Schedule Dependency of Orally Administered Bis-acetato-ammine-dichloro-cyclohexylamine-platinum(IV) (JM216) in Vivo

Mark J. McKeage, Lloyd R. Kelland, Frances E. Boxall, Melanie R. Valenti, Mervyn Jones, Phyllis M. Goddard, Jean Gwynne, and Kenneth R. Harrap

ABSTRACT
JM216 is a novel antitumor platinum(IV) complex displaying oral activity, dose-limiting myelosuppression, and a lack of nephro- and neurotoxicity in rodents. It has been selected for clinical evaluation. The schedule dependency of its antitumor action against a murine (ADJ/PC6 plasmacytoma) and a human tumor model (PXN109T/C ovarian carcinoma xenograft) was studied in vivo. Single dose (q2ld), once a day for 5 consecutive days (q2ld or q2Sd), and once a day dosing indefinitely (chronic daily dosing) administration schedules were compared. Against the murine ADJ/PC6 plasmacytoma, daily x5 administration improved the tumor regression, antitumor potency, and therapeutic index of oral JM216, compared to single dose administration, whereas no advantage was found for fractionating cisplatin dosages. Against the PXN109T/C human ovarian carcinoma xenograft, oral JM216, given at dose levels delivering a equivalent total dose on single dose (200 mg/kg q2ld), daily x5 (40 mg/kg/day q2ld) and chronic daily dosing (9.5 mgfkg/day) schedules, showed superior tumor growth delays (55 ± 15 days; P < 0.05) and maximal tumor regression (10 ± 11% of initial tumor volume; P < 0.001) with the daily x5 schedule. Gastrointestinal toxicity (P < 0.05) and mild nephrotoxicity (P < 0.01) complicated the chronic daily dosing schedule, while leukopenia (P < 0.02) and thrombocytopenia (P < 0.01) were dose-limiting for the single dose and daily x5 administration, respectively. Peak plasma ultrafiltrate (PUF) platinum levels did not increase significantly with a 5-fold increase in dosage from 40 mgkg (PUF Cmax 1.5 ± 0.11 mg/l) to 200 mg/kg (PUF Cmax, 2.4 ± 0.44 mg/l; P > 0.05). In conclusion, these data demonstrate antitumor schedule dependency for oral JM216 in vivo, independently in two tumor model systems, and with nonlinear pharmacokinetics after its oral administration to mice. Optimal antitumor activity, tolerance, and pharmacokinetics occurred with daily x5 dosing, and this has prompted the clinical evaluation of this administration schedule.

INTRODUCTION
JM216 is a lipophilic platinum(IV) complex with in vitro activity against human tumor cell lines both sensitive and resistant to cisplatin (1). It shows a partial lack of cross-resistance to cisplatin in models of acquired resistance, and, unlike cisplatin, displays marked time-dependency of its in vitro cytotoxic action (1). JM216 has oral antitumor activity and bioavailability in mice bearing murine and human tumors (1, 2). Rodent toxicological studies have shown dose-limiting myelosuppression, a lack of nephro- and neurotoxicity, and less gastrointestinal toxicity than i.v. cisplatin and i.v. carboplatin (3–5). JM216 has been selected for clinical testing as an orally administered platinum drug (6, 7). The optimal administration schedule has not yet been identified. The marked time-dependence of its in vitro activity prompted this in vivo comparison of single dose and fractionated administration schedules.

Schedule is an important factor influencing the efficacy and tolerance of cancer chemotherapy. In small cell lung cancer, fractionation of the single daily dose of the topoisomerase inhibitor etoposide into once a day doses for 5 consecutive days results in improved tumor response rates (from 10 to 89%) with changes in neither the incidence nor severity of toxicity (8). Continuous protracted i.v. infusions of the antimetabolite 5-fluouracil results in improved response rates in advanced colorectal carcinoma and also reduced hematological and gastrointestinal toxicity, in comparison to bolus schedules (9). The antitumor action of the existing clinical platinum drugs do not appear dependent upon administration schedule (10), while their toxic effects are schedule dependent since the myelosuppression and neurotoxicity of cisplatin is more prominent with daily x5 administration (11, 12), whereas its nephrotoxicity and emesis are worse with single dose administration (12–15).

