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Phase I Study of Spiroplatin

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Spiroplatin was investigated in a multicentre phase I study. 67 patients with advanced solid tumours received 151 cycles either by short-term or prolonged infusion, repeated every 3 weeks, at 2.5–40 mg/m². Myelosuppression and renal toxicity were dose-limiting. Proteinuria, which was dose- and schedule-dependent, indicated glomerular and tubular damage. The maximum tolerated doses (MTD) for poor-risk and good-risk patients were 35 and 40 mg/m², respectively. The area under the curve (AUC) at the MTD did not correspond with the AUC at the LD_{10} in mice with ratios of 0.3 for free platinum and 2.6 for total platinum; these were not suitable for predicting the MTD. 1 complete response was observed in a patient with breast cancer and lung metastases and 1 partial response in a patient with adenocarcinoma of the lung. The recommended dose for phase II studies was 30 mg/m² by 4 h infusion every 3 weeks.
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INTRODUCTION

THE MOST important toxicities of cisplatin are kidney damage and severe nausea and vomiting; other toxicities are bone-marrow depression, neurotoxicity, ototoxicity, electrolyte disturbances and allergic reactions [1, 2]. In The Netherlands extensive research has been done on the development of less toxic platinum analogues at the Institute of Applied Chemistry, Utrecht. Several cisplatin congeners were synthesised in which the ammonia was substituted by a diaminomethylcyclohexane. One of these analogues was chosen for phase I evaluation because of its favourable toxicity profile and antitumour activity in preclinical studies, as well as its increased potency and suggested lack of cross-resistance with cisplatin [3, 4] We summarize here our phase I experience with the drug.

It has been suggested that the area under the concentration vs. time curve (AUC) in man at the maximum tolerated dose (MTD) and in the mouse at the LD_{10} are comparable for toxicity during phase I studies [5]. With this hypothesis, it might be possible to decrease the number of dose-escalation steps in phase I studies. We have retrospectively investigated the validity of the hypothesis for spiroplatin.

PRECLINICAL DATA

Antitumour and toxicity screening of spiroplatin was done at the Radiobiological Institute, Rijswijk, The Netherlands, in collaboration with the Free University, Amsterdam, and Bristol Laboratories, Syracuse, USA. The anti-leukaemic activity of spiroplatin in L1210 bearing mice is similar or marginally superior to that of cisplatin [3, 6]. In cisplatin-resistant L1210 leukaemia, spiroplatin's efficacy is similar to that in cisplatin-sensitive leukaemia, suggesting a lack of cross-resistance with cisplatin [3, 4]. A similar antitumour effect to cisplatin was found in B16 melanoma, while the activity of spiroplatin in Lewis lung carcinoma, murine osteosarcoma and Madison 109 lung carcinoma is inferior to that of cisplatin [3, 6]. In the L1210 tumour model no schedule dependency was observed.

The acute LD_{50} in mice after a single intraperitoneal dose ranged from 11 to 20 mg/kg [3, 4, 7], and after a single intravenous dose, was 9 mg/m² [3, 7]. The LD_{10} in mice after a single intraperitoneal injection was 7.9 mg/kg (23.7 mg/m²) [4]. Spiroplatin was nephrotoxic, like cisplatin. However, comparative studies in mice and rats suggested that in therapeutic doses nephrotoxicity was lower with spiroplatin [7].

Severe nephrotoxicity was observed in two dogs after a single lethal intravenous dose of spiroplatin 2 mg/kg [8]. In both animals, major degenerative changes of renal tubular epithelium were observed. Bone marrow toxicity, usually mild after cisplatin, was found to be more severe after spiroplatin. In addition, experimental data in rats suggested that some myocardial damage could be induced with high doses of spiroplatin [4].

Table 1. Patients' characteristics

Total no.	67
M/F	38/29
Median age (range)	64 (21–79)
Median performance status (range)	80 (50–100)
Previous treatment	
Chemotherapy (cisplatin)	57 (27)
Radiotherapy	42
Both	35
None	3

PATIENTS AND METHODS

Patients

67 patients with advanced solid tumours (histologically confirmed) were included in our multicentre phase I study (Tables 1 and 2). 64 patients were resistant to conventional therapies and 3 had malignancies for which no standard therapy was available. Patients had to be off previous therapy for more

