Cancer Chemother Pharmacol (1982) 9:140–147

Cancer Chemotherapy and Pharmacology

Early Clinical Studies with *cis*-Diammine-1,1-Cyclobutane Dicarboxylate Platinum II

A. H. Calvert, S. J. Harland*, D. R. Newell, Z. H. Siddik, A. C. Jones, T. J. McElwain, S. Raju, E. Wiltshaw, I. E. Smith, J. M. Baker, M. J. Peckham, and K. R. Harrap

[1] Department of Biochemical Pharmacology, Institute of Cancer Research, Sutton, Surrey
Divisions of [2]Medicine and [3]Radiotherapy, Royal Marsden Hospital, Sutton, Surrey, Great Britain

Summary. *cis-Diammine-1,1-cyclobutane dicarboxylate platinum II (CBDCA, JM8), an analogue of cisplatin showing reduced toxicity in preclinical studies, was evaluated in 60 patients. Doses were given initially every 3 weeks and escalated from 20 to 520 mg/m^2. Following this, doses were given every 4 weeks and escalated from 300 to 500 mg/m^2. The dose-limiting toxicity, thrombocytopoenia, occurred in four-fifths of patients treated at 520 mg/m^2, with the nadir occurring 3 weeks after treatment. Leucopoenia and anaemia also occurred but were less severe. Vomiting occurred in all patients receiving over 120 mg/m^2 but seldom persisted beyond 24 h. Serial measurements of ^{51}Cr-EDTA clearances, urinary N-acetylglucosaminidase, urinary leucine aminopeptidase, and β_2-microglobulin did not reveal significant evidence of nephrotoxicity. Detriment to the audiogram has not been seen in the first 13 patients studied. Pharmacological studies showed that most of the dose of platinum was excreted in the urine, and that impairment of renal function may be associated with drug retention and an increased risk of myelosuppression. The previous therapy and age of the patient also affected the tolerance of the drug. Clinical responses were seen in patients with ovarian carcinoma receiving > 120 mg/m^2.*

A further dose escalation was performed on a 4-week schedule in patients under 65 with good renal function. The maximum dose it was possible to administer repeatedly without incurring myelosuppression was in the range 400–500 mg/m^2.

JM8 is not significantly nephrotoxic and is less emetic than cisplatin. It has antitumour activity in man and deserves wider evaluation, along with the other analogues under study in various centres, as an alternative to cisplatin.

Introduction

Since its introduction into clinical practice in 1972, cisplatin has assumed a major role in the treatment of testicular teratoma and ovarian carcinoma [1, 3, 9, 14, 20, 21, 24]. It also shows useful clinical activity in head and neck tumours, bladder cancer, and various other tumours [8, 10, 13, 19, 22, 23]. Toxicity of cisplatin includes emesis, renal impairment, peripheral neuropathy, high-frequency hearing loss, and anaemia [15, 17]. Although the nephrotoxicity may be ameliorated by hydration and diuresis [7], progressive decline of both glomerular [2, 24] and tubular function occurs [11].

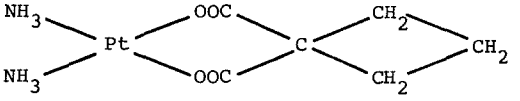

Fig. 1. Structure of JM8

Thus the total number of courses which may be given is limited. Further, the neurotoxicity of cisplatin may necessitate cessation of treatment, while the severe vomiting may lead to the patient refusing further treatment. Thus, many centres have been searching for an analogue of cisplatin with reduced toxicity. The compound under discussion, JM8 (Fig. 1), was selected on account of reduced nephrotoxicity in rats coupled with increased antitumour selectivity in several test systems [6, 18]. It was also less emetic than cisplatin in dogs [5].

Materials and Methods

Drug. *cis*-Diammine-1,1-cyclobutane dicarboxylate platinum II was synthesised by Johnson Matthey Research Centre (Sonning, Great Britain) and formulated by Bristol-Myers International (Laboratoire Allard, Nogent sur Marne, France). It was supplied as a white powder in 50-mg vials, which was > 99.5% pure as estimated by high-performance liquid chromatography. No soluble impurities were detected. The desired dose was dissolved in 300 ml 5% dextrose and infused into a peripheral vein over 1 h. No hydration or diuretics were given.

Patients. Patients with malignant disease for whom no known satisfactory treatment existed were included subject to conventional criteria (Hb > 100 g/l, WBC > 3 × 10^6/l, platelets > 100 × 10^9/l, normal liver function tests, blood urea and creatinine, Karnovsky score of > 50%, and absence of serious intercurrent conditions). In the later stages of the trial patients with abnormal renal function and with raised liver function tests due to metastatic disease were also included. The characteristics of the patients included in this study are summarised in Table 1.

Doses. In stage I of the study doses were escalated in a modified Fibronacci fashion. Three new patients were admitted at each dose level and doses were escalated at 3-week intervals within patients. After the first stage of the study, when it became clear that the platelet nadir occurred at 3 weeks, the dosage interval was increased to 4 weeks, good-risk patients only were included, and dose escalations

Reprint requests should be addressed to A. H. Calvert
* In receipt of CRC Fellowship

0344-5704/82/0009/0140/$ 01.60

Table 1. Characteristics of the patients[a] included in the study

Diagnosis	No. of patients
Carcinoma of ovary	38
Testicular teratoma	5
Bronchus	3
Squamous cell carcinoma	
Alveolar cell carcinoma	1
Pleural mesothelioma	3
Colonic carcinoma	2
Unknown primary	2
Thyroid carcinoma	1
Cervical carcinoma	1
Renal cell carcinoma	1
Synoviosarcoma	1
Mixed mesodermal sarcoma	1
Melanoma	1

[a] Mean age 51 (range 21–77) years. Sex distribution: 45 female, 15 male

were reduced to increments of approx. 15%, starting from 300 mg/m^2 (stage II). In stage III of the study poor-risk patients were studied.