This paper describes antitumor schedule dependence for oral JM216 against a murine and a human tumor model in vivo. A cisplatin-responsive human ovarian carcinoma xenograft, PXN109T/C (16), was used which would be expected to be sensitive to changes in dosage and schedule of administration. Single dose administration was compared to two divided dose schedules in which oral JM216 was given either once a day for 5 consecutive days or once a day continuously. The schedule dependency of antitumor activity was related to plasma pharmacokinetics at equivalent total dose levels for the three administration schedules. The effect of schedule on hemato- logical toxicity and renal function at equitoxic doses was also investigated. Additionally, the comparative antitumor effects of i.p. cisplatin and oral JM216 given as either a single dose or once daily for 5 consecutive days against the solid murine AD/PC6 plasmacytoma was investigated.

MATERIALS AND METHODS
Drug Administration. JM216 was synthesized and supplied by the Johnson Matthey Technology Centre, Blount’s Court, Sonning Common, Reading, Berkshire RG4 9NH, United Kingdom. JM216 was suspended in arachis oil (10 mg/kg) by sonication (MSE 150 Watt Ultrasonic Disintegrator, 15 µm for 15 s) immediately before being given by oral gavage. JM216 was administered either as a single dose repeated once every 21 days (single dose q2ld), once a day for 5 consecutive days repeated once every 21 or 28 days (daily x5 q2ld or daily x5 q2Sd), or once a day indefinitely (chronic daily dosing). Cisplatin was dissolved in sterile sodium chloride (0.9% w/v) by sonication (MSE 150 watt Ultrasonic Disintegrator, 15 µm for 15 s) and given i.p. as a single dose or once a day for 5 consecutive days.

Assessment of Antitumor Activity. A human ovarian carcinoma xenograft (PXN109T/C), whose biological properties have been described previously, was used for this work (16). This xenograft has been established from a cell line, which in turn was raised from an ascites sample taken from a patient.
with poorly differentiated papillary adenocarcinoma of the ovary. The patient had a history of clinical responses to cisplatin and carboplatin prior to the collection of the sample. The xenografted tumor has been shown previously to be of human karyotype, histologically similar to the original explant, and sensitive to cisplatin, carboplatin, and irinotecan. Its doubling time has been estimated to be 8.4 days (16).

Implants were made s.c. to female nude (nu/nu) mice (aged 6 to 8 weeks) under halothane anaesthesia using a 2-mm² fragment. Animals were housed in negative pressure flexible film isolators and maintained on Labsure 21% protein diet (irradiated at 2.5 Mrads) with access to autoclaved tapwater ad libitum. Mice bearing comparably sized tumors were randomized into treatment or control groups (6–10 mice). JM216 was given orally on single dose q21d, daily ×5 q21d, daily ×5 q28 day, and chronic daily dosing administration schedules at doses up to an approximate MTD. Control animals were treated with the oral drug vehicle according to the respective schedule. Tumor diameters, (a) and (b), were measured with a slide calliper, where (a) is the longest diameter and (b) is the longest diameter at right angles to (a). Tumor volumes (V) were calculated according to the equation $V = \frac{a \times b^2 \times \pi}{6}$ and were normalized to the volume at the start of treatment. The ratio of mean volumes ($V_a$) were calculated according to the equation $V_a = \frac{V}{V_0^{\frac{1}{6}}}$ and estimated to be 8.4 days (16).

Be of human karyotype, histologically similar to the original explant, and collection of the sample. The xenografted tumor has been shown previously to be sensitive to cisplatin, carboplatin, and irinotecan. (PXNJO9T/C)y

