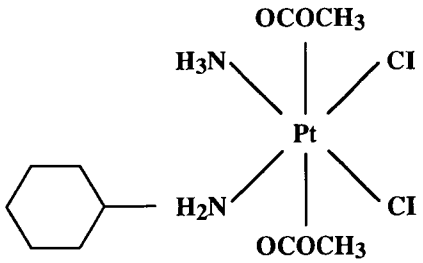

Figure 1. Chemical structure of JM216.

and rats [3]; there was no neurotoxicity [4]. The emetic potential was higher in dogs, but comparable to that of carboplatin in ferrets, and could be partially controlled by the administration of ondansetron. The bioavailability of JM216 in animals could not be assessed due to its high insolubility and production of a series of metabolites, some of them still cytotoxic; it was shown, however, that cytotoxic concentrations of platinum could be achieved in plasma ultrafiltrate in mice.

In humans JM216 was first studied on a single intermittent schedule, subsequently abandoned because of non-linear pharmacokinetics with saturable absorption and dose-limiting nausea and vomiting [5]. A daily administration for 5 consecutive days to improve absorption and tolerability was then evaluated, and its effectiveness was later confirmed [6]. The maximum tolerable dose (MTD) was fixed at 140 mg/m^2/d, and daily doses of 100 mg/m^2 and 120 mg/m^2 for, respectively, previously treated and untreated patients were recommended for phase II studies. Myelosuppression was dose-limiting and non-cumulative, while two-thirds of the patients presented nausea and vomiting despite antiemetic prophylaxis, and diarrhea, in most instances mild to moderate. Pharmacokinetic studies showed a linear pharmacokinetics with a high interpatient variability and a significant correlation between plasma ultrafiltrate AUC and degree of thrombocytopenia.

Evaluation of lower daily doses administered over longer time periods was begun in an effort to further decrease GI toxicity and to develop an oral platinum regimen suitable for combination with cytotoxic agents or radiation. A two-week period of treatment was chosen because it could provide an adequate exposure time with an acceptable degree of GI toxicity.

Patients and methods

Patients

Adult patients, aged 18 to 75 years, with histologically/cytologically-confirmed diagnoses of solid tumours not amenable to conventional local or systemic treatments were eligible for this trial. Patients must have recovered from the toxic effects of prior therapy, with a treatment-free period of at least four weeks for those who had received chemotherapy (six for those given nitrosoureas, carboplatin, mitomycin) and eight for those who had undergone large field irradiation. Eligibility criteria also included an ECOG performance status (PS) of ≤ 2, life expectancy of ≥ 3 months, no previously severe or unresolved toxic effects of cisplatin or carboplatin, adequate bone marrow (neutrophil count (ANC) $\geq 2.0 \times 10^3/\mu l$, platelet count $\geq 100 \times 10^3/\mu l$), liver (bilirubin ≤ 25 µmol, ALT and alkaline phosphatase $\leq 1.5 \times$ normal, unless secondary to malignancy, for which a value $\leq 2.5 \times$ normal was acceptable) and renal function (24-hour creatinine clearance between 73 and 120 ml/min), feasibility and willingness to participate in pharmacokinetic studies, written informed consent. Serious concomitant medical disease, gastrointestinal disorders likely to hamper drug absorption, and significant ECG abnormalities were criteria for exclusion.

Study design

A starting dose of 10 mg/m^2, corresponding to the daily dose to be given for two weeks if the MTD was 140 mg/m^2 as found in the day × 5 study, was selected. Treatment was first scheduled every four weeks or when a ANC of $\geq 2.0 \times 10^3/\mu l$ had been reached, whichever occurred first. Because of the subsequent observation of delayed neutropenia and thrombocytopenia, the protocol was amended and patients were treated again after at least four weeks if the ANC and platelet counts had begun to increase and were (of) $\geq 2.0 \times 10^3/\mu l$ and $\geq 100 \times 10^3/\mu l$, respectively. From the 35 mg/m^2 dose onward treatment was scheduled every five weeks. At least three patients, and six in case of grade ≥ 3 haematologic or GI toxicity or of other non-haematologic toxicity of grade ≥ 2, had to be evaluable for toxicity at each dose level. At least two weeks had to elapse between completion of treatment of the first patient and the entry of other patients at the same dose level; at least three patients per dose level had to be evaluable after one cycle prior to opening of the next higher dose level. Intrapatient dose escalation was not allowed. The dose was increased by 25%–100% increments according to the degree and variability of the haematologic toxicity observed. The dose was reduced at subsequent cycles in instances of myelosuppression of grade ≥ 3, non-haematologic toxicity (except for nausea and vomiting) of grade ≥ 2. Treatment was discontinued in instances of non-haematologic toxicities of grade ≥ 3.

