Anti-Cancer Drugs, **3**, pp. 9–15

Anti-tumor properties of the organometallic complex *cis*-dimethylbis[sulfinylbis[methane]-S]platinum(II)

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The water-soluble organometallic complex *cis*-[Pt(Me)$_2$(Me$_2$SO)$_2$] (Me = methyl; Me$_2$SO = dimethyl sulfoxide) (*cis*-dimethylplatinum(II); CDMP) was evaluated for its toxicity on the rat and for its efficacy against two tumors of this animal: the Yoshida ascites sarcoma and the T$_8$ sarcoma of Guérin. The lethal dose for 50% of normal animals was 46.4 mg/kg; the predominant toxic effects were loss of weight, decrease in leukocytes and necrosis of the kidneys after i.v. or of the liver after i.p. administration. Doses of drug varying from 2 to 40 mg/kg were administered once by i.p., i.v., i.m. and intra-tumor (i.t.) route from 1 to 7 days after i.p. injection of 10^6 Yoshida ascites sarcoma cells and s.c. implantation of approximately 300 mg of T$_8$ sarcoma of Guérin. The compound showed anti-tumor activity increasing both the average life span and survival of the rats. A comparison between the therapeutic properties of the title complex with those of *cis*-[PtCl$_2$(NH$_3$)$_2$] (CDDP) reveals that *cis*-dimethylplatinum(II) exhibits the same anti-tumor activity associated with 6 times reduced toxicity.

Key words: cis-dichlorodiammineplatinum(II) (cisplatin; CDDP), *cis*-dimethylbis[sulfinylbis[methane]-S]-platinum(II) (*cis*-dimethylplatinum(II); CDMP), T$_8$ sarcoma of Guérin, Yoshida ascite sarcoma.

Introduction

Since the anti-tumor properties of *cis*-[PtCl$_2$(NH$_3$)$_2$] (cisplatin, CDDP) were reported by Rosenberg,[1] a vast number of direct derivatives of the complex have been synthesized and tested with the aim of obtaining higher anti-neoplastic activity, lower toxic side effects and enhanced water solubility. Of the hundreds of compounds evaluated, only a few have entered in clinical trials.

Recently, platinum compounds with a structure very different from that of cisplatin have been reported to show good anti-tumor activity, thus violating the structure–activity relationship empirically established for platinum complexes. In fact, anti-neoplastic activity is shown from the cationic complexes [PtCl(RR'SO)(diam)]$^+$ (diam = bidentate amine; RR'SO = substituted sulfoxides), with the activity depending upon the lability and the chirality of the sulfoxide ligand.[2] Good anti-tumor activity *in vitro* is also displayed from platinum complexes of vitamin C, characterized by the presence of a Pt–C bond.[3]

During our study of the displacement of dimethyl sulfoxide from *cis*-[PtMe$_2$(Me$_2$SO)$_2$] by nitrogen-containing bases,[4] we found that this neutral organometallic complex is soluble in water.[5] This interesting property and the above reported evidence that anti-tumor activity is not strictly limited to direct derivatives of cisplatin, prompted us to check the anti-tumor properties of CDMP. We report the results in this paper.

Materials and methods

Chemicals

cis-Dimethylbis[sulfinylbis[methane]-S]platinum(II) (*cis*-dimethylplatinum(II), CDMP) was prepared by reacting *cis*-[PtCl$_2$(Me$_2$SO)$_2$] with SnMe$_4$ in Me$_2$SO according to the method of Eaborn *et al.*[6] Platinex (cisplatin, CDDP) was purchased from Bristol Europe SPA, Sermoneta, Italy. All other chemicals were of analytical or HPLC grade.

Animals

Sprague-Dawley rats of both sexes, 4–6 months old, weighing 300–400 g, reproduced and maintained in our laboratory, were used throughout these experiments. They were housed five to a cage and given food and water *ad libitum*. The animals were

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always anesthetized with ether inhalation before any kind of intervention.

Tumors

The Yoshida ascite sarcoma, maintained by weekly i.p. transfer of 0.5 ml of ascitic fluid, and T_8 sarcoma of Guérin, maintained by fortnightly s.c. transfer of about 300 mg of neoplasia, corresponding to $2–3 \times 10^7$ living cells, were used for our experiments.