Monitoring. Blood counts, urea and electrolytes, creatinine, liver function tests, urinary *N*-acetylglucosaminidase (NAG), leucine aminopeptidase (LAP), and β_2-microglobulin were measured on days 0, 1, 2, 4, 6, 10, and 21 following each course. Glomerular filtration rate was estimated by the ^{51}Cr-EDTA method [4] prior to each course, *N*-acetyl-glucosaminidase and leucine aminopeptidase by the method of Jones et al. [11], and β_2-microglobulin using a radioimmunoassay kit (Pharmacia [Great Britain] Ltd). Monitoring of the patients' disease was carried out by clinical examination and measurement, radiography, isotope or ultrasonic scanning or computer-assisted tomography as appropriate. Urinary recovery of platinum in the period 0–24 h was studied in 38 patients. In 15 patients urine collections were made in the periods 0–4 and 4–24 h following JM8 administration. In selected patients plasma pharmacokinetics were studied, samples being taken at 0.5, 1, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 12.0, and 24.0 h after the beginning of the infusion. Area under the curve was calculated by the trapezoidal rule. Platinum levels were measured in plasma and urine by atomic absorption spectrometry. Audiography was performed in an anechoic room using either an Amplade 300 or a Peters audiometer. Bone and air conduction were measured at 250, 500, 1,000, 2,000, and 4,000 Hz, and air conduction only at 8,000 Hz.

Results

a) Toxicity

i. Haematological Toxicity

Stage I (24 patients): The dose-limiting toxicity of JM8 was myelosuppression, with thrombocytopoenia being more severe than leucopoenia. During the first stage of the study doses were escalated to 520 mg/m^2, at which dose four-fifths of the patients experienced thrombocytopoenia (platelets $< 100 \times 10^9$/l), which necessitated platelet transfusion for haemorrhage in one. Certain patients receiving 200 and 320 mg/m^2 also experienced myelosuppression. The platelet nadirs are shown in Fig. 2 and the leucocyte nadirs in Fig. 3. The great

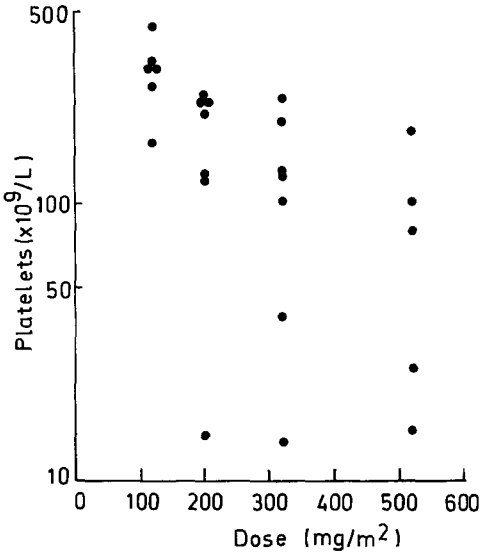

Fig. 2. Nadirs of platelet counts achieved in individual patients following various doses of JM8 in stage I of the study

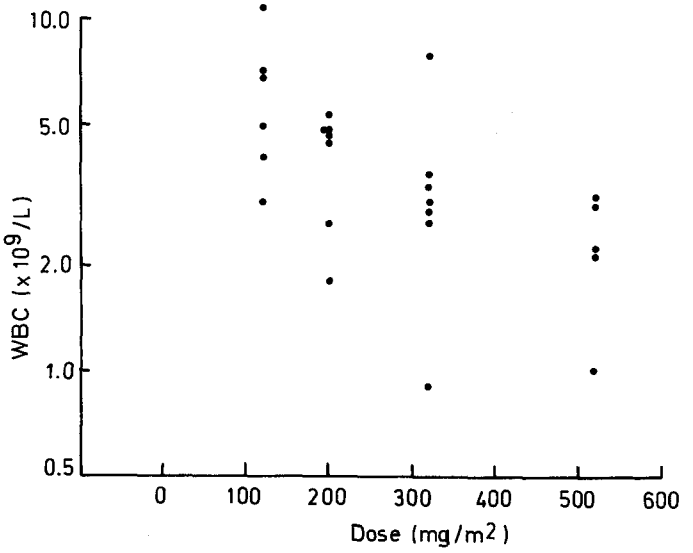

Fig. 3. Nadirs of the total leucocyte counts recorded (same patients as Fig. 2)

variability in the response of the platelet count to a particular dose (e.g., 320 mg/m^2) is evident. Studies of clinical pharmacology (see below) suggested that impaired renal function was associated with a greater exposure to the drug. Figure 4 relates renal function, age, and previous treatment to thrombocytopoenia in patients receiving 200 mg/m^2 or 320 mg/m^2. All 10 patients who developed thrombocytopoenia were over 70 years old, had a clearance of < 60 ml/min, or had received previous melphalan or treosulphan. Only four of the 27 patients who did not experience severe thrombocytopoenia had one of these risk factors.

