Phase I Study of Ethylenediamine Platinum(II) Malonate (NSC 146 068), a Second Generation Platinum Analogue

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ABSTRACT

Ethylenediamine platinum(II) malonate (JM-40 (NSC 146 068)) has been selected for clinical studies because of its favorable preclinical toxicity profile as a "second generation" platinum analogue. When compared to cisplatin, JM-40 was less emetic in the ferret and less nephrotoxic in the dog, while its antitumor activity approached that of cisplatin. Twenty-nine patients received 86 courses of JM-40 as a single dose every 3–4 wk. After 13 dose escalation steps the maximum tolerable dose was reached at 1200 mg/m². The dose limiting toxicities were nausea, vomiting, and nephrotoxicity. The renal damage seemed reversible up to a dose level of 1000 mg/m² and consisted of a glomerular and tubular dysfunction. JM-40 did not cause any other dose related side effect or myelosuppression. Pharmacokinetic studies at a dose of 1000 mg/m² revealed mean terminal half-lives of 5.0 and 1.9 days for platinum in plasma and plasma ultrafiltrate, respectively. The mean cumulative excretion of platinum in urine accounted for 57% of the dose up to day 5. Two partial responses were observed in a patient with a large cell carcinoma of the lung and in one with a carcinoma of the lacrimal gland. Limited evaluation of JM-40 in phase II studies is warranted. The recommended dose is 1000 mg/m² every 4 wk and 800 mg/m² for patients pretreated with platinum analogues.

INTRODUCTION

The introduction of the metal complex cisplatin (2) into cancer chemotherapy has had a major impact on the improvement of cancer treatment. However, the use of cisplatin is restricted by a distinct toxicity profile including renal toxicity, severe nausea and vomiting, neurotoxicity, ototoxicity, electrolyte imbalances, and allergic reactions. The combination of these positive and negative qualities of cisplatin stimulated the search for analogues with a better therapeutic index, the so-called "second generation platinum complexes."

JM-40 (NSC 146068, Fig. 1), has been synthesized by the Johnmathey Research Center (3) and further characterized by Cutbush et al. (4). JM-40 is one of the compounds to finish phase I study under a collaborative agreement on new drug development between the National Cancer Institute and the European Organization for Research and Treatment of Cancer. In the National Cancer Institute antitumor screen JM-40 was active in P388, L1210, colon 26, Lewis lung, Sarcoma M5076, and MX-1, the results being comparable to those of cisplatin (5). JM-40 was cross-resistant in a M5076 subline resistant to and MX-l, the results being comparable to those of cisplatin active in P388, L1210, colon 26, Lewis lung, Sarcoma M5076. The development between the National Cancer Institute and the Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesrmanlaan 121, 1066 CX Amsterdam (W. W. t. B. H., G. S. J. G. M. J, The Netherlands called "second generation platinum complexes.

RESULTS

Thirty-six patients were entered into this phase I study. Twenty-nine patients were considered evaluable for toxicity and response, 5 patients died before completing one course, and 2 patients were lost to follow-up. Two of the 29 patients received one course of JM-40 each, although they were ineligible (impaired renal function). One patient with a renal carcinoma of JM-40 the single dose LD₅₀ was 321 mg/m² for male and 396 mg/m² for female mice. The target organs of toxicity in mice were the kidneys and the gut. The results of the present study with JM-40 indicate that the dose limiting toxicity in man for this compound are nausea, vomiting, and nephrotoxicity, but at a much higher equivalent dose than in rodents.

MATERIALS AND METHODS

Patient Selection. All patients who entered this trial had a histologically confirmed cancer which had proven to be resistant to existing conventional therapeutic modalities. Prior to the administration of JM-40, patients had been off therapy for more than 4 wk; in cases involving therapy including nitrosoureas, mitomycin or extensive radiotherapy, the interval was 6 wk. Criteria for eligibility included a performance status of 0–3 (WHO scale); a life expectancy of at least 2 mo; a WBC greater than 4,000 cells/mm³ and a platelet count of greater than 125,000 cells/mm³; a normal liver function unless abnormalities were clearly due to metastatic disease; and a normal renal function (serum creatinine <1.4 mg/dl and creatinine clearance >60 ml/min). Prior to entry written informed consent was obtained from all patients. The treatment protocol had been approved by the local medical ethical committee.