Toxicity

Toxicity was tested in adult rats of either sex using the following different dosages of the CDMP: 20, 30, 40, 50, 60 and 70 mg/kg dissolved in saline and given by i.p. or i.v., and doses of 40, 70 and 100 mg/kg given i.m.; groups of at least six rats were used for each dose and for each route, and lethal doses were determined from the acute lethal effects observed. Acute lethal effects were defined as those causing death of an animal within 7 days of injection. All animals were autopsized and tissues from kidneys and liver were subjected to microscopic examination.

Chemotherapy experiments

These were carried out using the same protocols by us employed to display anti-tumor activity of other drugs.[7,8] Sprague-Dawley rats of both sexes were randomly divided into groups of five animals each. After trypan blue exclusion test (viability about 95%), 10^6 viable Yoshida ascites sarcoma cells suspended in 1 ml of saline were inoculated i.p. into every animal. About 300 mg of T_8 sarcoma of Guérin were transplanted s.c. into each rat; to obtain the transplantable fragments the tumor mass was excised, accurately cleaned from the necrotic center, minced and washed in sterile saline. We chose to transplant s.c. a fragment of solid tumor to obtain a condition resembling that occurring in humans at the beginning of chemotherapy.

To discover the smallest quantity able to exert efficacious anti-neoplastic activity, the drug, dissolved in saline, was injected once at doses of 2, 4 and 8 mg/kg at day 1 by the i.p. route into 45 rats implanted with 10^6 viable Yoshida ascites sarcoma cells.

To study the effect of the CDMP on Yoshida ascite sarcoma, 13 groups of 10 animals, each injected i.p. with 10^6 tumor cells, received i.p. 8, 20 and 30 mg/kg of drug on day 1, 3 or 7; i.v. 30 mg/kg and i.m. 40 mg/kg of drug on day 1 or 3. To study the effect of the CDMP on T_8 sarcoma of Guérin, eight groups of 10 rats s.c. transplanted with 300 mg of tumor received i.v. or i.p. 20 mg/kg of drug on day 1 or 4, and i.m. or i.t. 40 mg/kg of drug dissolved in 1 ml of saline at day 1 or 4, respectively.

Growth curves were obtained from rats bearing T_8 sarcoma of Guérin treated as above, estimating at intervals after implantation in each animal lightly anesthetized with ether, the length (the longest dimension), width (the distance perpendicular to end in the same plane as the length) and height (the distance between the exterior tumor edge and the rat's body) of the tumor with vernier calipers. From these three dimensions and taking into account the double thickness of the skin overlaying the tumor, the volume of the tumor (in cm^3) is calculated from the following formula: $\pi/6 \times L \times W \times H$, where L = length, W = width and H = height, as suggested by Tomayko and Reynolds.[9]

To compare the anti-neoplastic activity of CDDP with that of the new compound, standard suspensions of drugs in saline were prepared immediately before the treatment and injected i.p. as above at 4 mg/kg on day 1 into animals implanted with 10^6 viable Yoshida ascite sarcoma cells.

Each experimental group was compared with a control group receiving only the drug-free vehicle on the same day and by the same route.

Evaluation of anti-tumor and side effects

The anti-neoplastic activity of the drug was expressed as the ratio of the mean survival time of test animals relative to the mean survival time of control animals and as deaths per total number of treated animals. Side effects were evaluated by blood urea nitrogen and transaminase levels, loss of body weight and decrease in leukocytes.

Statistical analysis

Mortality data were compared using the chi-square test with Yates' correction, the differences between the means were evaluated by Student's t-test, and considered significant at $p \leq 0.05$. The lethal dose for 50% of normal rats (LD_{50}) was evaluated by the Spearman–Karber method.