Stage II (10 patients): To define the maximum tolerated dose in good-risk patients a further dose escalation study was carried out using a 4-week schedule. Doses were escalated from 300 to 500 mg/m^2. Only patients under 65 who had a GFR of $>$ 60 ml/min and had not previously received melphalan, treosulphan, busulphan, nitrosoureas or large-field irradiation

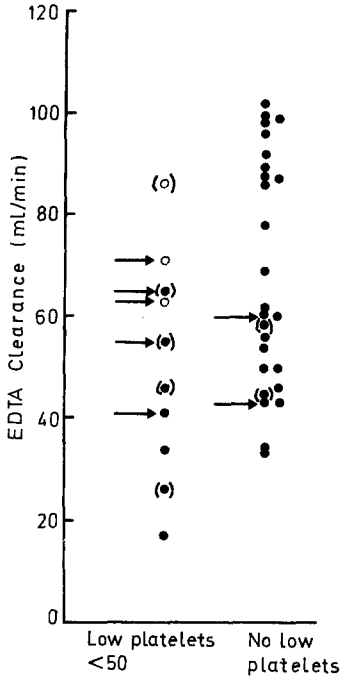

Fig. 4. Relationship between ^{51}Cr-EDTA clearance and thrombocytopoenia. → indicates patient over 70 years old and (■) indicates that the patient had had previous myelosuppressive therapy, viz. melphalan, treosulphan, busulphan, or large-field radiation therapy. Seven of the patients who developed thrombocytopoenia did so following their first course of treatment (●) while in three this occurred following subsequent courses (○). NB: This chart includes patients from stage I and stage II of the study

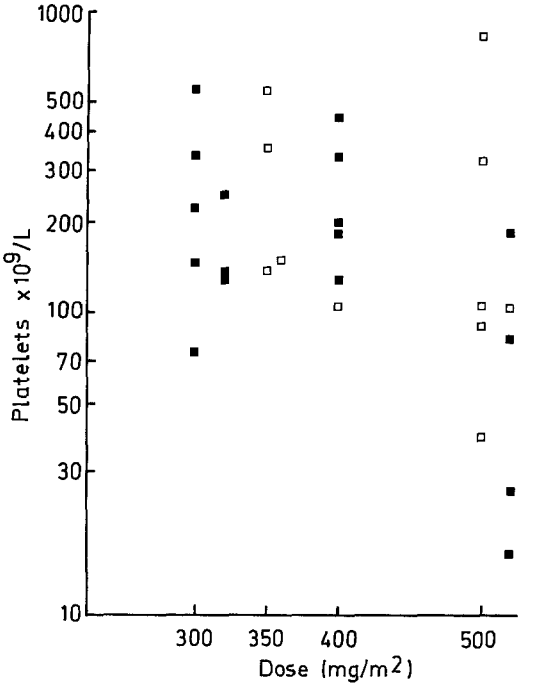

Fig. 5. Platelet nadirs in good-risk patients treated with JM8 in the dose range 300–520 mg/m^2. (■) nadir recorded following first course of treatment; (□) nadir recorded following second course of treatment

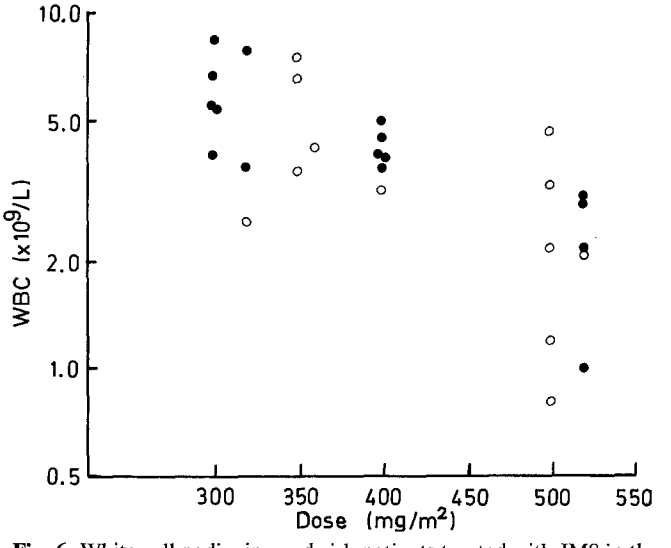

Fig. 6. White cell nadirs in good-risk patients treated with JM8 in the dose range 300–520 mg/m^2. (●) nadir recorded following first course of treatment; (○) nadir recorded following second course of treatment

were included. Repeated courses were increased in the same patient by 50 mg/m^2 if the previous platelet nadir had exceeded 150 × 10^9/l. The combined results of this experience and that gained in the first stage of the study on the good-risk patients are shown in Figs. 5 and 6. Thrombocytopoenia was not seen in patients in this category receiving up to 400 mg/m^2. However, 13 of 15 additional good-risk patients receiving three or more courses of treatment at 400 mg/m^2 experienced modest myelosuppression (platelets < 100 × 10^9/l or WBC < 3.0 × 10^9/l) on subsequent courses. Thus the escalation was stopped at this level.

Mild reductions in haemoglobin were seen in patients receiving higher doses, but these were only statistically significant at the 520 mg/m^2 dose (Table 2).

Stage III (26 patients): If patients had any one of the three risk factors (above) starting doses were reduced by 100 mg/m^2 for each, but subsequent doses to the same patient were increased in the same way. These patients are included in this communication only to illustrate the effects of JM8 in patients with impaired renal function and are included in the response data (below).

All Stages: When myelosuppression occurred, the platelet nadir was at 19 days after treatment (median), with a range of 16–24 days. Recovery invariably occurred. The time to recovery (i.e., platelets > 100 × 10^9/l) varied from 7 to 10 days, with the patients who had experienced more severe thrombocytopoenia taking longer to recover. Preliminary evidence (data not shown) suggests that leucopoenia may be a more prominent feature when myelosuppression occurs following several courses of treatment.