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Table 2. Tumour types

Primary tumour site	No. of patients
Gynaecological organs (ovary)	10 (8)
Breast	9 *
Lung	9 *
Renal cell	8
Gastrointestinal (colorectal)	7 (4)
Sarcoma	6
Testicular	6
Head and neck	5
Melanoma	5
Unknown	3

*In 1 patient a second tumour was present: lung and breast cancer.

than 4 weeks. In cases of previous therapy with nitrosoureas, mitomycin or extensive radiotherapy, this interval was 6–8 weeks. Other inclusion criteria were: Karnofsky performance status of 50 or higher; life expectancy of more than 6 weeks; white blood cells (WBC) over 4.0×10^9/l (although 5 patients had 3.2, 3.2, 3.4, 3.6 and 3.7×10^9/l, respectively; platelets over 100×10^9/l; normal liver function, unless abnormalities were clearly due to metastatic disease; and normal renal function (serum creatinine under 120 μmol/l), although 6 patients had 138, 150, 155, 160, 205 and 220 μmol/l, respectively. Besides these patients, 15 more had decreased renal function when creatinine clearances were also taken into account. Before entry, informed consent was required. The treatment protocol was approved by the local medical ethical committee.

Treatment

Spiroplatin was supplied by Bristol Myers in ampoules containing an aqueous solution of 10 mg/ml. An appropriate volume was further diluted in 5% glucose within 1 h before administration. This solution was thought to be stable at room temperature for at least 24 h. During the first part of the study, 34 patients received spiroplatin intravenously by short-term infusion over 10 min, once every 3 weeks. No additional hydration was given. A total of 84 cycles was given to these patients. The starting dose was 2.5 mg/m^2 (one-tenth of mouse equivalent LD_{10}). The dose was escalated up to 40 mg/m^2 (Table 3). Except for 2 cases no dose escalations were done in individual patients. Because of the observed toxicities during the first phase, the duration of infusion was prolonged. 1 patient received a 1 h infusion, while 32 received 3–6 h infusions. Again, courses were repeated every 3 weeks. Prolonged infusions were initially given in a small volume of 40 ml dextrose 5%. Because this led to severe irritation of the veins in 14 out of 15 patients, in later patients the drug was dissolved in 250–500 ml dextrose 5%. Prolonged infusions of spiroplatin were given only at the 30, 35 and 40 mg/m^2 dose levels. 34 patients received prolonged infusion (33 patients from the start and 1 patient who had received one bolus injection before). These patients received a total of 67 cycles. Therefore the overall number of cycles was 151 (Table 3).

Table 3. Number of courses at each dose level

Dose (mg/m^2)	Short-term infusion		3–6 h infusion		Total
	Initial	Subsequent	Initial	Subsequent	
2.5	1	0	0	0	1
5	2	3	0	0	5
10	3	2	0	0	5
15	2	3	0	0	5
20	3	7	0	1	11
25	3	16	0	3	22
30	10	13	18	15	56
35	9	6	14	13	42
40	1	0	1	2	4
All	34	50	33	34	151

Assessment of clinical status, body weight, performance status, blood biochemistry and routine urine examination were planned for at least once a week. Electrocardiograms and audiograms were scheduled before each consecutive course.

Pharmacokinetics

Blood samples were obtained just before administration of the drug and at 0, 10, 20, 30 and 60 min, at 1½, 2, 2½, 3, 3½, 4, 6, 8, 16 and 24 h and 2, 3, 4 and 5 days after administration. Urine was sampled over at least 24 h. Pharmacokinetics was studied at each dose level. Platinum concentrations in plasma (total platinum), plasma ultrafiltrate (free platinum), red blood cells and urine were measured by flameless atomic absorption spectrophotometry [9]. The distribution half-life of total platinum was calculated by the NONLIN curvefitting procedure [10]. The half-life of distribution of free platinum was only calculated over the first linear part of the semilogarithmic concentration vs. time curve by the least squares method. The final half-life of total platinum was also calculated by the least squares method over days 1–5. AUCs were calculated with the trapezoidal rule. The AUCs in patients after short-term infusions at the MTD and in mice after bolus intravenous injection at the LD_{10} (6.75 mg/kg, 20.3 mg/m^2) [11] were calculated over 60 min and over 5 days. The AUCs over these periods could be calculated in 4 patients at 25 mg/m^2 and in 1 patient at 30 mg/m^2. Because platinum compounds show linear pharmacokinetics over at least small dose ranges [9, 12], the AUCs of the patients were linearly extrapolated to the MTD (35 mg/m^2). The mean values of these extrapolated AUCs were compared with the AUCs at the LD_{10} in mice.