Results

The lethal dose for 50% of normal rats (LD_{50}) was calculated to be 46.4 mg/kg by i.p. and 51.2 mg/kg by i.v. injection, the highest non-toxic dose (HNTD) corresponded to 30 mg/kg. In normal rats treatment with CDMP at doses up to 20 mg/kg did not produce undesirable symptoms. The blood counts, blood urea nitrogen and transaminases remained within normal limits. At necroscopy, histological examination did not reveal abnormalities. Treatment with 30 mg/kg of the drug by i.p. and i.v. routes caused a 3% loss of body weight in 40% of the animals, a very modest increase of the blood urea nitrogen or transaminases, an unimportant decrease in leukocytes and all values returned to control values by day 7. When CDMP was given to normal rats at doses of 40, 50, 60 or 70 mg/kg by i.p. or i.v. routes, 43, 45, 78 or 100%, respectively, died within 7 days at the lower doses and 3 days at higher doses. After i.p. treatment, post-mortem examination of the liver showed reduced mass and consistency, and very dark color; when examined by microscopy, it showed centrilobular and middle-lobular diffuse necrosis and marked steatosis of the surviving cells. At 2 weeks after drug treatment 50% of the surviving rats developed ascites and the remainder sacrificed after 1 month showed an enlarged liver with globous lobes covered by a thick white membrane; microscopic observation showed the typical aspect of a regenerating liver. After i.v. treatment, post-mortem examination showed whitish kidneys up to half parenchima and atrofied intestine; when examined by microscopy the kidneys showed degeneration and necrosis of the epithelium of the proximal convoluted tubules. The animals surviving more than 7 days developed uremia after 5–7 days, loss of body weight (4–15% recovered by 11–20 days according to the dose of the drug) and a decrease in leukocytes. The i.m. injection of the drug in rats weighing 500 g at a dose of 50 mg/kg produced only an ulcer in the injection area and loss of body weight of 7.3% which recovered after 12 days and gained after 4 weeks, a dose of 70 mg/kg produced an ulcer in the injection area and a progressive loss of body weight (11.6% after 40 days); a dose of 100 mg/kg produced a very severe ulcer in the injection area followed by necrosis and amputation of the corresponding paw, a progressive loss of body weight up to 30% followed by death of the animals after 60 ± 5 days, a decrease in leukocytes and an increase of the blood urea nitrogen, and histological examination revealed degeneration of tubular epithelial cells with intertubular oedema and lymphocyte infiltration.

Table 1 reports the effect of different doses of CDMP i.p. administered into animals implanted with 10^6 Yoshida ascite sarcoma cells. By increasing the dose of the drug a simultaneous increase both in the life span and survival was observable. A dose of only 2 mg/kg increased the average life span 42% and permitted 20% of the treated animals to survive. A dose of 4 mg/kg was the smallest quantity of the drug able to exert good anti-neoplastic activity, at the same time significantly increasing the life span (56%) and the survival (60%) of tested animals. Furthermore, a dose of 8 mg/kg defended the rats against some millions of Yoshida ascite sarcoma cells.

Table 2 shows the anti-tumor activity of the complex against Yoshida ascite sarcoma evaluated in relation to the day of administration. The i.p. administration of 8 mg/kg of the drug 24 h after i.p. inoculation of 10^6 tumor cells allowed 100% to survive. The drug administered at day 3 allowed 60% to survive and a 0.17-fold extended average survival time; if administered 7 days after the tumor cells the complex was ineffective. A dose of 20 mg/kg i.p. injected 3 days after tumor cells was

Table 1. Effect of different doses of CDMP injected i.p. into Yoshida ascite sarcoma cells *in vivo*

No. of tumor cells on day 0	Drug (mg/kg) day 1	Average life span (days ± SD)	Median survival time		Dead/total	Long-term survival (>60 days)
			Treated/control (days)	Increased life span (%)		
10^6	—	11.4 ± 0.84	—	—	15/15	0
10^6	2	16.1 ± 3.74[a]	16.1/11.4	41.23	12/15	3
10^6	4	17.75 ± 4.68[a]	17.75/11.4	55.7	6/15[b]	9
10^6	8	>60[a]	>60 /11.4	>426.3	0/15[b]	15

[a] $p < 0.001$ by unpaired Student's *t*-test.
[b] $p < 0.01$ by chi-square test with Yates correction.