Table 2. Haemoglobin levels before and 3 weeks after JM8 treatment

Dose (mg/m^2)	x̄ Hb before (g/dl) ± SD	x̄ Hb after (g/dl ± SD	No.	*P*
20	12.1 ± 1.4	11.3 ± 0.8	3	0.43
40	11.6 ± 1.1	12.1 ± 1.4	5	0.51
80	13.3 ± 1.2	12.9 ± 1.4	5	0.60
120	12.7 ± 1.2	11.6 ± 1.5	6	0.19
200	12.3 ± 1.6	12.1 ± 2.2	10	0.82
320	11.8 ± 1.0	11.4 ± 1.3	16	0.38
400	13.2 ± 1.5	11.4 ± 1.5	6	0.07
520	12.0 ± 1.1	10.0 ± 1.4	8	0.008

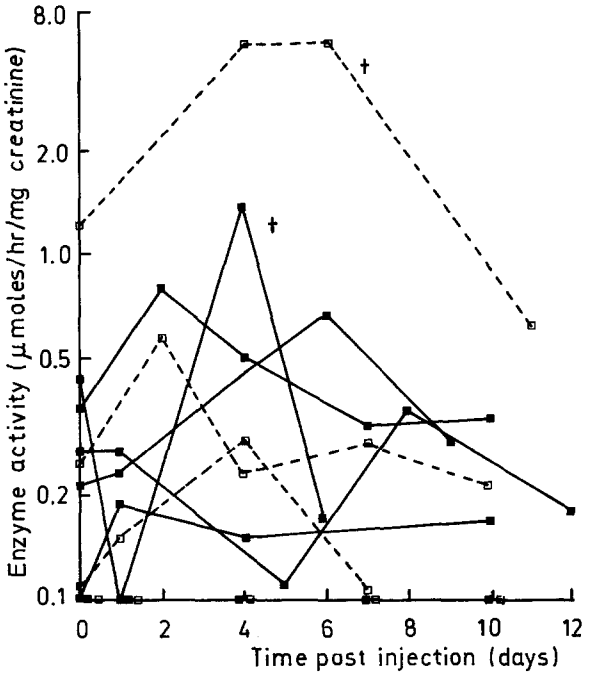

Fig. 7. Changes in *N*-acetylglucosamidase activity in the urine of patients treated with JM8 at (———) 320 mg/m^2 (■) or (- - - -) 520 mg/m^2 (□). † Patient was subsequently shown to have a vesicocolic fistula

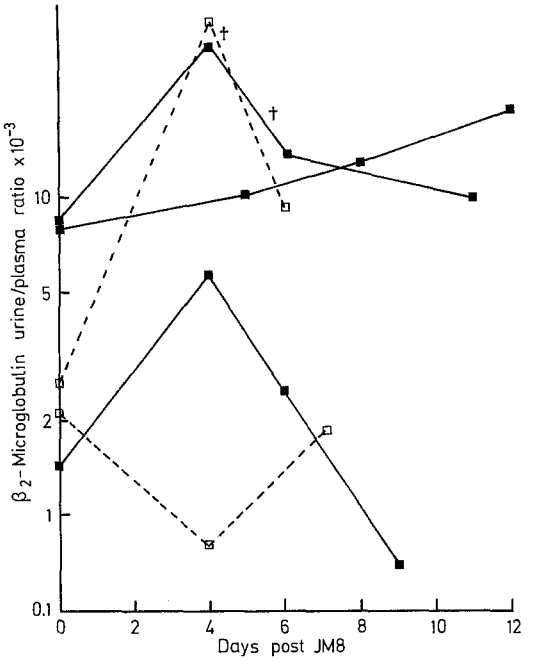

Fig. 9. Changes in β_2-microglobulin urine/plasma ratio in patients treated with JM8 at 320 mg/m^2 (■) or 520 mg/m^2 (□). † Patient was subsequently found to have a vesicocolic fistula

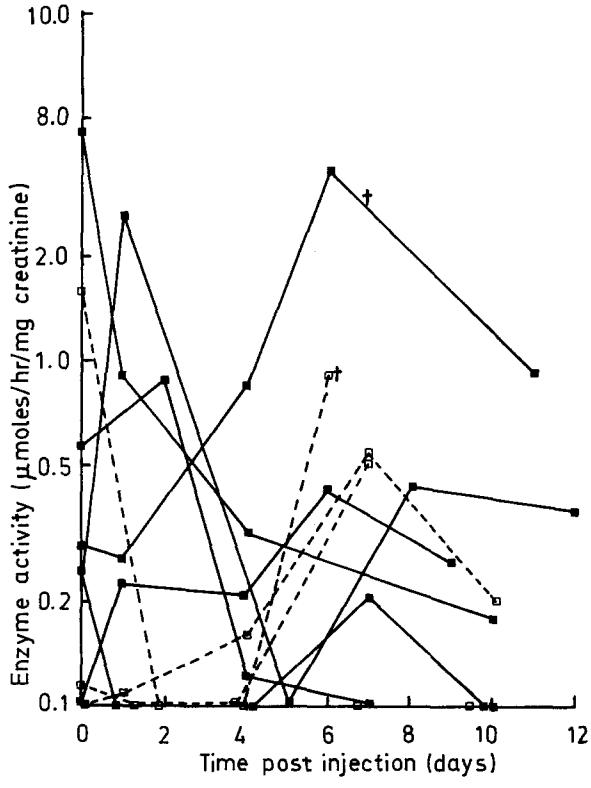

Fig. 8. Changes in leucine aminopeptidase activity in the urine of patients treated with JM8 at (———) 320 mg/m^2 (■) or (- - - -) 520 mg/m^2 (□). † Patient was subsequently shown to have a vesicocolic fistula

ii. Renal Toxicity

N-Acetylglucosaminidase, Leucine Aminopeptidase and β_2-Microglobulin: Serial measurements of these markers were made for all patients in the study. No significant changes from the baseline were noted in patients receiving doses less than 320 mg/m^2. The levels seen in patients receiving 320 and 520 mg/m^2 are shown in Figs. 7–9. There was considerable variation within patients in the times of peak urinary enzyme excretion. The increases, which were generally in the 2- to 5-fold range, occurred 2–8 days after administration, irrespective of the doses used. In all cases, the levels fell to pre-injection values by days 10–12. In three patients no significant changes in the levels of urinary markers were noted at these two doses.

