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Phase I study of the cisplatin analogue 1,1-diamminomethylcyclohexane sulfatoplatinum (TNO-6) (NSC 311056)

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Summary. The cisplatin derivative TNO-6 was evaluated for clinical toxicity in a phase I trial. TNO-6 was given daily for 5 days every 3 weeks as a 30-min IV infusion without hydration. In all, 39 patients with advanced cancer were treated at doses of 2.5–9.0 mg/m^2. No dose-limiting nephrotoxicity occurred, but evidence of mild, reversible tubular damage was found. Dose-limiting toxicity was hematologic with both thrombopenia and leukocytopenia, which with high dose levels reached WHO grade 4. Hematologic toxicity was most pronounced for pretreated patients. No antitumor activity was seen. The recommended dose for phase II trials will be 9.0 mg/m^2 for previously untreated and 8.0 mg/m^2 for pretreated patients.

Introduction

Cis-Diaminodichloroplatinum (DDP) has been established as an important cytostatic agent in the treatment of solid tumors, especially testicular and ovarian cancer [6, 7]. Nephrotoxicity is still considered the main dose-limiting toxicity of DDP [1, 2], even though the use of intensive IV hydration has significantly reduced this clinical problem. Other significant side effects are nausea and vomiting, neuro- and ototoxicity, and occasionally, thrombocytopenia [14].

A number of analogues of DDP have recently been synthesized in attempts to find compounds with less toxic side effects and equivalent or higher antitumor activity.

One of these analogues is 1,1-diamminomethylcyclohexane sulfatoplatinum-II (TNO-6), in which the ammine ligands of DDP have been substituted by a diamminomethyl-cyclohexane group (Fig. 1) [13]. TNO-6 was synthesized at the Institute of Organic Chemistry TNO, Utrecht, the Netherlands, and it has been screened extensively for antitumor activity in various experimental models. The antileukemic activity of TNO-6 in L1210 is comparable or marginally superior to DDP, and TNO-6 in L1210 is comparable or marginally superior to DDP, and TNO-6 also has a high degree of therapeutic efficacy in DDP-resistant L1210 leukemia, suggesting lack of cross-resistance with DDP [13]. The activity of TNO-6 in B16 melanoma is comparable to that of DDP, while the activity in Lewis lung carcinoma, colon 26 carcinoma, and Madison 109 lung carcinoma is either inferior to that of DDP or lacking [13].

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Structural formula of TNO-6

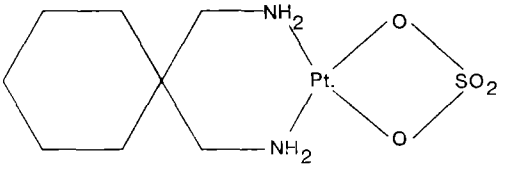

Fig. 1. Structural formula of TNO-6. TNO-6 is a 1,1-diaminomethyl cyclohexane sulfate–platinum II complex with the molecular formula $C_8H_{18}N_2O_4SPt$ and a molecular weight of 442.41

Animal toxicology studies of TNO-6 showed revealed dose-related leukopenia comparable to that caused by DDP, with nadirs of leukopenia observed on days 3–5 [13], while the effect on bone marrow hematopoietic stem cells was more pronounced for TNO-6 than for DDP.

A dose-dependent increase in blood urea nitrogen and serum creatinine was found in rats after repeated TNO-6 treatment at 2-week intervals, though it was less marked than that observed after DDP [9].

Because of the different preclinical toxicity pattern from DDP and the acceptable preclinical antitumor spectrum, TNO-6 was chosen for clinical phase I trials within the Early Clinical Trials Group of the EORTC. The drug was given IV each day for 5 days every 3 weeks in the present study at the Finsen Institute, Copenhagen, Whereas an intermittent dose schedule where the drug was given once every 3 weeks was chosen in a parallel study in Amsterdam [11].

Materials and methods

All patients entering this trial had histologically confirmed malignancy and either had been unsuccessfully treated with appropriate standard therapy, including surgery, radiotherapy, and chemotherapy or had remained untreated because, there was no treatment of proven benefit currently available. No patient had received prior DDP and all had normal renal function confirmed by normal serum creatinine and ^{m}Tc-DTPA clearance.