RESULTS

Myelosuppression

Only 56 of 67 patients were considered to be evaluable for haematological toxicity. 5 patients had WBC below 4.0×10^9/l at the start of spiroplatin administration and in 6 patients haematological indices were insufficiently investigated. Myelosuppression was found in most patients at the higher dose levels and in fact was dose-limiting. In the first treatment cycle alone, both leukopenia and thrombocytopenia were observed for the first time at 30 mg/m^2. However, when consecutive cycles were considered as well, the first observation of myelosuppression was already evident at 5 mg/m^2, showing a grade 1 toxicity of WBC (3.2×10^9/l) and a grade 3 toxicity for platelets (49×10^9/l), which indicates a cumulative effect. For patients pretreated with chemotherapy the MTD was determined at 35 mg/m^2 (Table 4). At this dose, 4 patients had received either no previous chemotherapy or chemotherapy which was not considered to be myelosuppressive. In these patients the WBC nadir was 3.7×10^9/l (range $2.4–5.5 \times 10^9$/l) and the platelet

Table 4. Myelosuppression after bolus injection of spiroplatin related to administered dose and previous therapy

Dose (mg/m²)	No. of evaluable patients	WBC (× 10⁹/l) Initial	WBC (× 10⁹/l) Nadir 1st cycle	WBC (× 10⁹/l) Nadir All cycles	Platelets (× 10⁹/l) Initial	Platelets (× 10⁹/l) Nadir 1st cycle	Platelets (× 10⁹/l) Nadir All cycles
20*	3	4.9 (4.3–6.7)	4.4 (4.3–4.4)	3.1 (2.3–3.7)	240 (195–265)	175 (145–180)	105 (85–170)
25†	3	5.3 (4.4–11.5)	4.0 (3.9–5.2)	2.4 (2.3;2.6)	183 (111–262)	175 (53–182)	125 (67;184)
30‡	6	6.1 (4.0–7.7)	3.0 (0.9–4.5)	2.1 (0.9–3.1)	175 (114–318)	129 (10–247)	75 (8–130)
35§	4	5.7 (4.8–8.0)	3.7 (2.4–5.5)	2.4 (2.3–3.2)	225 (209–660)	166 (137–270)	128 (98–120)
35§	3	8.0 (4.9–9.8)	2.0 (1.3–2.1)	1.85 (1.7;2.0)	232 (155–320)	36 (20–66)	51 (36;66)
40‖	1	8.9	3.4	—	380	215	—

Median (range).
*All 3 had been heavily pretreated with cisplatin.
†2 out of 3 had had previous cisplatin containing chemotherapy.
‡5 out of 6 had had previous chemotherapy (3 with cisplatin).
§3 were heavily pretreated, 4 were not or were mildly pretreated.
‖5-fluouracil as previous therapy.

nadir 166 × 10⁹/l (137–270 × 10⁹/l). In 3 patients who had received either platinum-containing chemotherapy before or severely myelosuppressive chemotherapy, the WBC nadir at 35 mg/m² was 2.0 × 10⁹/l (1.3–2.1 × 10⁹/l) and the platelet nadir was 36 × 10⁹/l (20–66 × 10⁹/l).

In the second part of the study, when spiroplatin was administered over 3–6 h, 1 patient was treated at 40 mg/m² after mildly myelosuppressive previous therapy. After the first cycle the WBC nadir was 0.7 × 10⁹/l and the platelet nadir 60 × 10⁹/l, indicating that the MTD for this category of patient was reached.

An interesting observation was made when the results were compared for patients with normal renal function with those with decreased renal function (Table 5). Myelosuppression was more severe in patients with a decreased renal function, suggesting that toxicity might be related to a pharmacokinetic determinant.

Table 5. Median platelet counts (× 10⁹/l) during first treatment cycle and after all cycles of spiroplatin related to dose and renal function (combined bolus and prolonged infusion)

Dose (mg/m²)	Creatine clearance (ml/min)	No. of cycles	No. of patients	First cycle	All cycles
25	≥60	18	2 (1)*	178 (175;182)	125 (67;184)
	<60	1	1 (1)	53	53
30	≥60	18	7 (4)	128 (60–247)	75 (42–247)
	<60	14	7 (5)	27 (10–129)	24 (8–129)
35	≥60	31	17 (2)	137 (9–270)	101 (9–220)
	<60	8	4 (2)	48 (19–104)	39 (19–59)
40	≥60	4	2 (0)	137 (60;215)	125 (36;215)

Median (range).
*Number of patients pretreated with cisplatin.