Table 2. Effect of the CDMP on Yoshida ascite sarcoma cells *in vivo*

No. of tumor cells on day 0	Drug (mg/kg)	Day	Route	Average life span (days ± SD)	Median survival time		Dead/total	Long-term survival (>60 days)
					Treated/control (days)	Increased life span (%)		
10^6	—	1	i.p.	11.4 ± 0.84	—	—	10/10	0
10^6	8	1	i.p.	>60[a]	>60.0 /11.4	>426.3	0/15[b]	15
10^6	8	3	i.p.	13.33 ± 2.51[a]	13.33/11.4	16.9	6/15[d]	9
10^6	8	7	i.p.	11.8 ± 0.92	11.8 /11.4	3.5	10/10	0
10^6	20	1	i.p.	>60[a]	>60.0 /11.4	>426.3	0/10[b]	10
10^6	20	3	i.p.	14.5 ± 0.5[e]	14.5 /11.4	27.2	2/10[d]	8
10^6	20	7	i.p.	12.2 ± 0.96	12.2 /11.4	7	10/10	0
10^6	30	1	i.p.	>60[a]	>60.0 /11.4	>426.3	0/10[b]	10
10^6	30	3	i.p.	15[e]	15.0 /11.4	31.6	1/10[d]	9
10^6	30	7	i.p.	13.22 ± 2.05[f]	13.22/11.4	15.9	9/10	1
10^6	—	1	i.v.	11.2 ± 0.6	—	—	10/10	0
10^6	30	1	i.v.	12.7 ± 1.15[g]	12.7 /11.2	13.4	10/10	0
10^6	30	3	i.v.	11.4 ± 1.7	11.4 /11.2	1.8	10/10	0
10^6	—	1	i.m.	11.6 ± 1.1	—	—	10/10	0
10^6	40	1	i.m.	13.0 ± 0.7[g]	13.0 /11.6	12.1	10/10	0
10^6	40	3	i.m.	11.3 ± 1.2	11.3 /11.6	−0.9	10/10	0

[a] $p < 0.0001$ by unpaired Student's *t*-test.
[b] $p < 0.001$ by chi-square test with Yates correction.
[c] $p < 0.05$ by unpaired Student's *t*-test.
[d] $p < 0.01$ by chi-square test with Yates correction.
[e] $p < 0.001$ by unpaired Student's *t*-test.
[f] $p < 0.02$ by unpaired Student's *t*-test.
[g] $p < 0.01$ by unpaired Student's *t*-test.

significantly effective on the average life span, extending it 0.27-fold and permitting the survival of 80% of the rats, while it was ineffective if administered on day 7. When inoculating the drug i.p. at a dose of 30 mg/kg even 7 days after tumor cells, we found a significant increase in average life span. The administration of the drug by the i.v. or i.m. route exerted anti-tumor effect on Yoshida ascite sarcoma only at the highest dosages (30 and 40 mg/kg, respectively) on day 1, significantly increasing the average life span. A comparison of the anti-tumor properties of the CDMP and CDDP is reported in Table 3.

The data show that the title complex exhibited cytostatic activity more or less equivalent to that of the CDDP when supplied in the same quantity (4 mg/kg).

Table 4 shows the anti-tumor activity of the CDMP against solid sarcoma T_8 of Guérin. The i.v. administration of 20 mg/kg and i.m. administration of 30 mg/kg of the drug 24 h after s.c. transplantation of about 300 mg of the tumor significantly increased the average life span of 22% and 27%, respectively. The i.p. treatment with 20 mg/kg of the drug was ineffective. An i.t. injection of 40 mg/kg even at day 4 significantly increased the median survival time.

Figure 1 shows the growth curves of the solid sarcoma T_8 of Guérin after treatment with CDMP by different routes. The administration of the drug by i.v. or i.t. routes immediately inhibited the development of the tumor up to 30 days after implantation; on the contrary, administration by

Table 3. Comparative effect of CDDP and CDMP on Yoshida ascite sarcoma cells *in vivo*

No. of tumor cells on day 0	Drug (4 mg/kg) day 1	Average life span (days ± SD)	Median survival time		Dead/total	Long-term survival (>60 days)
			Treated/control (days)	Increased life span (%)		
10^6	—	11.4 ± 0.84	—	—	15/15	0
10^6	CDDP	18.5 ± 7.42	18.5/11.4	62.3	4/15	11
10^6	CDMP	17.7 ± 4.68	17.7/11.4	55.2	6/15	9

Table 4. Effect of the CDMP on T_8 sarcoma of Guèrin *in vivo*

Day	Dose (mg/kg)	Route	Average life span (days ± SD)	Median survival time		Dead/total	Long-term survival (>60 days)
				Treated/control (days)	Increased life span (%)		
1	—	i.p.	36.2 ± 6.8	—	—	10/10	0
1	20	i.p.	39.6 ± 7.7	39.6 /36.2	9.4	10/10	0
4	20	i.p.	37.8 ± 5.6	37.8 /36.2	4.4	10/10	0
1	—	i.v.	35.87 ± 5.54	—	—	10/10	0
1	20	i.v.	43.75 ± 5.12[a]	43.7/35.9	21.96	10/10	0
4	20	i.v.	38.36 ± 6.4	38.4/35.9	6.9	10/10	0
1	—	i.m.	35.43 ± 5.5	—	—	10/10	0
1	40	i.m.	45.0 ± 7.54[a]	45.0/35.4	27.0	9/10	1[d]
4	40	i.m.	39.4 ± 7.3	39.4/35.4	11.2	10/10	0
1	—	i.t.	35.65 ± 5.8	—	—	10/10	0
1	40	i.t.	51.4 ± 8.1[b]	51.4/35.6	44.2	10/10	0
4	40	i.t.	41.5 ± 5.9[c]	41.5/35.6	16.4	10/10	0