Clinical evaluation and laboratory tests (serum values of sodium, potassium, calcium, magnesium, and creatinine, complete blood count and GOT, alkaline phospha-

tase, LDH, bilirubin, and normotest) were performed before, during, and after each treatment series of TNO-6. ECG and audiogram were performed before every treatment. The 24-h urines were examined for $beta_2$ microglobulin and protein, for $beta_2$ microblobulin by means of radioimmunoassay [12]. Renal function was evaluated by ^{99m}Tc-DTPA clearance before treatment on the first day in each course, while ^{125}I-orthoiodohippurate clearance was evaluated before (^{125}I-OH-Cl I) and immediately after (^{125}I-OH-Cl II) TNO-6 administration on day 1 in each course.

The TNO-6 was supplied by Bristol Myers Company in ampules and was diluted in 500 ml 5% glucose and given as 30-min IV infusions daily for 5 days every 3 weeks. No additional hydration was given. At least three patients were treated at each dose level, starting at 2.5 mg/m^2 daily. There was no dose escalation for individual patients but TNO-6 was continued according to a 3-weekly schedule at the same dose level until progression of disease occurred. If no or only minor toxicity was encountered during the 16 days following drug administration in three patients at one dose level the next three patients received 0.5–1 mg/m^2 more per dose.

Table 1. Patient characteristics

Sex	19 male 20 female
Age median (range)	57 years (28–69 years)
Performance median (range) (Karnofsky scale)	70 (60–100)
No. of evaluable pts	39
No. with prior chemotherapy	11 (28%)
No. with prior radiotherapy	6 (15%)
No. with prior chemo- and radiotherapy	6 (15%)
No. previously untreated	16 (41%)
Diagnosis (pt no.)	
Lung cancer	(18)
Colon cancer	(7)
Cervical cancer	(4)
Unknown primary tumor	(3)
Bladder cancer	(2)
Mesothelioma	(2)
Breast cancer	(1)
Uterus cancer	(1)
Gall bladder cancer	(1)

Results

A total of 39 evaluable patients entered the study (Table 1), 41% of whom were previously untreated while 28% had received prior chemotherapy. The dose-limiting toxicity was hematologic, consisting of leukopenia in 13/39 patients (33%) with white blood cell nadirs below 3×10^9/l and thrombocytopenia with nadirs below 75×10^9/l in 9/39 patients (23%). The hematologic nadir values are shown in Table 2. Thrombocyte and leukocyte nadir values were generally recorded on days 12 and 21 in each series. The hematologic toxicity as related to the dosage of TNO-6 and prior therapy is shown in Table 3.

At a TNO-6 dose level of 9 mg/m^2 4 of 10 patients had WHO grade 4 toxicity. No patients experienced sepsis or significant bleeding episodes. In 10 patients (26%) hemoglobin decreased to WHO grade 2 (5.0–5.8 mmol/l). Serum creatinine did not rise significantly in any patient (Wilcoxon-Rank sum test). Ten patients (25%) had a slight decrease in plasma magnesium but without clinical symptoms. The lowest level encountered was 0.62 mmol/l (normal range 0.76–1.05 mmol/l), and no other disturbances in plasma electrolytes were observed.

Sixteen patients (41%) had transient proteinuria ($\leq$3 g/l), which occurred mostly on days 1–5. However, no significant decline in ^{99m}Tc-DTPA clearance was observed (Table 4).

There was no acute change in ^{125}I-hippurate clearance (Table 4), but the ratio of ^{125}I-OH-Cl II to ^{125}I-OH-Cl I declined significantly with increasing cumulative TNO-6 dose ($P < 0.01$; linear regression analysis) (Fig. 2). This sign of tubular toxicity was paralleled by the fact that urine $beta_2$ microglobulin increased significantly ($P < 0.02$) at high dose levels (i.e., >4.0 mg/m^2), with a maximum seen on days 5–10 in each series. The excretion returned to initial values before the next treatment (Fig. 3).

The audiogram was unchanged in all patients, and ECG did not show any sign of cardiac toxicity.

Thirty-seven patients (95%) experienced nausea or vomiting, mainly on day 1 in each course, and especially with high TNO-6 dose levels, where it reached WHO grade 3 (i.e., vomiting requiring therapy).

No objective responses were observed during the study.