Anaemia was observed at all doses and a cumulative effect was also observed on haemoglobin. After successive cycles red cell transfusions had to be given in 26 patients. However, 11 out of these 26 had initially low haemoglobin (under 6.8 mmol/l). 12 out of 20 patients who had an impaired renal function (creatinine clearance under 60 ml/min) needed blood transfusions. 5 of these 12 started with haemoglobin under 6.8 mmol/l.

Nephrotoxicity

57 out of 67 patients were considered evaluable for renal toxicity. In 10 renal function was insufficiently investigated. An unexpected side-effect during the first part of the study, when spiroplatin was given as a rapid infusion, was the occurrence of proteinuria. This was observed at 25 mg/m² and higher. Proteinuria was dose-dependent and cumulative (Table 6). The median day at which the maximum degree of proteinuria

Table 6. Spiroplatin induced proteinuria related to dose and treatment cycle after bolus and prolonged infusions

Dose (mg/m²)	No.	First cycle	Second cycle	Third cycle
Bolus infusion (10 min)				
25	3/3*	1.3 (0.2–1.4)	1.1 (1.0–1.3)	3.0 (1.0–5.1)
30	3/5	1.3 (0.9–1.9)	2.4 (0.3–4.5)	2.3 (1.1–3.5)
35	6/6	2.0 (0.4–10.0)	5.2 (3.8–6.3)	7.7
Prolonged infusion (3–6 h)				
30	5/10	2.4 (0.3–6.5)	2.4 (0.9–2.9)	—
35	7/13	2.2 (0.4–6.7)	2.5 (1.4–7.7)	6.3 (3.3–9.4)
40	1/1	1.8	—	—

Median (range) of maximum proteinuria (g per 24 h).
*No. with proteinuria/no. evaluable.

Table 7. Electrolyte disturbances observed after spiroplatin administration in patients with normal renal function

Dose (mg/m²)	No. of evaluable patients	Hypo-kalaemia	Hypophos-phataemia	Hypomag-nesaemia
Bolus infusion				
10	1	0	0	1 (10%)
15	1	0	1 (25%)	1 (15%)
20	1	0	1 (23%)	0
25	2	1 (15%)*	2 (48%)	0
30	4	3 (19%)	3 (47%)	1 (12%)
35	8	4 (22%)	4 (46%)	2 (24%)
40	1	0	0	0
Prolonged infusion				
30	7	4 (20%)	6 (35%)	2 (18%)
35	10	6 (20%)	7 (30%)	1 (18%)
40	1	1 (15%)	1 (29%)	

*Percentage decrease in potassium, phosphate and magnesium after all cycles.

occurred was day 5 (range 2–13) and recovery was evident mostly within 2 weeks. Because of the severity of the proteinuria (up to 10 g per day), indicating glomerular damage, we searched for methods to avoid this side-effect. The use of corticosteroids or hydration did not prevent the effect. However, prolongation of the infusion did diminish the degree of proteinuria. Only 3 out of 24 patients who received prolonged infusions showed a severe degree of proteinuria (up to 6.7 g per day) in the first treatment cycle, but the severity was again cumulative. 7 out of the 23 patients at the 30 and 35 mg/m² dose level showed grade 2 proteinuria: up to 9.4 g per day in the third cycle. Protein electrophoresis showed that proteinuria was not selective.

Electrolyte disturbances were observed at all dose levels with bolus injections. Most striking was the severity of hypophosphataemia, but hypomagnesaemia and hypokalaemia also occurred. Overall, hypophosphataemia occurred in 27 out of 57 evaluable patients (47%), hypokalaemia in 28 (49%) and hypomagnesaemia in 13 (23%) (see also Table 7). Again these electrolyte disturbances were cumulative [13]. The electrolyte disturbances coincided with proteinuria in all patients except 1. Tubular damage was also evident from β_2-microglobulin measurements in the urine, which we did in 5 cases (2 at 25 mg/m², 2 at 30 mg/m² and 1 at the 35 mg/m²: in all cases, excretion was increased.