Chemistry (including electrolytes, calcium, creatinine, urea, total protein, albumin, bilirubin, transaminases, alkaline phosphatase) and urinalyses were repeated weekly, and CBC counts with differential more often in case of toxicity. Twenty-four-hour creatinine clearance was repeated before each cycle. Baseline ECG, audiometry and tumour measurements were requested.

Toxicity was evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria.[1] When no CTC criteria were available, a score of mild, moderate or severe was assigned. Patients were asked to keep a log of symptoms during the chemotherapy period, especially with respect to GI symptoms.

Patients were evaluable for haematological toxicity if they had received at least 12 days of treatment and if at least weekly CBC counts with differential were available for a minimum of four weeks; patients were evaluable for non-haematological toxicity after at least one day of treatment; retreatment cycles at lower doses were not included in the toxicity analyses which were performed per dose level.

The MTD was defined as the dose at which two or more of six patients developed either haematological or GI toxicity of grade ≥ 3, or non-haematological toxicity (excluding GI) of grade ≥ 2. Additional patients were treated at the dose recommended for phase II studies, which was one step below the MTD, to define risk factors and degree of toxicity variability.

In patients with measurable or evaluable disease tumour response was assessed after two cycles and classified according to WHO criteria [7]. Patients with stable disease or tumour response continued treatment with JM216 until tumour progression or unacceptable toxicity, whichever occurred first, while patients with progressive disease went off study.

Drug administration

JM216 was supplied by Bristol-Myers Squibb Company (Wallingford, CT) as 10 and 50 mg hard gelatin capsules with excipients (microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium

Table 1. Patient characteristics

Characteristics	Number of patients
Total number of patients	46
Sex	
Female	14
Male	32
Age (in years)	
Median	57
Range	29–74
Prior therapy	
Chemotherapy alone	23
Chemo + radiotherapy	12
Radiotherapy	3
None	8
Tumour types	
Colorectal	14
Non-small-cell lung cancer	11
Ovary	4
Other	17

Table 2. Patients and cycles evaluable for hematologic toxicity.

Dose (mg/m^2)		Patients			Evaluable cycles	
Daily	Total	Entered	Evaluable	$\geqslant 2$ evaluable cycles	Initial	Subsequent
10	140	5	5	3	5	3
20	280	3	3	3	3	5
30	420	7	5	2	5	5
35	490	10	9	4	8[a]	4
40	560	7	6	4	6	4
45	630	8	6	4	6	5
50	700	6	5	3	5	10
Total		46	39	23	38	36

[a] First cycle only not evaluable because of treatment discontinuation due to severe nausea and vomiting.

stearate). Capsules were packaged in light-resistant bottles and stored at +2 to −30 °C. The number of capsules to be taken daily was based on the dose level, the patient's body surface area (BSA), the total dose to be given over 14 days, and the attempt to maintain as constant as possible the number of capsules to be taken each day, with the rule of administering the highest dose on the first day, and identical doses on the days when pharmacokinetics was assessed. Patients were given a chart with the number of capsules to be taken each day, and asked to refrain from eating solid food from the previous midnight up to four hours after dosing on the days when pharmacokinetic studies were to be performed. On the other days, patients were asked to take the JM216 at the same time each day and to eat no solid food for at least one hour afterward. Administration of antiemetic prophylaxis with 5-HT_3 antagonists was started at 35 mg/m^2 because of the occurrence of moderate nausea and vomiting at the previous dose; antiemetics were given i.v. on the days when pharmacokinetics was assessed, while the oral route was recommended for the other days of treatment. Oral loperamide was administered in case of diarrhea, premedication with oral paracetamol (500 mg t.i.d.) was given to patients suffering from drug-associated fever and chills.