[a] $p < 0.01$ by unpaired Student's *t*-test.
[b] $p < 0.001$ by unpaired Student's *t*-test.
[c] $p < 0.05$ by unpaired Student's *t*-test.
[d] Dead after 162 days as a consequence of diffuse metastasis.

i.m. route inhibited the growth of the neoplasia later. Treatment by i.p. route inhibited tumor growth only in toxic doses (almost 40 mg/kg).

Discussion

The most interesting property of this platinum derived complex is the low toxicity, compared with that of the CDDP, associated with a good anti-tumor effect. The LD_{50} for CDMP after one i.p. injection was 46.4 mg/kg. Under the same conditions the LD_{50} for CDDP was 7.7 mg/kg. Therefore, the new drug showed a toxicity 6 times lower than CDDP. The toxicity of the new drug was directed, in the rats, against bone marrow, kidneys and liver; we observed a prevalent renal toxicity after i.v. administration and a prevalent hepatic toxicity after i.p. injection of the drug. After i.m. administration the drug induced local necrosis associated with chronic toxicity only at the largest dose tested by us (100 mg/kg). This fact points to a slow absorption of the drug which reaches toxic concentrations in the kidneys, liver and bone marrow approximately 1 month after administration, and causes the death of the rats after 2 months (data not shown).

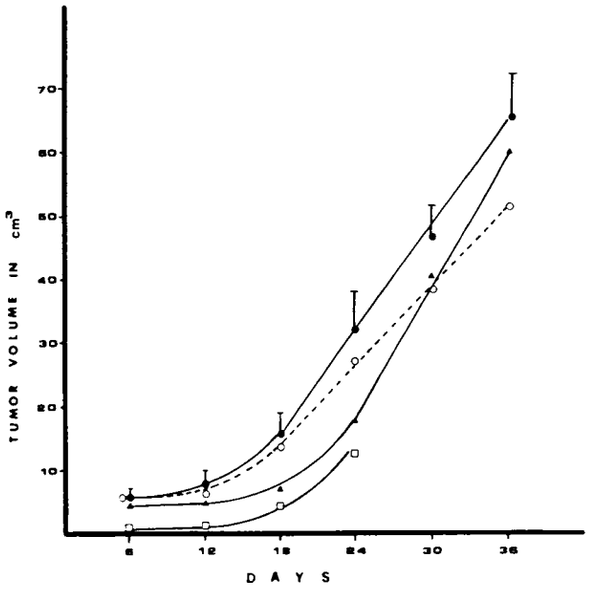

Figure 1. Effect of CDMP on the growth of T_8 sarcoma of Guérin: (●—●) control; (▲—▲) 20 mg/kg i.v., day 1, and 40 mg/kg i.t., day 4; (○——○) 40 mg/kg i.m., day 1; (□—□) 40 mg/kg i.p., day 1 (toxic dosage).

The comparison between the anti-tumor effects of CDMP and CDDP using a dose of 4 mg/kg given i.p. against Yoshida ascite sarcoma (Table 1) showed no substantial differences. The new drug showed a 7% smaller increased life span and a 13.4% higher mortality compared with CDDP. Its anti-cancer activity has to be considered very good inasmuch as 4 mg/kg represents the HNTD for CDDP, 30 mg/kg being the HNTD for CDMP. It showed a significant increase of the average life span of the rats treated i.p. even 7 days after the implantation of 10^6 viable Yoshida ascite sarcoma cells (Table 2) when the number of tumor cells calculated from the growth curve was about 5×10^8.[10,11] The i.m. and i.v. treatment was