The antitumor activity of oral JM216 and i.v. cisplatin given as either a single dose or once daily for five consecutive days was compared in the murine ADJIPC6 plasmacytoma model. Neither the toxicity, antitumor potency, nor the therapeutic index changed when i.v. cisplatin was given as a fractionated rather than a single dose (cisplatin single dose: LD$_{50}$ 11.5 mg/kg; ED$_{50}$ 0.88 mg/kg; TI 13; 300 mg/kg, 40 mg/kg, and 200 mg/kg and on the fifth day of a daily X5 treatment course at 40 mg/kg/day X5. Blood was collected under terminal halothane anesthesia from three mice after oral JM216 at 0, 10, 20, 30, and 60 min and 2, 3, 4, 6, and 8 h after drug ingestion into tubes containing heparin (10 units) for plasma total platinum and plasma ultratrace platinum analysis. Blood samples were centrifuged (2000 × g for 5 min at 4°C) immediately after collection to prepare plasma. A aliquot was set aside on ice for plasma total platinum analysis. An ultratrace sample was prepared immediately from the remaining plasma using an Amicon Centriprep Filter (M$, 30,000$ cutoff; Amicon, Beverley, MA). The filters were centrifuged at 2000 × g for 20 min at 4°C.

Platinum analysis was undertaken by flameless atomic absorption spectrometry using a Perkin Elmer Spectrometer (Models 1100B and HGA700; Perkin Elmer, Uberlingen, Federal Republic of Germany). Absorption was measured at 265.9 nm. Platinum concentrations were calculated by an external standard curve. The area under the platinum concentration versus time curve (AUC$_{0-\infty}$) was calculated by the trapezoidal rule when successive values were increasing and by the logarithmic trapezoid rule when successive values were decreasing, up to 8 h. The slope of the input phase on a semilogarithmic plot of platinum concentration versus time was taken as the absorption rate constant (Ka). The mean residence time was estimated by dividing the AUC by the AUMC and corrected for the mean absorption time by subtracting the inverse of the absorption rate constant. The free plasma platinum fraction was assessed by dividing the free plasma platinum AUC by the total plasma platinum AUC and expressing the fraction as a percentage.

**RESULTS**

The antitumor activity of oral JM216 and i.v. cisplatin given as either a single dose or once daily for five consecutive days was compared in the murine ADJIPC6 plasmacytoma model. Neither the toxicity, antitumor potency, nor the therapeutic index changed when i.v. cisplatin was given as a fractionated rather than a single dose (cisplatin single dose: LD$_{50}$ 11.5 mg/kg; ED$_{50}$ 0.88 mg/kg; TI 13; 300 mg/kg, 40 mg/kg, and 200 mg/kg and on the fifth day of a daily X5 treatment course at 40 mg/kg/day X5. Blood was collected under terminal halothane anesthesia from three mice after oral JM216 at 0, 10, 20, 30, and 60 min and 2, 3, 4, 6, and 8 h after drug ingestion into tubes containing heparin (10 units) for plasma total platinum and plasma ultratrace platinum analysis. Blood samples were centrifuged (2000 × g for 5 min at 4°C) immediately after collection to prepare plasma. A aliquot was set aside on ice for plasma total platinum analysis. An ultratrace sample was prepared immediately from the remaining plasma using an Amicon Centriprep Filter (M$, 30,000$ cutoff; Amicon, Beverley, MA). The filters were centrifuged at 2000 × g for 20 min at 4°C.

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**Statistical.** The significance of differences between means were assessed using a $t$ test. $P < 0.05$ was regarded as significant.

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose (mg/kg)</th>
<th>T-C ratio</th>
<th>Max. tumor regression</th>
<th>Growth delay</th>
<th>Body weight loss</th>
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<tr>
<td></td>
<td>Level²</td>
<td>Rate³</td>
<td>Total⁴</td>
<td></td>
<td></td>
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<tr>
<td>Single dose q21 days</td>
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<td>100</td>
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<tr>
<td>200</td>
<td>200</td>
<td>1000</td>
<td>0.368</td>
<td>&lt;0.05</td>
<td>53 (d7)</td>
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<tr>
<td>Daily ×5 q21 days</td>
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<td>50</td>
<td>300</td>
<td>0.199</td>
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</tr>
<tr>
<td>40</td>
<td>200</td>
<td>1000</td>
<td>0.101</td>
<td>&lt;0.01</td>
<td>14 (d10)</td>
</tr>
<tr>
<td>60</td>
<td>300</td>
<td>1500</td>
<td>0.073</td>
<td>&lt;0.01</td>
<td>17 (d10)</td>
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<tr>
<td>Daily ×5 q28 days</td>
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<td>75</td>
<td>300</td>
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<tr>
<td>40</td>
<td>150</td>
<td>600</td>
<td>0.072</td>
<td>&lt;0.01</td>
<td>18 (d10)</td>
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<tr>
<td>60</td>
<td>225</td>
<td>900</td>
<td>0.045</td>
<td>&lt;0.01</td>
<td>8 (d10)</td>
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<tr>
<td>Chronic daily dosing</td>
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<td>400</td>
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<tr>
<td>14.3</td>
<td>300</td>
<td>600</td>
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<td>N.S.</td>
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<tr>
<td>20</td>
<td>420</td>
<td>840</td>
<td>0.184</td>
<td>&lt;0.01</td>
<td>27 (d14)</td>
</tr>
</tbody>
</table>