^{51}Cr-EDTA Clearances: No dose-related fall in the ^{51}Cr-EDTA clearance was noted following a single dose of JM8 during stage I of the study.

Figure 10 summarises the changes in ^{51}Cr-EDTA clearances in patients with good renal function receiving three courses of JM8 at doses of over 200 mg/m^2 in both stages of the study. The mean clearance before treatment (78.7 ml/min) fell to 72.6 ml/min (P = 0.074, paired t-test). However, this fall was largely due to the three patients marked †. One of these patients had progressive abdominal disease with the development of hydronephrosis. The second became pancytopoenic following the second course of JM8 treatment and developed pyelonephritis associated with *E. coli* septicaemia, which was treated with aminoglycoside antibiotics. The third patient also developed pancytopoenia and symptoms of septicaemia, and was treated with aminoglycosides although no organism was isolated. If these patients are excluded from the analysis the mean clearance before treatment is 81.9 ml/min and after, 79.3 ml/min. The difference is not significant (P = 0.39). There was no relationship between dose and effect on renal function: A sub-group of six patients treated with mean doses of 400–467

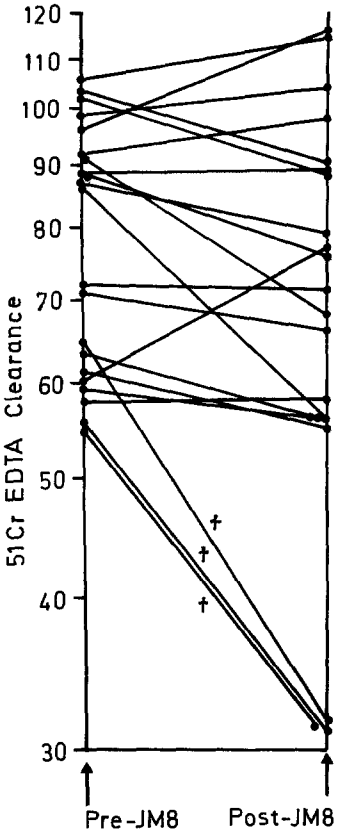

Fig. 10. Changes in ^{51}Cr-EDTA following treatment with three courses of JM8 at therapeutic doses > 200 mg/m^2. † Patients were subject to other potentially nephrotoxic events (see text)

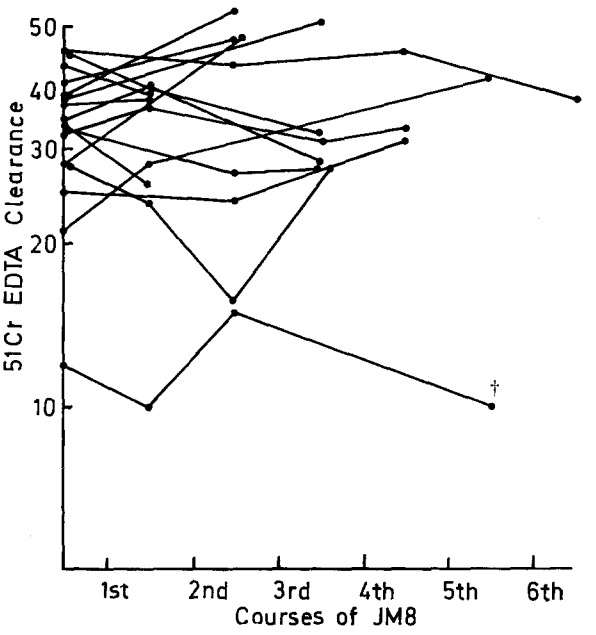

Fig. 11. Changes in ^{51}Cr-EDTA clearance with JM8 treatment in patients in whom renal function was impaired prior to treatment

mg/m^2 had a mean clearance of 97.2 ± 4.6 (SD) before, and 95.7 ± 16.4 after three courses. Furthermore, after six courses of JM8 the mean clearance was seen to rise from 84.8 ± 20.1 to 85.8 ± 17.3 in another sub-group of six individuals.

Figure 11 shows similarly the results obtained in patients with previously impaired renal function, who were treated at lower (but potentially therapeutic) doses. It was possible to treat patients with severely impaired renal function without further detriment. The renal impairment in nine of these patients was apparently consequent upon previous therapy with cisplatin. The patient marked † received six courses of JM8 at a dose of 140–170 mg/m^2 and had a > 50% reduction in a metastatic ovarian tumour. The ^{51}Cr-EDTA clearance (initially 12 ml/min) did not change as a result of this treatment. The dose was not increased above 170 mg/m^2 because of thrombocytopoenia.

iii. Nausea and Vomiting

The incidence of vomiting in the initial phase of the study is shown in Table 3. Most patients receiving over 120 mg/m^2 experienced nausea or vomiting. Antiemetics (lorazepam and metoclopramide) were given routinely to all patients receiving these doses. Typically the onset was delayed by 6–12 h from the time of the infusion, and most of the symptoms had resolved by 24 h. However, in two patients symptoms persisted for several days. Of eight patients who had received high-dose cisplatin previously (100 mg/m^2), seven reported that the degree of nausea experienced following JM8 was considerably less than that experienced following cisplatin, while one reported that it was subjectively greater. In two patients the vomiting was sufficiently severe to preclude a further increase of the dose. No patient refused treatment on account of this effect, and one patient who had previously refused cisplatin therapy for this reason was able to tolerate JM8.