Discussion

As assumed from the preclinical toxicity studies the nephrotoxicity of TNO-6 was not pronounced or dose-limiting,

Table 2. Hematologic nadir values

TNO-6 dose level (mg/m^2 × 5)	No. of pts	Median (range)		
		Hb nmol/l	WBC × 10^9/l	Platelets × 10^9/l
2.5	3	7.2 (5.6–9.5)	4.8 (3.9–8.4)	205 (48–246)
3.0	4	6.4 (5.8–6.8)	3.9 (3.0–4.5)	120 (103–141)
4.0	3	6.2 (5.4–7.5)	5.6 (2.8–18.2)	204 (120–231)
5.0	3	6.6 (5.5–6.9)	4.3 (2.2–5.3)	144 (108–225)
6.0	3	5.8 (5.5–6.3)	2.6 (1.9–4.1)	145 (120–197)
7.0	7	6.4 (5.3–6.8)	5.9 (2.6–10.7)	290 (100–444)
8.0	6	6.9 (5.6–8.3)	3.1 (2.4–4.3)	89 (66–204)
9.0	10	6.9 (5.0–9.4)	3.9 (0.7–9.3)	36 (6–269)

Table 3. Hematologic toxicity and previous therapy

TNO-6 dose level ($mg/m^2 \times 5$ days)	Toxicity (leuko- or thrombocytopenia)			
	No. of pts	≥ WHO grade 2	≥ WHO grade 3	WHO grade 4
2.5–7	23	6/23 (26%)	2/23 (9%)	1/23 (4%)
8	3 (u)[a]	1/3 (33%)	0	0
	3 (t)[b]	2/3 (66%)	0	0
9	4 (u)[a]	2/4 (50%)	2/4 (50%)	1/4 (25%)
	6 (t)[b]	4/6 (66%)	3/6 (50%)	3/6 (50%)
		WBC $< 3 \times 10^9$/l platelets $< 75 \times 10^9$/l	WBC $< 2 \times 10^9$/l platelets $< 50 \times 10^9$/l	WBC $< 1 \times 10^9$/l platelets $< 25 \times 10^9$/l

[a] Previously untreated
[b] Previously treated

Table 4. Renal function tests during one TNO-6 course

Dose level $mg/m^2 \times 5$ days	% Change in ^{99m}Tc-DTPA clearance Median (range)	% Change in ^{125}I-orthoiodohippurate clearance Median (range)
2.5	−5 (−31 to +5)	−4.4 (−61.7 to +20.6)
3.0	+6 (+2 to +10)	+14.6 (−22.5 to +18.2)
4.0	+40 (+12 to +67)	+13.7 (+1.0 to +18.1)
5.0	+1 (−5 to +8)	−1.0 (−4.0 to +11.8)
6.0	+7 (−13 to +7)	+16.5 (−12.1 to +36.3)
7.0	−1 (−18 to +2)	+4.0 (−18.4 to +16.1)
8.0	−11 (−24 to +44)	+12.2 (−18.4 to +16.1)
9.0	−14 (−25 to +18)	+9.4 (−7.6 to +39.1)
All patients	0 (−31 to +67) (not significant)	+10.8 (−22.5 to +39.1) (not significant)

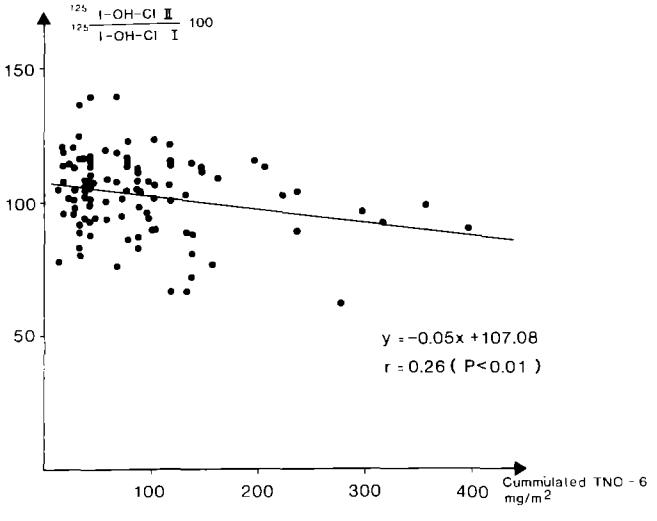

Fig. 2. Renal toxicity. Ratio between pretreatment (^{125}I-OH-Cl I) and posttreatment (^{125}I-OH-Cl II) hippurate clearance, shown as function of cumulative TNO-6 dose