$^a$ Daily dose.
$^b$ Total dose administered in a 3-week treatment cycle.
$^c$ Total dose administered in a treatment course.
$^d$ Ratio of mean tumor volume of treated and control groups at 28 days.
$^e$ $t$ test of mean treated versus control tumors at 28 days.
$^f$ Time in days required for tumors in treated animals to double in volume minus that required for control animals.

Table 1 Antitumor activity of oral JM216 given either as a single dose, once a day for 5 consecutive days, or once a day indefinitely to nude mice bearing human ovarian carcinoma xenografts (PXNJO9T/C)
and cisplatin daily ×5: LD₅₀, 12 mg/kg; ED₅₀, 1.1 mg/kg; TI 12). A single dose of oral JM216 by comparison caused less toxicity and had a greater therapeutic index than a single dose of i.v. cisplatin (JM216 single dose: LD₅₀, 330 mg/kg; ED₅₀, 5.8 mg/kg; TI 56). Moreover, dose fractionation (daily ×5) of oral JM216 resulted in increased tolerance, antitumor potency, and therapeutic index compared to single dose JM216 (JM216 daily ×5: LD₅₀, 825 mg/kg; ED₅₀ < 2.0 mg/kg; TI > 423).

The antitumor activity of oral JM216, given as either a single dose, daily ×5, or on a chronic dosing schedule, was compared in nude mice bearing human ovarian carcinoma xenografts (PXN109 T/C; Table 1; Fig. 1). At an equivalent total dose of 200 mg/kg per 21 days, tumor growth delays were greater with daily ×5 treatment (55 ± 15 days) than with single dose JM216 (35 ± 13 days; P < 0.05) or chronic daily dosing (12 ± 5.8 days; P < 0.001). At the MTD for the respective schedules, tumor growth delays with daily ×5 q3 weeks (60 mg/kg/day ×5: 81 ± 31 days) and daily ×5 q4 weeks schedules (60 mg/kg/day ×5: 71 ± 28 days) were superior to either single dose JM216 (200 mg/kg: 35 ± 13 days; P < 0.02) and chronic daily dosing (14.3 mg/kg/day ×5: 16 ± 15 days; P < 0.05). Also, tumor regression at the MTD was greater with the daily ×5 q3 week (60 mg/kg/day ×5: 9.2 ± 21%; P < 0.001) and daily ×5 q4 week schedules (60 mg/kg/day ×5; 4.8 ± 4.9%; P < 0.001) than with single dose JM216 (51 ± 15% of initial tumor volume). No statistically significant differences in tumor regression and growth delays were recorded between the daily ×5 q3 week and daily ×5 q4 week dosing regimens.

At an equivalent total dose of 200 mg/kg per 21 days, there was greater loss of body weight with chronic daily treatment (12.4 ± 7.4% loss of body weight compared to controls) than either single dose (4.8 ± 1.7% loss of body weight compared to controls; 0.05 > P > 0.02) or daily ×5 dosing (6.2 ± 3.7% loss of body weight compared to controls; 0.02 > P > 0.01). In BALB/c mice, hematological toxicity occurred with all administration schedules at the MTD. The severity of leukopenia was greater with single dose JM216 [nadir, peripheral WBC count: 1.2 ± 0.4 (10⁹/liter); day 2] than with daily ×5 dosing [nadir, peripheral WBC count: 2.7 ± 0.1 (10⁹/liter); day 12; P < 0.02]. Conversely, the severity of thrombocytopenia was worse with the daily ×5 regimen [nadir, platelet count: 159 ± 39 (10⁹/liter); day 14] than with single dose administration (nadir, platelet count: 541 ± 92; day 10; P < 0.01). No significant reduction in [¹⁴C]inulin clearance was recorded with the single dose or daily ×5 regimens, but a small reduction occurred with chronic daily dosing (−11% of control; P < 0.01).