Table 3. Incidence of vomiting in stage I of the study

Dose (mg/m^2)	No. of courses	Vomiting (duration)	
		< 6 h	> 6 h
20	3	0	0
40	6	0	0
80	7	3	0
120	6	3	1
200	6	3	3
320	6	3	3
520	5	1	4

iv. Ototoxicity

Audiograms were obtained in 13 patients before and after treatment with JM8. No detriment in any of the audiograms was observed following JM8 treatment. Neither the air nor the bone conduction changed (± 10 db) at any of the frequencies tested. Of the patients who had normal audiograms prior to JM8, one received six courses at 200 mg/m^2, three received six courses at 300–400 mg/m^2, and three received three courses at 300–400 mg/m^2. Of four patients who had pre-existing presbycusis, two received three and two received six courses of JM8 at 300–400 mg/m^2 without further detriment to the audiogram. One patient with high-frequency hearing loss due to previous cisplatin treatment received three courses of JM8 at 300–400 mg/m^2 and one received six. In neither was there any further detriment to the audiogram.

v. Neurotoxicity

Mild paraesthesiae were reported by three patients who had received cumulative doses of 1.8 g/m^2, 1.6 g/m^2 and 1.7 g/m^2.

Table 4. Urinary excretion of platinum following treatment with JM8

Dose (mg/m^2)	No. of patients	24 h recovery of dose in urine (%)
20	3	67
40	5	71
80	7	73
120	6	63
200	8	64
320	6	65
520	3	72
Total	38	mean 67 ± 2

Two further patients who had paraesthesiae of the feet following previous therapy with cisplatin developed more severe paraesthesiae, stocking distribution sensory loss, and absent ankle jerks following three courses of JM8. However, in three other patients who had a pre-existing cisplatin neuropathy no detriment was seen.

vi. Other Toxicities

One patient developed an erythematous rash in exposed areas following the third, fourth, fifth, and sixth courses of therapy.

No disturbances of liver function or plasma electrolytes were noted on the routine follow-up of these patients.

b) Clinical Pharmacology

Sixty-seven percent of the administered dose of platinum was consistently recovered in the urine during the first 24 h, the range found in the 38 patients being 63%–73%, suggesting that the major route of elimination of JM8 is via the kidneys (Table 4).

The ratio of the excretion of JM8 in the periods 0–4 and 4–24 h, used as an indication of the rapidity of the excretion of JM8, correlated significantly with GFR (Fig. 12).

In patients in whom plasma pharmacokinetics were measured there was a linear relationship between the dose administered and the total area under the curve (AUC) (Fig. 13). One patient (marked) who had severely impaired renal function (clearance 12 ml/min) had an AUC significantly higher than expected. This patient developed thrombocytopoenia but also had a dramatic antitumour response after receiving a dose of only 170 mg/m^2.

c) Antitumour Effects

Significant antitumour effects were observed in patients with ovarian carcinoma receiving > 120 mg/m^2, who comprised the largest single group in this study. No antitumour responses were seen in five patients with testicular teratoma, although a transient reduction in the tumour markers was observed in one patient. All five patients had become resistant to cisplatin-containing combination therapies before commencing JM8 treatment. These results are summarised in Table 5. Twenty-four patients with ovarian cancer had received previous cisplatin therapy. Of these, 14 had had cisplatin therapy discontinued either because they had completed a protocol course or because of nephrotoxicity. Of these 14, six responded to subsequent treatment with JM8. The remaining

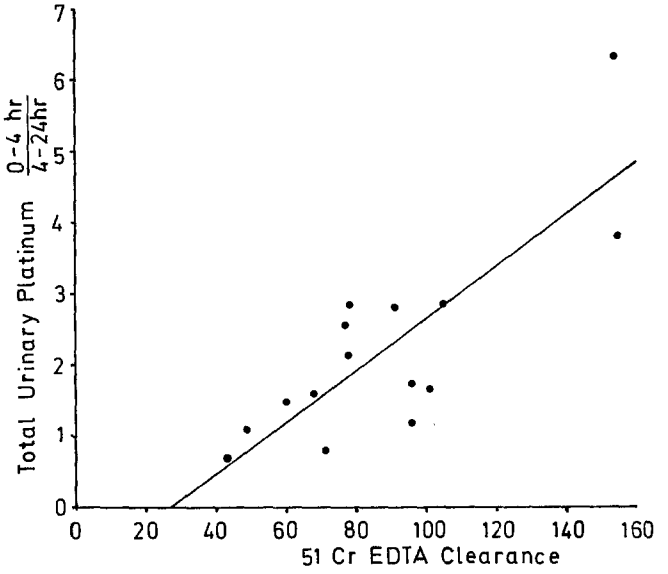

Fig. 12. Rapidity of platinum excretion correlated with GFR in patients receiving JM8. The correlation is significant ($r = 0.83$, $P < 0.001$)

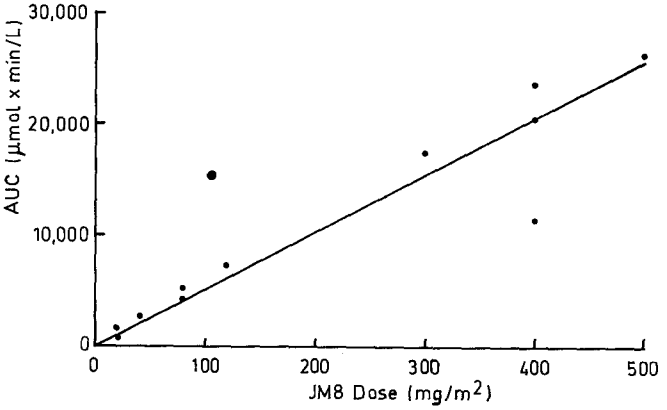

Fig. 13. Correlation between the area under the plasma decay curve (AUC) of total platinum and the dose of JM8 administered. ● Patient had severely impaired renal function. *Line* shown is origin-weighted linear regression line. Unweighted linear regression gave AUC = 1859 + 45.2 × dose, $r = 0.906$, $P < 0.001$. 95% confidence limits of intercept were −1432 to +5150