Pharmacokinetics

Sampling procedure

Pharmacokinetics studies of JM216 were performed in all patients on days 1 and 14 of the first cycle. Blood samples (5 ml) were collected in tubes containing EDTA before and then at 0.5, one, two, three, four, six, eight, 12 and 24 hours after treatment. In selected cases, additional samples were collected up to two weeks after the end of the cycle. Urine fractions (0–8 hours and 8–24 hours) were collected on days 1 and 14, their volume measured, and an aliquot of 5 ml kept for analysis. To prepare plasma, blood was centrifuged at 2000 *g* for 15 min at 4 °C within 30 min after sampling. Plasma was separated and divided into two portions, one for determination of total platinum (Pt) and one for preparation of the plasma ultrafiltrate using AMICON Centrifree filters (30.000 MW cut off). The filters were centrifuged at 2000 *g* for 20 min at 4 °C and the ultrafiltrate used for determination of the free fraction of platinum (UPt).

Platinum assay

Plasma, ultrafiltrate and urine samples were thawed in a warm bath immediately before analysis. Pt and UPt determinations were performed by Inductively Coupled-Mass-Spectrometry (ICP-MS) Elan 5000 Perkin Elmer Sciex equipped with Cool flow CFT-75 Neslab, autosampler AS90. Instrumental specifications and analytical conditions have been reported elsewhere [8].

Biological samples were diluted to varying degrees (1 : 10 to 1 : 100 v/v) with ultrapure water (Milli-Ro, Mill/Q, Millipore) depending on the matrix, before analysis. Ir 193, an isotope with chemical-physical properties similar to those of Pt, was used as internal standard to eliminate a matrix effect.

A calibration curve was prepared using the standard addition method by adding Pt standard solutions to plasma for the determination of total Pt and to ultrapure water for the analysis of ultrafiltrate and urine. Linear responses were observed for four orders of magnitude; the detection limit of the method was 0.001 ng/ml.

Pharmacokinetic analyses

Pt and UPt plasma concentrations determined in each subject were fitted on a general non-linear fitting program [9] according to one-, two- or three-compartment open models depending on the data points available. The experimental area under the curve of concentration vs. time AUC from time 0 to 24 hours was calculated according to the trapezoidal method.

Results

Forty-six patients with an ECOG Performance Status of 0–1 entered the study; their characteristics are listed in Table 1. The most frequently represented tumour types were colorectal in 14 patients, and non-small-cell lung cancer in 11 patients, seven of whom had received no prior chemotherapy and were treated at the two highest dose levels. Thirty-five patients had already received chemotherapy, 12 of them with cisplatin and/or carboplatin. Six of eight patients were given JM216 at the MTD as first antitumour treatment.

Hematologic toxicity

A total of 39 patients and 74 cycles were evaluable for hematologic toxicity (Table 2). Seven patients (15%)

Table 3 Severe neutropenia, median neutrophil nadir ($\times 10^3/\mu l$) and median time to nadir (days) per dose level.

Dose (mg/m^2)	Number of evaluable patients/cycles	Number of patients with CTC toxicity		ANC nadir at cycle		Time to nadir first cycle
		3	4	First	Subsequent	
10[a]	5/8			3.2 (2.0–4 77)	1.9 (1.4–5.8)	23 (14–29)
20[a]	3/8			4.3 (4.0–5.1)	1.6 (1.2–2.1)	15 (14–29)
30[a]	5/10	1		1.35 (0.6–1.6)	1.1 (1.0–1.8)	35 (22–43)
35[a]	9/12	2		2 2 (0.6–3.4)	1 0 (0.5–2.2)	29 (1–35)
40[a]	6/10	1	1	2.2 (1.5–3 4)	1.7 (0.1–4.5)	27 (16–41)
45[b]	6/11	2	1	2.4 (0.9–4.9)	1.1 (0.4–1.8)	28 (21–40)
50[c]	5/15	1	1	2.4 (0.9–4.6)	2.4 (0.3–2.8)	32 (2–44)

Prior chemotherapy: [a] > 2 regimens; [b] ≤ 2 regimens; [c] none.