Plasma total and ultrafiltrate platinum pharmacokinetics were studied in mice after JM216 orally at 9.5, 40, and 200 mg/kg (Table 2; Fig. 2), doses corresponding to the delivery of an equivalent total dose of 200 mg/kg per 21 days for the three administration schedules. Peak ultrafiltrate platinum levels increased by over 10-fold with only a 4-fold increase in dose from 9.5 mg/kg (PUF Cmax, 0.11 ± 0.066 mg/l) to 40 mg/kg (PUF Cmax, 1.5 ± 0.11 mg/l; P < 0.01) but then did not significantly increase (1.6-fold) with a further 5-fold increase in dose to 200 mg/kg (PUF Cmax, 2.4 ± 0.44 mg/l; P > 0.05). Similarly, peak total platinum levels increased by over 8-fold with only a 4-fold increase in dose from 9.5 mg/kg (Total Cmax, 0.37 ± 0.15 mg/l) to 40 mg/kg (Total Cmax, 3.0 ± 0.31 mg/l; P < 0.001) but then did not significantly increase (2.4-fold) with a further 5-fold increase in dose from 40 to 200 mg/kg (Total Cmax, 5.7 ± 0.44 mg/l; P > 0.05). Total and ultrafiltrable plasma platinum AUCs also increased disproportionately by about 10-fold with only a 4-fold increase in dosage from 9.5 mg/kg (AUC₀₋₈; total 13 mg·h⁻¹; PUF 0.18 mg·h⁻¹) to 40 mg/kg (AUC₀₋₈; total 14 mg·h⁻¹; PUF 1.7 mg·h⁻¹) but then increased less than proportionately (2-fold) with a further 5-fold increase in dose from 40 to 200 mg/kg (AUC₀₋₈; total 25 mg·h⁻¹; PUF 3.5 mg·h⁻¹). Tmax, MRT, and Kₑ showed no dose related changes. A comparison of pharmacokinetics on days 1 and 5 of a 40 mg/kg/day ×5 treatment protocol showed no change in total plasma platinum Cmax (day 1, 3.0 ± 0.31 mg/l; day 5, 2.9 ± 0.60 mg/l; P > 0.05) or AUC (day 1, 14 mg·h⁻¹; day 5, 14 mg·h⁻¹). However, decreases in ultrafiltrable plasma platinum Cmax (day 1, 1.5 ± 0.11 mg/l; day 5, 0.59 ± 0.099 mg/l;
P < 0.001, AUC (day 1, 1.7 mg·h; day 5, 0.97 mg·h) and free plasma fraction (PUF AUC/day 1; 12% : day 5; 6.9%) were recorded on day 5 compared to day 1.

**DISCUSSION**

We have demonstrated the dependence upon administration schedule of the antitumor activity of a novel oral platinum agent (JM216) independently in two in vivo tumor models. Against the murine ADJ/PC6 plasmacytoma, daily ×5 administration of oral JM216 resulted in improved tolerance, antitumor potency, and therapeutic index compared to single dose administration. Against a human ovarian carcinoma xenograft, antitumor activity was best for daily ×5 administration compared to single dose or once daily dosing indefinitely administration schedules, both at their respective MTDs and at dose levels delivering an equivalent amount of total drug. In contrast, antitumor schedule dependency is not a well recognized property of either the existing clinical platinum drugs (10) or alkylating agents (19). In keeping with this, we found no advantage for a fractionated schedule (daily ×5) of cisplatin compared to its single dose administration in the murine ADJ/PC6 plasmacytoma. Small functional differences in toxicity were found with the different schedules of oral JM216, such as mild nephrotoxicity and greater body weight loss, suggestive of more severe gastrointestinal toxicity with chronic daily dosing and more severe thrombocytopenia and less leukopenia with daily ×5 dosing. These data show that oral JM216 has antitumor schedule dependent properties in vivo, which is an unusual feature for this class of agent, and suggest that the optimal clinical protocol may be daily ×5 dosing, since this schedule showed the best activity and tolerance in these preclinical model systems.