Table 5. Therapeutic responses[a] (WHO criteria) observed in JM8 study

Tumour	NA	CR	PR	MR	NC	PD	Total
Ovary	5	1	14	3	2	13	38
Bronchus	0	0	0	0	0	4	4
Renal cell	0	0	0	0	0	1	1
Abdominal adenocarcinoma	0	0	1	0	0	0	1
Testis	1	0	0	0	0	4	5
Colon	1	0	0	0	0	1	2
Synovial sarcoma	0	0	0	0	0	1	1
Melanoma	0	0	0	0	0	1	1
Squamous carcinoma[b]	0	0	0	1	0	0	1
Melanoma	0	0	0	0	0	1	1
Mixed mesodermal sarcoma	0	1	0	0	0	0	1
Cervix uteri	0	0	1	0	0	0	1

[a] NA, not assessable; CR, complete remission; PR, partial remission; MR, minor or mixed response; NC, no change; PD, progressive disease

[b] Site of primary tumour not known

10 patients had all been resistant to cisplatin therapy. One of these responded to subsequent treatment with JM8. Of 11 assessable patients with ovarian cancer who had not received prior therapy with cisplatin eight had a partial response to JM8 treatment.

Discussion and Conclusions

JM8 was selected for clinical study in the hope that it might prove to be less toxic than cisplatin, but equally active.

The results on nephrotoxicity suggest that JM8 is significantly less nephrotoxic than is cisplatin. Even at the dose of 520 mg/m^2, which was not used routinely on account of myelosuppression, the elevations in urinary enzymes were only in the 2- to 5-fold range. This contrasts with the results reported by Jones et al. [11], who found a median increase of over 10-fold in NAG following the administration of cisplatin at 100 mg/m^2 with hydration and forced diuresis. We have observed similar increases to these in patients receiving cisplatin therapy.

It appears that there was no decrease in the glomerular filtration rate (GFR) (estimated by the clearance of ^{51}Cr-EDTA) of the patients as a consequence of JM8 therapy. Although three patients showed a significant drop in GFR after three courses, they were all subject to other potentially nephrotoxic events. The observations that it was possible to treat patients with severely reduced GFR without further detriment, and that a number of patients who received six courses of JM8 at doses $>$ 400 mg/m^2 did not show any reduction in GFR also support the conclusion that JM8 is not significantly nephrotoxic and that the minor elevations of urinary enzymes seen at higher doses indicate only reversible damage. Myelosuppression proved to be the dose-limiting toxicity of JM8, although this was always reversible. However, clinical responses were seen in patients receiving nonmyelosuppressive doses (e.g., 120 mg/m^2), suggesting that the therapeutic ratio of the drug could be substantial. There was considerable variation in the individual tolerance of the drug and this variation seemed, at least in part, to be correlated with pharmacokinetic parameters.

Nausea and vomiting is a severe side-effect of cisplatin treatment which may lead to patients refusing further treatment. Preclinical studies of JM8 showed it to be substantially less emetic than cisplatin in dogs. Although it caused emesis in humans, this appeared to be rather less severe than the emesis induced by cisplatin, and patient compliance was easier to obtain.

Ototoxicity was reported in early studies of cisplatin [17], and its incidence appears to be related to cumulative dose and protocol [16], with bolus administration being more ototoxic than infusion therapy. Although no ototoxicity was seen as a consequence of JM8 therapy in any of 13 patients in this study, it could be argued that this was because of the 1-h infusion therapy used. However, Reddel et al. [16] reported ototoxicity in six of/14 patients receiving cisplatin at 100 mg/m^2 over 2 h. Thus it seems that JM8 at the doses used was not ototoxic.

Peripheral neuropathy, another toxic effect of cisplatin, was also observed in five patients included in this study. Thus peripheral neuropathy is a side-effect of JM8 therapy, although not enough patients have been treated for long enough to know whether it will be more or less severe than that seen with cisplatin.

The pharmacokinetics of JM8 were linear over the dose range studied. The urinary excretion of platinum following JM8 therapy was high (65%–75%) compared with the lower excretion (30%–40%) seen when cisplatin is given [12]. Moreover, most of the platinum present in the urine was in the form of intact JM8 (preliminary observations). These studies suggest that renal function may be an important predictor of JM8 toxicity.

The dose-limiting toxicity of JM8 in this study was myelosuppression which occurred at a level of 400–500 mg/m^2 in good-risk patients. At these doses damage to the other targets of cisplatin toxicity was largely minimal or absent. However, it should be noted that the mean age even of the patients in the good-risk group was 51 years, so that younger patients (e.g., with testicular teratoma) might tolerate higher doses. It is possible that such doses might, for example, do more damage to the kidneys, although in the light of the extremely minimal changes seen in urinary enzymes at the 520 mg/m^2 dose it seems unlikely that any toxicity other than myelosuppression could become dose-limiting.

It is concluded that JM8 is an analogue of cisplatin which has reduced toxicity in all aspects except myelosuppression. Almost all patients tolerated the drug much better than cisplatin, and irreversible damage to major organ systems (with the possible exception of the peripheral nervous system) did not occur. A number of clinically significant antitumour responses were seen during this study, which lends support to the hope that the activity of JM8 may be comparable to that of cisplatin. Studies aimed at answering this question are in progress.