Only a slight elevation of serum creatinine was observed at all dose levels in patients with normal serum creatinine at the start of treatment [13]. However, in patients with pre-existing impaired renal function increases in serum creatinine of more than 25% were observed in more than 50% of the patients at 30 and 35 mg/m², and showed some cumulative effect. It may therefore be concluded that from 30 mg/m², and higher there is a risk of renal toxicity. After consecutive cycles of spiroplatin at all dose levels, only 6 patients out of the 32 patients who could be evaluated on the basis of creatinine clearances, remained with a creatinine clearance over 60 ml/min. No correlation could be observed between the severity of proteinuria and impaired renal function.

Gastrointestinal toxicity

Nausea and vomiting were observed in nearly all patients (64 out of 67) and was dose-related. However, this side-effect was considered less severe compared with that usually caused by cisplatin [14] and generally lasted for less than 6 h.

Nausea and/or vomiting started rapidly after administration of spiroplatin (under 3 h). Vomiting responded to some degree to conventional antiemetics.

Diarrhoea was observed in 15 patients and was not dose-related. The diarrhoea was mild in 10 patients and moderate in 5. The gastrointestinal side-effects did not occur differently in patients who received rapid infusions compared with those who received prolonged infusion.

Other side-effects

When spiroplatin was given at a high concentration, prolonged infusions were complicated by the occurrence of moderate to severe phlebitis in nearly all patients. This side-effect could be diminished by diluting the compound further in 250–500 ml dextrose 5%. On extravasation severe cellulitis and necrosis were observed in 1 patient.

Other side-effects were: dry mouth on the day of administration (16 patients), loss of taste (10), paraesthesias (4, of whom 2 had been treated previously with neurotoxic agents), tinnitus (3), drowsiness (3) and myalgia (1). 1 patient had an anaphylactic-like reaction with hypotension immediately after administration of spiroplatin, and recovered after infusion of human albumin solution.

Responses

1 complete response was observed in a patient with breast cancer and lung metastases as indicator lesion, and 1 partial response was observed in a patient with adenocarcinoma of the lung. 2 patients showed a minor response: 1 with ovarian cancer and 1 with small cell lung cancer. Moreover, a drop in alpha$_1$ fetoprotein was observed in a patient with testicular cancer. Except for the patient with breast cancer, all other patients with some antitumour effect had received cisplatin before and were considered resistant to the parent compound.

Pharmacokinetics

Figure 1 shows the concentration vs. time curves of platinum in a patient at the MTD (35 mg/m²) after a 10 min infusion and in mice at the LD_{10} after a bolus injection. The following half-lives were obtained in patients: $t_{\frac{1}{2}\alpha}$ of total platinum was 2.2

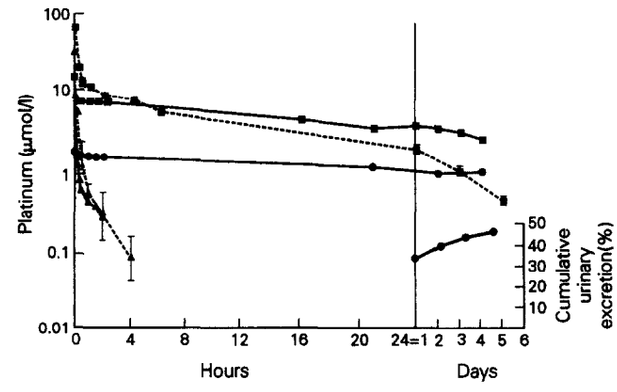

Fig. 1. Semilogarithmic plot of platinum concentrations in plasma (■—■), plasma ultrafiltrate (▲—▲) and red blood cells (●—●) vs. time in a patient who received 35 mg/m² spriroplatin in 10 min, and in plasma (■--■) and plasma ultrafiltrate (▲--▲) in mice at LD_{10} (mean of 3 mice) after bolus (▲--▲) injection.

(S.D. = 0.6) min (n = 11), $t_{\frac{1}{2}\alpha}$ of free platinum was 4.4 (0.7) min (n = 6), $t_{\frac{1}{2}}$ of total platinum was 4.0 (0.6) days (n = 17) and $t_{\frac{1}{2}}$ of platinum in red blood cells was 8.7 (3.0) days (n = 13). A mean maximum concentration of 1.6 (0.2) μmol/l (n = 3) was reached in red cells immediately after administration of the drug. The cumulative urinary excretion of free platinum over the first 24 h was 30 (6)% (n = 23) of the administered dose and 47 (7)% (n = 12) over the first 5 days. The AUCs for free and total platinum over 0–60 min and for total platinum over 0–5 days were 104, 676 and 38 261 μmol min/l in patients at the MTD (35 mg/m^2) and 351, 1196 and 14 812 μmol min/l in mice at the LD_{10}, respectively. The ratios of the mean AUCs in patients at the MTD and mice at the LD_{10} were 0.3 for free platinum, and 0.6 and 2.6 for total platinum over 0–60 min and 0–5 days, respectively.