Further experiments addressed the pharmacokinetics of oral JM216 and the possible mechanistic basis of its in vivo antitumor schedule dependency. At the MTD for the chronic dosing schedule (9.5 mg/kg), peak plasma ultrafiltrate levels were 0.62 μM, whereas the IC₅₀ for JM216 in the cell line from which the PXN1097/C xenograft tumor was established is 2.7 μM. Previous work has demonstrated that the cytotoxicity of JM216 is highly time dependent, with optimal in vitro activity occurring with drug exposure durations of 24 to 96 h (1). This suggests that the poor in vivo antitumor activity of the chronic dosing schedule is due to plasma drug levels failing to reach cytotoxic concentrations for an adequate time.

Nonlinear pharmacokinetic behavior is characterized by disproportionate changes in drug levels and AUC with changes in dosage (20). Following oral JM216 at 9.5 and 40 mg/kg, plasma platinum Cmax and AUCs in mice increased by 10-fold and out of proportion to this 4-fold increase in dosage. This effect may be due to a dose-related increase in the extent of oral absorption. Platinum drugs effect gastrointestinal mobility and transient time and such phenomena could be a basis for an apparent dose-related enhancement of oral absorption, such as seen in this dose range. Conversely, a further 5-fold increase in dose from 40 mg/kg to 200 mg/kg (the MTD for single dose administration) was accompanied by less than proportionate (about 2-fold) increases in plasma platinum Cmax and AUC, consistent with a dose-related fall in the extent of drug absorption. A Phase I study of oral JM216 made a similar finding of an apparent reduction in the extent of drug absorption and less than proportionate increases in Cmax and AUC with dose escalation above 200 mg·m² (6). We hypothesize that this finding may relate to the poor aqueous solubility of JM216, limiting dissolution from its dosage form within the gastrointestinal tract and availability for absorption as dosages exceed its limit of solubility. Interestingly, a similar pattern of nonlinear pharmacokinetic behavior has been reported for etoposide, an oral anticancer agent with schedule-dependent properties and poor aqueous solubility (21). The complex nonlinear pharmacokinetic behavior of oral JM216 in mice meant that optimal plasma pharmacokinetics occurred at dosages used in the daily ×5 administration schedules and may be the basis for the in vivo antitumor schedule dependency of the drug in these model systems.

A further pharmacokinetic comparison in mice treated with oral JM216 found falls in ultrafiltrable plasma platinum Cmax, AUC, and free fraction on the fifth compared to the first day of a daily ×5 administration schedule. This finding did not appear due to a reduction in oral absorption since there were no changes in total plasma platinum Cmax or AUC over a 5-day treatment period. JM216 is a platinum(IV) complex, and such complexes are thought to require activation by reduction to platinum(II) species as a prelude to interactions with biological macromolecules (22). In keeping with this, metabolism studies have found very little parent JM216 after its oral administration in rodent or human plasma but a series of platinum(II) metabolites including ammine-dichloro-cyclohexylamine-platinum(II) (JM118) (23). This suggests that JM216 is a pro-drug and that the time-dependent changes in plasma ultrafiltrable platinum pharmacokinetics may relate to the induction of its activation to platinum(II) metabolites.

In summary, oral JM216 displays antitumor schedule dependency in vivo in preclinical tumor model systems and nonlinear pharmacokinetics after its oral administration to mice. Its schedule-dependent properties appear to relate to dose-related changes in the extent of absorption. Optimal antitumor activity, tolerance, and pharmacokinetics occurred with daily ×5 dosing, and these findings have prompted the clinical evaluation of a daily ×5 administration schedule (7).

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5 L. R. Kelland, unpublished data.
6 S. E. Morgan, personal communication.
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