Acknowledgements. We are extremely grateful to Mr Patrick Chapman, St. Marys's Hospital, Praed Street, London for his help in the organisation and interpretation of the audiograms, to Mrs Frances Boxall for her expert technical assistance in measuring the urinary enzyme levels, to the Nuclear Medicine Department, Royal Marsden Hospital for performing the ^{51}Cr-EDTA clearances, and to the nursing staff of the Royal Marsden Hospital for their continued help in caring for the patients.

We should like to thank Bristol-Myers International, who made the formulated drug available free of charge and also paid the expenses involved in performing the audiograms.

This work was supported in part by grants from the Medical Research Council and the Cancer Research Campaign.

References

1. Bruckner HG, Cohen CJ, Wallach RC, Kabakow B, Deppe G, Greenspan EM, Gusberg SB, Holland JF (1978) Treatment of advanced ovarian cancer with *cis*-dichlorodiammineplatinum (II): Poor risk patients with intensive prior therapy. Cancer Treat Rep 62: 555
2. Bruno S, Poster DS, Higby DJ, Burke P, Mittelman A (1980) Parameters of nephrotoxicity in relation to the administration of *cis*-DPD. Proc Am Assoc Cancer Res 21: 150
3. Carter SK, Wasserman TH (1975) The chemotherapy of urologic cancer. Cancer 36: 729
4. Chantler C, Garnett ES, Parsons V, et al. (1969) Glomerular filtration rate measurement in man by the single injection methods using Cr^{51} EDTA. Clin Sci Mol Med 37: 169
5. Harrap KR (to be published) Platinum analogues: Criteria for selection: In: Muggia FM (ed) Cancer chemotherapy. Martinus Nijhoff, Massachusetts
6. Harrap KR, Jones M, Wilkinson CR, Clink HMcD, Sparrow S, Mitchley BCV, Clarke SA, Veasy A (1980) Antitumour, toxic and biochemical properties of cisplatin and eight other platinum complexes. In: Prestayko AW, Crooke ST, Carter SK (eds) Cisplatin. Current status and new developments. Academic Press, New York, p 193

7. Hayes DM Cvitkovic E, Golbey RB, Scheiner E, Helson L, Krakoff IH (1980) High-dose *cis*-platinum diamminedichloride. Cancer 39: 1372
8. Herr HW (1980) *cis*-Diamminedichloride platinum II in the treatment of advanced bladder cancer. J Urol 123: 853
9. Higby DJ, Wallace HJ Jr, Alberts D, Holland JF (1971) Diamminodichloroplatinum in the chemotherapy of testicular tumors. J Urol 112: 100
10. Jacobs C (1980) The role of cisplatin in the treatment of recurrent head and neck cancer: In: Prestayko AW, Crooke ST, Carter SK (eds) Cisplatin. Current status and new developments. Academic Press, New York, p 423
11. Jones BR, Bhalla RB, Mladek J, Kaleya RN, Gralla RJ, Alcock NW, Schwartz MK, Young CW, Reidenberg MM (1980) Comparison of methods of evaluating nephrotoxicity of cisplatinum. Clin Pharmacol Ther 27: 557
12. Loo TL, Hall SW, Salem P, Benjamin RS, Lu K (1978) Clinical, pharmacological and toxicological studies of *cis*-diamminedichloroplatinum (II) by continuous infusion. Biochimie 60: 957
13. Merrin C (1978) Treatment of advanced bladder cancer with *cis*-diamminedichloroplatinum (II) (NSC 119875): A pilot study. J Urol 119: 493
14. Merrin CE (1979) Treatment of genitourinary tumors with *cis*-dichlorodiammineplatinum (II): Experience in 250 patients. Cancer Treat Rep 63: 1579
15. Prestayko AW, D'Aoust JC, Issell BF, Crooke ST (1979) Cisplatin (*cis*-diamminedichloroplatinum II). Cancer Treat Rev 6: 17
16. Reddel RR, Kefford RF, Grant JM, Coates AS, Fox RM, Tattersall MHN (1982) Ototoxicity in patients receiving cisplatin: Importance of dose and method of drug administration. Cancer Treat Rep 66: 19
17. Von Hoff DD, Schilsky R, Reichert CB, Reddick RL, Rozencweig M, Young RC, Muggia FM (1979) Toxic effects of *cis*-dichlorodiammineplatinum (II) in man. Cancer Treat Rep 63: 1527
18. Wilkinson R, Cox PJ, Jones M, Harrap KR (1978) Selection of potential second generation platinum compounds. Biochimie 60: 851
19. Williams CJ, Whitehouse JMA (1979) *cis*-Platinum: A new anticancer agent. Br Med J I: 1689
20. Wiltshaw E, Carr T (1974) *cis*-Platinum(II)diamminedichloride: Clinical experience of the Royal Marsden Hospital and Institute of Cancer Research. Recent Results Cancer Res 48: 178
21. Wiltshaw E, Kroner T (1976) Phase II study of *cis*-dichlorodiammineplatinum (I) (NSC 119875) in advanced adenocarcinoma of the ovary. Cancer Treat Rep 60: 55
22. Witman G, Cadman E, Browerman I (1981) Cisplatin treatment of cutaneous T-cell lymphoma. Cancer Treat Rep 65: 920
23. Yagoda A, Watson RC, Gonzalez-Vitale JC, Grabstald H, Whitmore WF (1976) *cis*-Dichlorodiammineplatinum (II) in advanced bladder cancer. Cancer Treat Rep 60: 917
24. Young RC, Von Hoff DD, Gormley P, Makuch R, Cassidy J, Howser D, Bull JM (1979) *cis*-Dichlorodiammineplatinum (II) for the treatment of advanced ovarian cancer. Cancer Treat Rep 63: 1539

Received June 9, 1982/Accepted July 14, 1982