Treatment Plan. JM-40 was formulated in sterile water (5 mg/ml) and supplied in vials of 100 and 500 mg. In this formulation JM-40 proved to be stable for 12 mo without refrigeration as determined by high pressure liquid chromatography analysis (10). Prior to use the vials were diluted 1:1 in 10% glucose. The solution was stable for at least 8 h (10). A single dose of JM-40 was administered i.v. over 10–60 min and repeated after 21 days (at more than 900 mg/m² after 28 days) until there was severe toxicity, progression of disease, or refusal by the patient.

Doses were escalated according to a modified "Fibonacci Scheme" after at least three patients had terminatced courses on the previous level. Dose escalations in individual patients were allowed up to a dose level at which toxicity was seen. In this case 2–3 more patients were entered at the same level and no further dose escalations per patient were allowed thereafter. The starting dose was 20 mg/m² (1/14 of mouse equivalent LD₅₀). Hematological, blood chemistry, and urine parameters were evaluated at least once a week and audiograms were performed before each consecutive course.

Pharmacokinetics. At a dose of 1000 mg/m² blood and urine were sampled from 3 patients at regular time intervals during 5 days after administration of JM-40. Plasma and plasma ultrafiltrate were separated immediately after collection of the blood samples. Platinum in plasma, plasma ultrafiltrate, and urine were analyzed by means of atomic absorption spectrophotometry as described by Boven et al. (7).
received JM-40 without prior therapy. Patients' characteristics are summarized in Table 1.

A total of 86 courses of JM-40 were given (Table 2). Up to the seventh dose level of 300 mg/m² no major side effects were seen apart from nausea and vomiting. At that point of the study the decision was made to escalate doses in small steps (25–33%) in individual patients according to the protocol and enter new patients again at dose levels at which toxicity was seen (800–900 mg/m²). This option was felt to be superior to that of entering new patients at the 400–800 mg/m² dose levels or taking larger escalation steps from above the 300 mg/m² dose level. With this decision the study could be terminated by evaluating 14 dose levels in a mere 36 patients.

At the 900 mg/m² level and above, no more dose escalations were made in the same patient. At the 1000 and 1200 mg/m² level 3 patients received a total of 6 subsequent courses with a 25% dose reduction because of severe side effects in the face of stable disease (2) and a partial response (1).

Myelosuppression. Myelosuppression was not one of the major side effects of JM-40. Low nadirs of the WBC and/or platelets occurred occasionally at all dose levels mainly in heavily pretreated patients. The median nadirs of the WBC and platelets were not related to the dose of JM-40. One patient with a leiomyosarcoma uteri developed platelet antibodies which were detected 3 wk after the first course of JM-40. At more than the 900 mg/m² level JM-40 caused anemia regularly at 900 mg/m² in 8 of 18 courses (WHO grade I = 7; WHO grade II = 1), at 1000 mg/m² in 6 of 11 courses (grade I = 3; grade II = 1), and at 1200 mg/m² in 5 of 6 courses (grade I = 4; grade II = 1).

Renal Toxicity. Renal toxicity became dose limiting at 1200 mg/m². Considering the median and the range, the increase in serum creatinine is related to the dose of JM-40 from above 400 mg/m² (Table 3). The same holds for the decrease in creatinine clearance (Table 4). Therefore above 900 mg/m² several consecutive courses of JM-40 were administered with hydration, prehydration with 1 liter saline prior to JM-40 and posthydration with saline 4–6 liters/day for 1–2 consecutive days. Courses administered with such hydration are evaluated separately in Tables 3 and 4.

Renal toxicity at the 900-mg/m² dose level was reversible within 4 wk. At the 1200-mg/m² dose some cumulation of renal toxicity was noted in one patient with 3 and one patient with 5 courses.

Two patients received JM-40 (900 and 1000 mg/m², one course each) despite the fact that they had an impaired renal function.
function (protocol violation). It became clear that a preexisting renal dysfunction evoked more severe renal toxicity. The values of these 2 patients are not included in Tables 3 and 4.