DISCUSSION

This extended phase I study indicated that both nephrotoxicity and myelosuppression were dose-limiting. The MTD was 35 mg/m^2 for pretreated patients, while non-pretreated patients tolerated a slightly higher dose (40 mg/m^2).

The nephrotoxicity observed is of a different order than that observed after other platinum compounds, such as cisplatin, carboplatin, iproplatin or JM-40 [15–17], especially for proteinuria. The magnitude of the proteinuria indicated glomerular damage. However, the observed electrolyte disturbances and the increase in β_2-microglobulin excretion in the urine also suggested tubular damage.

The proteinuria may be caused by the varying amounts of hydrolysed spiroplatin in the infusion fluid as a result of varying times between solution preparation and administration as well as changes in the constitution of the drug solution during infusion [18]. In animal experiments this can most probably be overcome, at least in part, by the addition of sodium sulphate to the infusion fluid [19]. This was not investigated in our study. However, other methods to alleviate the proteinuria were investigated. The use of hydration and corticosteroids did not diminish the proteinuria, however, prolongation of infusion did. This may be the result of a decreased peak plasma concentration of the drug [20]. The unpredictable nephrotoxicity of spiroplatin compared with other platinum compounds has been confirmed in a patient who developed fatal acute renal failure after spiroplatin [17]. Pretreatment with cisplatin might have played a role in this renal failure. Histopathological investigation showed no changes in the glomeruli but, in contrast, extensive pathological alterations in the interstitium and renal tubules.

Myelosuppression consisted of leukopenia and thrombocytopenia. Severity was related to the dose of spiroplatin, and also to pre-existing renal function. Therefore, not unexpectedly in our pharmacokinetic study, a relation was suggested between AUC and severity of myelosuppression (especially for thrombocytopenia).

The drop in haemoglobin was more pronounced after spiroplatin than after cisplatin administration at the higher dose levels, which can be related to the more extensive pretreatment in patients who participate in phase I studies. Moderate to severe phlebitis occurred in nearly every patient after prolonged infusion, which could be diminished by diluting the compound. Cellulitis and necrosis was observed in 1 patient after extravasation. This complication was most probably related to the high chemical reactivity of the drug [21]. For cisplatin this complication is rare [22, 23].

A parallel phase I study of spiroplatin was performed in the Finsen Institute, Copenhagen [24]. This confirmed our data in that nephrotoxicity was related to dose. Moreover, it supported our observation that glomerular damage in particular will be observed at higher dose levels.

The half-life of free platinum (4.4 min) was longer than that of total platinum (2.2 min), due to differences in calculating these variables. The initial half-lives observed after spiroplatin were shorter than those after cisplatin (24 [6] min and 14 [4] min for free and total platinum, respectively) [20]. These differences in half-life are caused by the high reactivity of spiroplatin compared with that of cisplatin, as reflected by faster protein binding [25, 26] and its higher uptake into red cells (2.4% vs. 1.2% [27], respectively). The half-life of elimination (4.0 days) was almost equivalent to that of cisplatin (5.4 [1.0] days) [20]. This agreement might be explained by the common rate of repair of the platinum-protein adducts. The cumulative urinary excretions after 1 and 5 days (30 and 47%, respectively) were similar to those of cisplatin [(28 [4]% (n = 7) and 40 [4]% (n = 7), respectively)] [9].

To verify the hypothesis of similar AUCs in patients at the MTD and mice at the LD_{10}, the ratios of the AUC were calculated for total as well as free platinum. The AUC ratio of total platinum (2.6) over the first 5 days after spiroplatin, like the ratios of total platinum after other compounds [11], was higher than 1.0, indicating that total platinum concentrations cannot be used to predict the MTD. In contrast to other platinum compounds, the AUC ratio of free platinum after spiroplatin (0.3) cannot be used either. An explanation for the deviating behaviour of spiroplatin might be its instability in aqueous solution [19].

From our phase I study the advised dose schedule for phase II studies was 30 mg/m^2 given by 3–4 h infusion. Unfortunately, later studies with spiroplatin were disappointing both in terms of antitumour activity and toxicity [28, 29]. It is regrettable that although renal toxicity was found during this phase I study, unpredictable renal failure, which was found in later phase II studies, could not be anticipated.