Table 4. Severe thrombocytopenia, median platelet nadir ($\times 10^3/\mu l$) and median time to nadir (days) per dose level

Dose (mg/m^2)	Number of evaluable patients/cycles	Number of patients with CTC toxicity		Platelet nadir at cycle		Time to nadir first cycle
		3	4	First	Subsequent	
10[a]	5/8			208 (170–365)	146 (123–328)	14 (13–23)
20[a]	3/8			195 (167–196)	143 (139–197)	14 (14–28)
30[a]	5/10	3		48 (37–115)	72 (61–107)	31 (29–33)
35[a]	9/12	1	1	134 (12–200)	99 (50–159)	30 (26–36)
40[a]	6/10		2	85 (15–104)	105 (9–173)	30 (19–36)
45[b]	6/11	1		106 (64–149)	61 (41–88)	29 (28–34)
50[c]	5/15		1	150 (122–197)	133 (18–256)	28 (10–31)

Prior chemotherapy: [a] < 2 regimens; [b] ≤ 2 regimens; [c] none.

received less than 13 days of therapy at the first cycle and were not included in the analysis of hematologic toxicity at this cycle. None of these patients showed hematologic toxicity. Treatment was interrupted in two patients treated at 30 mg/m^2 because, respectively, of dizziness and tumor-related early death, in one patient at 35 mg/m^2 due to grade 3 vomiting, in one at 40 mg/m^2 due to uncontrolled drug-related fever with chills, in two at 45 mg/m^2 due, respectively, to grade 3 vomiting and tumor-related early death, and in one at 50 mg/m^2 because of drug-related fever with chills. In all patients but one treatment with JM216 was then definitively discontinued.

The dose-limiting toxicity was neutropenia, with grade 3 neutropenia first observed at 30 mg/m^2 in pretreated patients; grade 3–4 neutropenia occurred in three of six patients with limited prior chemotherapy (≤ 2 regimens) at 45 mg/m^2 and in two of five with no prior chemotherapy at 50 mg/m^2, thereby defining the MTD in these groups of patients (Table 3). The overall median time to nadir was between days 27 and 35, with recovery in 7 to 10 days. Severe neutropenia was always associated with moderate to severe thrombocytopenia. Overall, neutropenia showed a wide interpatient variability only partly related to the extent of prior treatment; at 50 mg/m^2, where JM216 was given as first treatment in all patients, neutrophil nadir counts ranged from $0.3 \times 10^3/\mu l$ to $4.6 \times 10^3/\mu l$.

Thrombocytopenia showed a comparable profile, with a median time to nadir between days 28 and 31, and recovery in the subsequent seven to 10 days (Table 4). The dose had to be reduced at the second cycle in one heavily pretreated patient receiving 30 $mg/m^2/d$ because of grade 3 thrombocytopenia. Severe thrombocytopenia was sporadic at the MTDs because of the more favorable selection of patients. In another patient, heavily pretreated at 45 mg/m^2, and in one previously untreated at 50 mg/m^2, the dose had to be decreased by one dose level after three and two cycles, because, respectively, of grade 3 and grade 4 thrombocytopenia.

In one of three patients who received repeated cycles at 20 $mg/m^2/d$ and in all five patients treated at 30 $mg/m^2/d$ treatment could not be resumed every four weeks because of delayed hematological recovery. From 35 $mg/m^2/d$ onward, JM216 was given every five weeks with only two cycles at 40 $mg/m^2/d$ requiring a further delay because of persisting thrombocytopenia.

Anemia was first observed at 35 $mg/m^2/d$; 50% of the patients treated at between 35 $mg/m^2/d$ and 45 $mg/m^2/d$ suffered from grade 1–2 anemia with no significant difference among dose levels.

Non-hematologic toxicity

Nausea and vomiting were the most common non-hematologic side effects, and required antiemetic prophylaxis with 5-HT_3 antagonists from the dose of 35 $mg/m^2/d$ onward (Table 5). Nevertheless, three patients discontinued the treatment during the first (two patients) or second cycles (one patient) because of uncontrolled nausea and vomiting and 22% of cycles with doses at ≥ 35 mg/m^2 were associated with grades 2 or 3 vomiting.

Table 5. Non-hematologic toxicity per dose level.

Dose (mg/m²)	Number of evaluable patients/ cycles	Number of cycles with toxicity grade														
		Nausea				Vomiting				Diarrhea				Drug-fever		
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3
10	5/8	2														
20	3/8	3	1			1				2					1	
30	7/12	6	2			1	2	1		5	1			1	2	
35	10/15	3	3			3	2	3[a]		3	3[b]	2			2	
40	7/11	2	3			1	2	1			1				1[c]	
45	8/14	2	2	1[c]		5		1[c]			1			1	5	
50	6/16	7	2			4				5	1				4	1[c]

Antiemetic prophylaxis from 35 mg/m².
Toxicity requiring treatment discontinuation in [a]one patient; [b]two patients; [c]one patient.