Reversible proteinuria was seen regularly from above 900 mg/m² for 2–12 days: at 900 mg/m² in 7 of 10 evaluable courses (0.1–1.5 g/day, maximum excretion); at 1000 mg/m² in 7 of 7 courses (0.4–1.7 g/day); and at 1200 mg/m² in 5 of 5 courses (0.5–7.4 g/day). Reversible changes in the serum electrolytes occurred frequently above 800 mg/m². A low potassium (minimum of 2.9 mmol/liter), phosphorus (0.45 mmol/liter), and magnesium (0.50 mmol/liter) in 8 courses each and a low calcium (2.03 mmol/liter) in 4 courses.

Gastrointestinal Toxicity. Besides renal toxicity, nausea and vomiting were dose limiting. Up to a dose of 800 mg/m² no antiemetics were given prophylactically; 4 of 5 courses caused grade 3, and 1 of 5 courses caused grade 4 toxicity (WHO classification). Therefore all courses at 900 mg/m² and above were given with prophylactic metoclopramide, which showed no consistent effect.

Other Side Effects. Peripheral neuropathy, WHO grade 1–2, was observed in 5 patients (Table 5). Only one of them had previously been treated with cisplatin. The neuropathy was not a consistent finding as one patient experienced paraesthesia in the extremities after courses 3 and 4, which disappeared after course 5. Other side effects, WHO grade 1–2, and their incidence are listed in Table 5 as well. In the serial audiograms which were performed prior to each course of JM-40 no major changes were noticed.

Pharmacokinetics. Fig. 2 shows the concentration-time curves of platinum in plasma and plasma ultrafiltrate in 3 patients after a short infusion of JM-40 of 1000 mg/m². Table 6 summarizes the pharmacokinetic data obtained in these 3 patients. Half-lives were calculated up to day 4 because blood samples on day 5 were not available for all patients. The best fit for the calculation of the initial and terminal half-lives of total platinum in plasma was obtained over the time intervals 0–20 min and 1–4 days, respectively. Ultrafilterable platinum was detected in plasma for at least 4 days after administration of JM-40. Initial and terminal half-lives for ultrafilterable platinum were calculated over the same time intervals as for total platinum.

Responses. Two partial responses were observed during this phase I study. Patient 22 with a large cell carcinoma of the lung had previously relapsed or progressed under treatment with cisplatin, etoposide, cyclophosphamide, vindesine, ametantrone, and n-methyl formamide. On day 18 after his first course of JM-40 (1000 mg/m²) evaluation of his chest film revealed a greater than 50% reduction of lung metastases. Despite this response the patient refused a second course of JM-40. Patient 35 had a carcinoma of the lacrimal gland which had previously been radiated with 7000 rads. He received 5 courses of JM-40 (2 of 1200 mg/m² and 3 of 900 mg/m²); courses 2–5 were given with prehydration and prolonged posthydration, whereas a dose reduction had been applied for courses 3–5 because of nephrotoxicity due to infusion. After the second course onwards a partial response was measured (lung metastases).

Three additional patients experienced subjective improvement of their symptoms and stable disease during several courses of treatment with JM-40. The tumor types were gastric carcinoma, squamous cell carcinoma of the lung, and colon carcinoma.

DISCUSSION

In the search for second generation platinum analogues, structure-activity studies of platinum-containing compounds have largely concentrated on complexes of the type [platinum A2 X2]. Initial structure-activity studies concentrated on variations of the A (amine) and the X (anionic) ligands separately, but it became apparent that the most successful compounds were combinations of effective A and X groups. The activity of the X-ligand in JM-40, malonate, was in the PC6 tumor comparable to the 1,1-cyclobutanedicarboxylate of carboplatin (3), whereas the A-ligand in JM-40, ethylenediamine, alone was less effective in this tumor than for instance the 1,2-diaminocyclohexane group (11).