1. Vermorken JB, Pinedo HM. Gastrointestinal toxicity of cis-diamminedichloroplatinum (II). Personal observations. *Neth J Med* 1982, **25**, 270–274.
2. Von Hoff DD, Schilsky R, Reichert CM, *et al.* Toxic effects of cis-dichlorodiammineplatinum (II) in man. *Cancer Treat Rep* 1979, **63**, 1527–1531.
3. Rose WC, Schurig JE, Huftalen JB, Bradner WT. Antitumor activity and toxicity of cisplatin analogs. *Cancer Treat Rep* 1982, **66**, 135–146.
4. Lee FH, Canetta R, Issell SF, Lenaz L. New platinum complexes in clinical trials. *Cancer Treat Rev* 1983, **10**, 39–51.
5. Collins JM, Zaharko DS, Dedrick RL, Chabner BA. Potential roles for preclinical pharmacology in phase I clinical trials. *Cancer Treat Rep* 1986, **70**, 73–80.
6. Lelieveld P. Platinum containing antitumour drugs. Preclinical screening and toxicology of organic platinum complexes [Thesis]. Leiden, Krips Repro, 1987, 23–30.
7. Lelieveld P, Van der Vijgh WJF, Veldhuizen RW, *et al.* Preclinical studies on toxicity, antitumour activity and pharmacokinetics of cisplatin and three recently developed derivates. *Eur J Cancer Clin Oncol* 1984, **20**, 1087–1104.
8. Lelieveld P, Van der Vijgh WJF, Van Velzen D. Preclinical toxicology of platinum analogues in dogs. *Eur J Cancer Clin Oncol* 1987, **23**, 1147–1154.
9. Vermorken JB, Van der Vijgh WJF, Klein I, *et al.* Pharmacokinetics of free and total platinum species following rapid and prolonged infusions of cisplatin. *Clin Pharmacol Ther* 1986, **39**, 136–144.
10. Metzler CM, Elfring GL, McEwen AJ. A package of computer programs for pharmacokinetics modeling. *Biometrics* 1974, **30**, 562.