Diarrhea was reported in 28% of cycles; it occurred after at least one week of treatment in most of the patients and was controlled by oral loperamide. One patient treated at 35 mg/m² requested to discontinue the treatment because of reappearance and worsening of diarrhea up to grade 2 within 48 hours from the start of the second cycle.

Drug fever, defined as an intermittent daily increase of temperature up to $\geqslant 38$ °C without concomitant neutropenia or signs of infection, and occurring within four to six hours after JM216 dosing, was observed in a total of 15 patients (32%), nine of them treated at doses equal to or greater than 40 mg/m²/d. In 12 patients drug fever was reported during the first cycle after a median of eight days of treatment while in three patients it occurred on day 1 or on day 2 of the second cycle. Treatment had to be interrupted after eight days in two patients, one of them treated at 40 mg/m²/d and the other at 50 mg/m²/d, because of grade 2 fever with chills despite paracetamol premedication. The fever did not recur after JM216 discontinuation. Overall, drug fever occurred in four of six patients treated at 50 mg/m², with discontinuation of treatment in one of them; in two of three patients who continued the treatment one did not present fever, while in two it was possible to either prevent or control the symptoms by premedication with paracetamol.

Antitumour response

One patient with hormone-resistent metastatic prostate cancer, failing anthracyclines, etoposide and 5-FU continuous infusion, obtained complete relief of tumour pain due to retroperitoneal nodes with no further need of analgesics after the first two cycles at 45 mg/m²/d. CT scan evaluation showed stable disease lasting four months. One patient with locally advanced malignant mesothelioma received eight cycles of JM216 at 50 mg/m² as initial treatment, with stable disease on chest CT but complete resolution of pericardial effusion and control of tumour-related pain and fever of nine months' duration.

Pharmacokinetics

The pharmacokinetics of JM216 on days 1 and 14 was studied in 15 patients treated at doses ranging from 20 mg/m²/d to 50 mg/m²/d.

Figure 2 shows the plasma pharmacokinetic profiles of Pt and UPt of four patients who received 45 mg/m². JM216 was rapidly absorbed, with Pt and UPt detect-