JM-40 was selected for clinical studies because of its more favorable preclinical toxicity profile, at equitoxic doses, as compared to cisplatin. Preclinical antitumor activity ap-

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Other side effects after JM-40</th>
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</thead>
<tbody>
<tr>
<td>Side effect</td>
<td>No. of patients/ no. of courses</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>5/8</td>
</tr>
<tr>
<td>Painful arm due to infusion</td>
<td>7/10</td>
</tr>
<tr>
<td>Phlebitis due to infusion</td>
<td>5/6</td>
</tr>
<tr>
<td>Pain in the flank</td>
<td>1/1</td>
</tr>
<tr>
<td>Pain in the abdomen</td>
<td>2/2</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>4/4</td>
</tr>
<tr>
<td>Elevated amylase</td>
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</tr>
</tbody>
</table>

Fig. 2. Concentration versus time profile of platinum in plasma (1–3) and plasma ultrafiltrate (1–5) in 3 patients after a short infusion of JM-40 at a dose of 1000 mg/m².

Table 6 Pharmacokinetic data of 3 patients at a dose of JM-40, 1000 mg/m²

<table>
<thead>
<tr>
<th>Patient no. in Table 2</th>
<th>Platinum in plasma</th>
<th>Platinum in plasma ultrafiltrate</th>
<th>Cumulative urine excretion (% of dose)</th>
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<tbody>
<tr>
<td></td>
<td>t₁/₂a (min)</td>
<td>t₁/₂b (day)</td>
<td>t₁/₂a (min)</td>
</tr>
<tr>
<td>1</td>
<td>32.7</td>
<td>3.2</td>
<td>30.2</td>
</tr>
<tr>
<td>2</td>
<td>31.2</td>
<td>6.9</td>
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<tr>
<td>3</td>
<td>27.8</td>
<td>4.8</td>
<td>28.8</td>
</tr>
<tr>
<td>Mean</td>
<td>±2.5</td>
<td>±1.9</td>
<td>±3.4</td>
</tr>
</tbody>
</table>

* a-phase determined over 0–20 min.  
* b-phase determined over 1–4 days.
proaches that of cisplatin (8, 9). At the time preclinical safety studies were performed it could not be anticipated that human maximum tolerated dose would be as high as 1200 mg/m² which is far higher than mouse LD₁₀ (276 mg/m²). These differences in tolerated dose levels between animals and humans might explain the poor prediction of preclinical toxicology for JM-40.

In the present study renal toxicity and gastrointestinal toxicity were dose limiting. Unlike the experience with cisplatin, pre- and postrhydration with saline hardly affected renal dysfunction caused by JM-40 (Tables 3 and 4). Although a limited number of patients received more than 2 courses of JM-40, nephrotoxicity was reversible within 4 wk in 3 of 3 patients at 900 mg/m², in 2 of 3 patients at 1000 mg/m² and in 0 of 2 patients at 1200 mg/m². Changes in serum electrolytes, elevated excretion in renal tubular enzymes, and microglobulins (not reported here) suggest that JM-40 may also cause renal tubular damage. JM-40 did not cause any other dose related side effects, which also holds for myelosuppression.

The shape of the platinum versus time curve in plasma for JM-40 showed the same characteristics as for cisplatin. Therefore calculations of the initial and terminal half-lives of platinum in plasma were performed in the same manner as described earlier for cisplatin (12). The mean terminal half-life was comparable to those of cisplatin and spiroplatin (13) indicating that the terminal half-life is determined by the turnover of the plasma proteins to which the platinum compounds are irreversibly bound. The mean initial half-lives of platinum in plasma and plasma ultrafiltrate do not differ from each other over the time interval of 0–20 min. These half-lives are greater than those determined for cisplatin and spiroplatin (13). This may be explained by the slower and less extensive protein binding of JM-40 as compared to cisplatin and spiroplatin (13). The reduced protein binding also explains the higher cumulative urinary excretion as compared to cisplatin and spiroplatin (12, 13). The cumulative urinary excretion of carboplatin is even higher because the protein binding of this drug is limited (14).

The reversibility of the nephrotoxicity, lack of myelosuppression, and the observed antitumor activity justify a limited evaluation of JM-40 in phase II studies. The recommended dose is 1000 mg/m² every 4 wk as a single dose. Patients pretreated with platinum analogues should receive no more than 800 mg/m². Some prevention of nephrotoxicity might be achieved by hydration. However, hydration with saline has not prevented nephrotoxicity.

REFERENCES

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