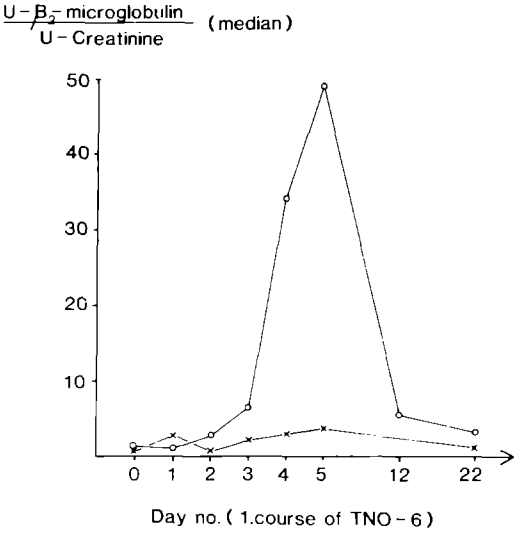

Fig. 3. Urine excretion of beta$_2$ microglobulin. O——O TNO-6 high level (>4.0 mg/m^2); x——x TNO-6 low level (≤ 4.0 mg/m^2) ($P<0.02$). Tubular function expressed as a ratio between u-beta$_2$ microglobulin and u-creatinine during first course of TNO-6 (days 1–22). Median values for patients with high TNO-6 levels (>4 mg/m^2) vs and with low TNO-6 levels (≤ 4 mg/m^2) are significantly different ($P<0.02$). Regarding confidence limits the quantile above the median was long, whereas the quantile below was low for both curves. The interquantile range was narrow on day 0 (0.45–2.36 and 0.8–3.9) and day 22 (0.75–2.05 and 1.5–8.1) for low and high TNO-6 levels, respectively

and no significant elevation of serum creatinine was observed in this study. In another clinical study of TNO-6, in which the drug was given as a single dose infusion every 3 weeks, a high grade of proteinuria (max. on day 5, 1–10 g/day) was noted [11], while in the present study this was modest (max. 3 g/l), did not persist, and was not dose-limiting.

As DDP can reduce the glomerular filtration rate during treatment even when intensive hydration is used, it is significant that TNO-6 did not produce any significant acute or chronic decrease in ^{99m}Tc-DTPA clearance. However, tubular toxicity was detectable: an acute decrease in ^{125}I-orthoiodohippurate-clearance was observed. It was not significant at low doses but became apparent with increasing cumulated dosage of TNO-6. Yet, the decrease in hippurate clearance with increasing cumulative TNO-6 dose of 7%/100 mg TNO-6 was only moderate.

Jones et al. found in 1980 [8] that persistence of high urinary beta$_2$ microglobulin excretion 6 weeks after a DDP dose was indicative of persistent renal injury. In this study a rise in beta microglobulin was observed during treatment at dose levels >4 mg/m^2. However, beta$_2$ microblobulin excretion returened to the initial values before the next course of in each case treatment. This indicates reversible tubular damage without functional consequences. The tubular damage, as measured by beta$_2$ microglobulin, is dose-dependent: it was significantly more pronounced with doses >4 mg/m^2 than at lower doese levels.

The dose-limiting toxicity in the present study was hematologic. Both leukopenia and thrombocytopenia occurred, and at a dose level of 9 mg/m^2 WHO grade 4 toxicity was seen. There was a tendency toward a higher degree of hematologic toxicity in pretreated patients, though the number of patients was too small to make statistically significant conclusions about the influence of former treatment.

Clinical phase I studies of the DDP analogues CIS-dichloro-transdihydroxy-bis(isopropylamine)platinum IV (CHIP) and carboplatin (CBDCA) have recently been reported to reveal dose-limiting hematologic toxicity with both leukopenia and thrombopenia [3–5]. However, in these studies there was only minor renal impairment, and in particular only low-grade proteinuria (<0.3 g/day) was seen.

From the present study it appears that 8 mg/m^2 daily for 5 days for pretreated patients and 9 mg/m^2 daily for 5 days for previously untreated patients are safe study dosages for phase II trials. The lack of signs of clinical activity in the present phase I trial and the few responses in other phase I–II trials with this compound [11] are somewhat disappointing, particularly as different and more toxic dose schedules were used in the other phase I–II studies. Obviously, the availability of other clinically active platinum analogues, such as CHIP and CBDCA, which involve lower nephrotoxicity than TNO-6 [3–5], must influence the decision to evaluate TNO-6 further.

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