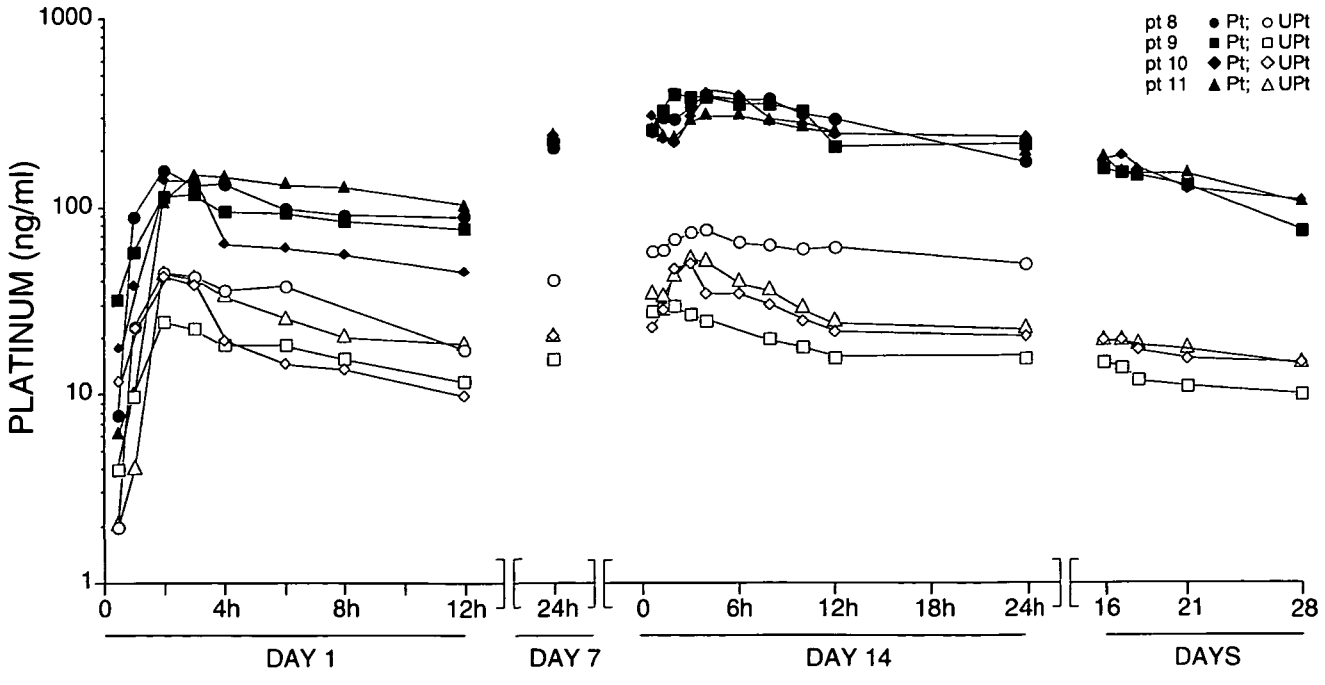

Figure 2. Plasma levels of total platinum (Pt) and plasma ultrafiltrate platinum (UPt) in patients treated with JM216 at 45 mg/m².

Table 6. Pharmacokinetic parameters (mean ± SD) of plasma ultrafiltrate platinum (UPt).

Dose (mg/m^2)	Cmax (ng/ml)		Tmax (h)		AUC 24-hour (ng/ml h)		$T_{1/2}\beta$ (h)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
20	10	29	6	0.5	–	528	–	3
30	16, 14	34, 19	1, 4	1, 6	230	505, 338	15	16, 29
35	18	33	2	4	213	657	14	30
40	23, 25	30, 38	2, 2	4, 1	180, 347	448, 703	13, 10	10, 45
45	40 ± 10 (4)	54 ± 20 (4)	2 ± 0 (4)	1.3 ± 0.9 (4)	409 ± 106 (4)	883 ± 442 (4)	8 ± 3 (4)	5 ± 4 (4)
50	23 ± 5 (4)	22, 49	2.5 ± 0.6 (4)	2,3	232 ± 29 (4)	420, 475	10 ± 5 (4)	30, 13

In brackets, number of patients studied.

Table 7. Pharmacokinetic parameters (mean ± SD) of total platinum (Pt).

Dose (mg/m^2)	Cmax (ng/ml)		Tmax (h)		AUC 24-hour (ng/ml h)		$T_{1/2}\beta$ (h)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
20	90	314	6	4	–	6385	–	14
30	150, 76	660, 194	3	2	2373	13220, 3753	16	45, 25
35	86	132	2	4	1459	3418	14	29
40	121 ± 12 (3)	502 ± 211 (3)	2.3 ± 0 6 (3)	3 ± 1.7 (3)	1797 ± 168 (3)	9794 ± 5142 (3)	13 ± 6.5 (3)	52 ± 25 (3)
45	145 ± 18 (4)	400 ± 53 (4)	2.7 ± 0.5 (4)	3.5 ± 1.7 (4)	1887 ± 410 (4)	7071 ± 653 (4)	14 ± 3 (4)	10 ± 6 (4)
50	135 ± 21 (4)	335, 190	2.5 ± 0.6 (4)	1.3	2126 ± 288 (4)	6942, 3025	39 ± 9 (4)	71, 23

In brackets, number of patients studied.

able in plasma as early as 30 min after the administration. On day 1 Pt and UPt peak levels were achieved in most cases within 3 hours, with median Tmax values of 2.5 and 2 h, respectively. Elimination was variable and slow for Pt and UPt; both platinum species were detectable at the time of subsequent dosing, with platinum accumulation in plasma during the cycle.

The main pharmacokinetic parameters are reported in Tables 6 and 7. At all dose levels, the Cmax and AUC of Pt on day 14 were two to five times higher than those of day 1, while a lower increase of 1.5–2 times was reported for UPt. Cmax and AUC values of UPt and Pt increased with the dose, with some overlap among different dose levels due to the high interpatient variability.