11. Van Hennik MB, Van der Vijgh WJF, Klein I, *et al.* Comparitive pharmacokinetics of cisplatin and three analogues in mice and humans. *Cancer Res* 1987, **47**, 6297–6301.
12. Calvert AH, Harland SJ, Newell DR, *et al.* Early clinical studies with cis-diammine-1,1-cyclobutane dicarboxylate platinum II. *Cancer Chemother Pharmacol* 1982, **9**, 140–147.
13. Vermorken JB, Ten Bokkel Huinink WW, McVie JG, Van der Vijgh WJF, Pinedo HM. Clinical experience with 1,1-Diamminomethylcyclohexane (Sulphato) Platinum (II) (TNO-6). In: Hacker MP, Double EB, Krakoff IH, eds. *Platinum Coordination Complexes in Cancer Chemotherapy*. Boston, Martinus Nijhoff, 1984, 330–342.
14. Vermorken JB. Clinical experience with platinum analogues in the Netherlands. *Pharm Weekb* 1984, **119**, 1161–1166.
15. Offerman JJG, Meijer S, Mulder NH, *et al.* Nephrotoxicity of 1,1-diaminomethylcyclohexane sulphato platinum II (spiroplatin; TNO-6). *Eur J Cancer Clin Oncol* 1985, **21**, 447–451.
16. Cunningham D, Soukop M, Gilchrist NL, *et al.* TNO-6 has no effect in gastrointestinal cancer: N-acetyl-glucosaminidase shows renal damage. *Med Oncol Tumor Pharmacother* 1986, **3**, 25–28.
17. Offerman JJG, Hollema H, Elema JD, Schraffordt Koops H, de Vries EGE. TNO-6 induced renal failure. A case report. *Cancer* 1985, **56**, 1511–1514.
18. Elferink F, Van der Vijgh WJF, Pinedo HM. Analysis of antitumor (1,1-bis(amminomethyl)-cyclohexane)platinum (II) complexes derived from spiroplatin by high-performance liquid chromatography with differential pulse amperometric detection. *J Chromatogr* 1985, **320**, 379–392.
19. Elferink F, Van der Vijgh WJF, van der Poort SEJM, Henzen-Logmans SC, Pinedo HM. Influence of hydrolysis products of aqua(1,1-bis(aminomethyl)cyclohexane) sulfatoplatinum(II) on toxicity in rats. *Cancer Lett* 1984, **25**, 61–69.
20. Van der Vijgh WJF, Elferink F, Vermorken JB, *et al.* Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of Aqua (1,1-bis (aminomethyl) cyclohexane) sulfatoplatinum (II) (Spiroplatin) during a phase I trial. *Eur J Cancer Clin Oncol* 1988, **4**, 621–627.
21. Vermorken JB, Winograd B, Van der Vijgh WJF. Clinical pharmacology of cisplatin and some new platinum analogs. In: Ishigami J ed. *Proc 14th Int Congress of Chemotherapy. Recent Advantages in Chemotherapy; Anticancer Section*. Tokyo, University of Tokyo Press, 1985, 96–99.
22. Lewis KP, Medina WD. Cellulitis and fibrosis due to cis-diamminedichloroplatinum(II) (Platinol)infiltration. *Cancer Treat Rep* 1980, **64**, 1162–1163.
23. Leyden M, Sullivan J. Full-thickness skin necrosis due to inadvertent interstitial infusion of cisplatin. *Cancer Treat Rep* 1983, **67**, 199.
24. Sorensen JB, Groth S, Hansen SW, Nissen MH, Rorth M, Hansen HH. Phase I study of the cisplatin analogue, 1,1-diamminomethylcyclohexane sulfatoplatinum II (TNO-) (NSC 311056). *Cancer Chemother Pharmacol* 1985, **15**, 97–100.
25. Van der Vijgh WJF, Klein I. Protein binding of five platinum compounds. Comparison of two ultrafiltration systems. *Cancer Chemother Pharmacol* 1986, **18**, 129–132.
26. Hecquet B, Adenis L, Demaille A. *In vitro* interactions of TNO-6 with human plasma. *Cancer Chemother Pharmacol* 1983, **11**, 177–181.
27. Vermorken JB, Van de Vijgh WJF, Klein I, Hart AAM, Gall HE, Pinedo HM. Pharmacokinetics of free and total platinum species after short-term infusion of cisplatin. *Cancer Treat Rep* 1984, **68**, 505–513.
28. Colombo N, Sartorini E, Landoni F, *et al.* Phase II study of the platinum analog TNO-6 in patients with advanced ovarian cancer. *Cancer Treat Rep* 1986, **70**, 793–794.
29. Franks CR, Nys G, Materman E. TNO-6 (1,1-diaminomethylcyclohexane sulphate platinum II, NSC 311056) in phase II trials. *Proc 4th NCI-EORTC Symp on New Drugs in Cancer Therapy*. Brussels, 1983, 36.

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Multimodality Treatment of Malignant Germ Cell Tumours of the Mediastinum

Giuseppe Giaccone

Of 15 patients with malignant germ cell tumours of the mediastinum, 9 patients had pure seminomas and 6 had non-seminomas. Resection was radical in only 4 non-seminomas, 1 of which was resected after chemotherapy; radiotherapy was delivered to all seminoma patients as sole therapy (2 patients) or as part of combined modality therapy. All patients with non-seminomatous tumours underwent chemotherapy (cisplatin-based combination). Therapy was generally well tolerated, but 1 seminoma patient died of sepsis. Chemotherapy achieved a 71% complete response rate in pure seminoma patients and a 33% complete response rate in non-seminoma patients. 53% of patients are alive and free of disease beyond 36 months from start of any treatment. Pure seminoma patients survived longer than non-seminoma patients (3 and 5 year survivals were 67% and 33%, respectively). Although cisplatin-based chemotherapy is highly effective in pure seminomas and also in non-seminomas, a better therapeutic approach is needed in non-seminomas.
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INTRODUCTION

GERM CELL tumours of the mediastinum are rare neoplasms, histologically indistinguishable from those arising in the gonads. The mediastinum represents the third most frequent site of malignant germ cell tumours, after testes and retroperitoneum; moreover, germ cell tumours represent about 10% of all mediastinal tumours [1, 2].

A few small series have been reported and therapy for this disease is a matter of debate. Complete resection is often impossible and pure seminomatous tumours are usually treated with mediastinal irradiation [3]. Non-seminomatous tumours are often treated with chemotherapy [4, 5]. The introduction of cisplatin in combination chemotherapy for testicular tumours in the late 1970s has dramatically improved the poor prognosis