Only the Cmax of Pt and UPt on day 1 showed a linear relation to the dose (Pt: $r = 0.67$, $P < 0.01$; UPt: $r = 0.60$, $P < 0.05$). $T_{1/2}\beta$ appeared variable among patients, ranging from eight to 15 hours for UPt and from 13 to 39 hours for Pt on day 1, from three to 30 hours for UPt and from 10 to 71 hours for Pt on day 14. Long terminal half-lives were found after the last administration on day 14, with Pt and UPt concentrations of, respectively, 100 ng/ml and 20 ng/ml still detectable two weeks after the last dosing.

In one patient who had limited pharmacokinetic evaluations in subsequent courses, plasma values of 12 ng/ml of UPt and 119 ng/ml of Pt three weeks after the end of the third course and of 15 ng/ml and 140 ng/ml three weeks after the end of the fourth course, were found, suggesting a very prolonged exposure to both platinum species.

The mean plasma-free fractions (ratio of ultrafiltrate and total plasma AUC) were 15.3% (range 9.7%–25.0%) and 10.5% (3.8%–19.2%) on days 1 and 14, respectively. The 24-hour urinary excretion of Pt varied from 1.5% to 18% of the dose.

Renal function, as assessed by creatinine clearance (CrCl) on 24-hour urine collection, was inversely proportional to the sum of UPt AUC on days 1 and 14 ($r = 0.71$, $P < 0.05$). No pharmacokinetic information is available in patients who presented diarrhea or who were taking loperamide to control this side effect of the treatment.

In one patient with mesothelioma who underwent pleural drainage (total volume 2500 ml), a Pt concentration of 63 ng/ml was found in the pleural fluid eight hours after the last dose of JM216. This concentration was half of the corresponding plasma Pt concentration and three times higher than the plasma UPt concentration, indicating that 0.45% of the daily dose was distributed in the pleural fluid.

No significant relationships could be established between Pt AUC or UPt AUC and myelotoxicity or GI toxicity.

Recommended doses for phase II studies

The doses recommended for phase II studies are 40 $mg/m^2/d$ for 14 consecutive days for patients with extensive prior treatment and 45 $mg/m^2/d$ for 14 consecutive days for patients with only limited/no prior treatment, to be repeated every five weeks with oral 5-HT_3 antagonists as antiemetic prophylaxis.

Discussion

The daily administration of JM216 for 14 consecutive days was investigated in the interest of improving the tolerability of treatment and developing a regimen suitable for combination studies on a chronic basis. While thrombocytopenia was the main toxicity in the day × 5 regimen [5], neutropenia was dose-limiting in the day × 14 schedule. Myelotoxicity was moderate and delayed, with an optimal interval before retreatment of five weeks. The characteristics of prior therapy were risk factors for myelotoxicity, and MTD_s were reached at 45 mg/m^2/d and 50 mg/m^2/d in patients with extensive (at least two prior chemotherapies) or limited/no prior treatment, respectively. The corresponding doses for phase II studies were 45 mg/m^2/d and 40 mg/m^2/d. Neutropenia was moderate at 50 mg/m^2/d; this dose, however, was considered the MTD and too high for phase II evaluation because of the occurrence of drug fever during the first cycle in five of six patients treated.

The occurrence of moderate to severe vomiting in 22% of cycles at doses equal to or greater than 35 mg/m^2/d suggests that oral antiemetic prophylaxis with 5-HT_3 antagonists should be given. With respect to other non-hematologic toxicities, diarrhea, which occurred in 28% of cycles irrespective of dose, was also observed by Mc Keage et al., while drug fever, controlled or prevented by paracetamol, was a feature exclusive to the present study.

Antitumour activity was observed in one patient with metastatic prostate cancer progressing after anthracyclines, and in one patient with malignant mesothelioma who showed a less than 50% decrease of pleural lesions on CT scan but a complete disappearance of tumour-related pain and fever lasting nine months.

The pharmacokinetics of JM216 was investigated in the two previous phase I studies, one on a single intermittent [5] and the other on a day × 5 schedule [6]. In the single intermittent regimen pharmacokinetics was non-linear at doses equal to or greater than 200 mg/m^2, probably due to saturable absorption and a decrease in the percentage of the dose excreted in urine at increasing doses. More promising results were achieved with the day × 5 schedule, for which linear pharmacokinetics was reported for doses between 30 mg/m^2/d and 140 mg/m^2/d, although with a significant inter-patient variability of AUC. Pt and UPt levels accumulated in plasma from day 1 to day 5 and UPt AUC appeared to be inversely related to the baseline glomerular filtration rate, suggesting that JM216 elimination depends to a minor extent on renal function.

An even higher inter-patient variability of the pharmacokinetics of JM216 was found in the present study and only the C_{max} of both total and ultrafiltrable platinum on day 1 was linearly related to the dose. In contrast to the report of Mc Keage et al. [6], we found no linear relationship to the dose and AUC on days 1 and 14 for Pt and UPt; one reason for this discrepancy could be the smaller range of doses investigated in our study (from 20 mg/m^2/d to 50 mg/m^2/d) as compared to the one of Mc Keage (from 30 mg/m^2/d to 140 mg/m^2/d), which might have amplified the overlapping of AUCs among doses. Another reason for the non-linear kinetics of UPt may have been the use of filters for ultrafiltration with a different cut-off from those used by Mc Keage et al. (30,000 Dalton instead of 10,000) which could have overestimated the UPt measurement. This is supported by the fact that we determined a free fraction of Pt of 11%–16% higher than the 6%–12% of Mc Keage et al.

Also in our study total and ultrafiltrable platinum accumulated significantly in plasma, and Pt and UPt levels were still detectable two to three weeks after the last dose. It seems reasonable to ascribe the UPt levels determined several days after treatment primarily to platinum, bound to filtrable macromolecules (e.g., small peptides), whose pharmacological activity is unknown. Analogous to that found by Mc Keage et al. after five days of treatment, AUCs on day 14 were about 1.5–2 (for UPt) and two to six (for Pt) times higher than the AUCs on day 1; these results suggest that a longer duration of treatment does not result in a significant increase of Pt and UPt plasma levels.

The largest increase of six times AUC on day 14 was reported in the patient who had the lowest CrCl and the lowest urinary excretion of JM216, suggesting that renal function could at least partly contribute to pharmacokinetics variability. This observation is consistent with the weak but significant relationship we found between CrCl and AUC of UPt. Again in contrast to McKeage, however, we could find no correlation between UPt AUC and thrombocytopenia.

The significant interpatient variability of neutropenia, which is only partly explained by the characteristics of prior treatment, might be related to a variety of reasons such as variability in drug absorption, variability in the accumulation of UPt levels during treatment and variability in the production of active or inactive metabolites, four of which have been identified [10]. The occurrence of drug fever, variable and unpredictable, and, to a lesser extent, that of diarrhea with no relationship to the occurrence of myelotoxicity, might be due to the production of toxic species in the GI tract.

The recommended doses of 40 mg/m^2/d and 45 mg/m^2/d for 14 consecutive days correspond to a total dose higher than that reached with those recommended for the day × 5 schedule of 100 mg/m^2/d and 120 mg/m^2/d. This difference, however, is irrelevant because of the high interpatient variability of pharmacokinetics and of the long $T_{1/2}\beta$ of JM216; a shorter duration and therefore better tolerability were the main criteria for the choice of the day × 5 schedule. A broad phase II program with single-agent JM216 given for five consecutive days in different tumour types is almost completed, with confirmation of the phase I toxicity data [11], while combination studies with etoposide have been started in sensitive tumour types because of the therapeutic synergy observed in the P_{388} leukemia model [12].

The administration of JM216 on a day × 14 schedule

has produced nausea and vomiting comparable to that observed with the day × 5 regimen but of longer duration. In addition, the pharmacokinetics and pharmacodynamics of the drug were highly variable, mainly at the higher doses evaluated of 45 mg/m^2/d and 50 mg/m^2/d. One theoretical advantage of the day × 14 regimen could be the prolonged exposure to still-cytotoxic UPt and Pt concentrations and the persistence two weeks after dosing of Pt and UPt plasma levels in the range of those required for radiosensitization. This might be useful if low dose single agent JM216 is given in combination with radiation. On the other hand, when JM216 was administered with UFT/leucovorin for 14 days, nausea and vomiting were dose limiting at daily doses of 20 mg/m^2 of JM216 and 300 mg/m^2 of UFT, respectively [13]. Different schedules of treatment with JM216, which take into account also its pharmacokinetic profile, should be therefore evaluated for combination studies with UFT/leucovorin.

Note

1. Common Toxicity Criteria from Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

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