successful on Yoshida ascite sarcoma only if the drug was administered 24 h after 10^6 tumor cell implantation and at the highest doses used by us (Table 2) significantly increasing the average life span exclusively. Other anti-cancer drugs such as Didemnin B and Rhodium(II)formamidinate tested by us under the same conditions were quite ineffective,[7,8] so the CDMP appears to show a better anti-tumor effect compared with that of the above-mentioned drugs. The poor effectiveness of the CDMP after i.m. injection may be attributed to a local accumulation of the drug followed by a slow release that does not achieve a concentration in the peritoneum capable of exercising anti-tumor effect when also taking into consideration the very rapid growth of the Yoshida ascite sarcoma. The slow release of the drug administered i.m. was shown by the growth curve of the T_8 sarcoma of Guérin (Figure 1), where the decrease of tumor development began about 24 days after drug injection, whereas by other routes it was immediate. Also, the i.v. treatment did not show important results on Yoshida ascite sarcoma, owing to dispersion in the body and/or rapid removal of the drug, associated with the fact that the peritoneum was probably a relatively closed compartment for the drug in question (which did not allow it to reach a very efficacious concentration in the peritoneal cavity). We obtained similar results by directly injecting in the peritoneum 1.5 mg/kg of the drug (data not shown). Therefore, starting from 40 mg/kg i.m. and 30 mg/kg i.v. only a very small quantity of the drug (3.75% and 5%, respectively) arrived in the peritoneal cavity to exert any anti-cancer effect. CDMP is also effective against a solid tumor of the rat, the T_8 sarcoma of Guérin, injected i.v., i.m. and i.t. Better results were obtained using the i.m. route, for which the average life span was longer than that of other routes, and 10% of the animals survived past 60 days and died 5 months later as a consequence of the growth of lymphonodal metastases. This fact can be explained by the above-mentioned slow release of the drug which, if unable to act against a very rapidly growing neoplasia such as Yoshida ascite sarcoma, was, however, satisfactorily effective against the solid sarcoma T_8 of Guérin, as was characterized by a slower growth. By inoculating the drug directly into the tumor mass even 4 days after tumor implantation, we obtained a significant increase in the average life span. However, the animals did not survive after therapy since the drug did not distribute homogeneously into the mass of the neoplasia. This allowed the survival of tumor cells that soon after, in the absence of new drug administration, swiftly reproduced. In contrast to the positive results obtained when the drug was injected i.v., i.m. and i.t., i.p. administration failed to give satisfactory results. We observed only a small (12.5%) and non-significant increase in the average life span; this was determined by the fact that the drug injected in the peritoneum was absorbed by tributary vessels of the liver, accumulated in the organ and was probably metabolized or not released again and distributed in the body. This was confirmed by the observation that i.p. injection of the drug caused degeneration and necrosis in the liver, whereas the kidneys remained undamaged.

The behavior of the growth curve shown by T_8 sarcoma of Guérin after drug administration by different routes is very interesting (Figure 1). After i.v. and i.t. treatment the drug acted immediately, inhibiting tumor growth for 3–4 weeks; i.m. treatment tardily inhibited the neoplasia growth after about 4 weeks. The i.p. route was immediately efficient only at toxic doses. Better results were obtained using the i.m. route and this can be attributed to the above-mentioned slow release of the drug, suggesting that a treatment with repeated low doses (that most resembles slow release) is more efficient than a single high dose in solid and relative slow-growing tumors such as T_8 sarcoma of Guérin.

The opposite therapeutical strategy showed better results in a very-rapidly growing fluid neoplasia such as Yoshida ascite sarcoma. In fact, the highest non-toxic dose i.p. (equivalent to i.t.) administered showed anti-tumor effect even 7 days after implantation of 10^6 tumor cells when the neoplasia was very much advanced.

Conclusion

Our results show that CDMP has very good tumor-inhibiting properties associated with low toxicity. This represents a further example of platinum complexes that do not obey the standard structure–activity relationships. It is noteworthy that the complex *cis*-$[PtCl_2(Me_2SO)_2]$ is inactive against tumors.[12] Thus, the substitution of chloride by a methyl group yields a compound with anti-tumor activity. We suggest that the high *trans* influence of methyl is necessary to increase the lability of the sulfoxide ligand and to produce active water-soluble species.[5] However, at this stage of our study, we do not know if the methyl groups remain

firmly bonded to platinum or if cleavage of the Pt–C σ bond[13] occurs in the biological media. Independent of the mechanism of action of this complex, the solubility in water is, in our opinion, the basic property that could permit the use of CDMP in clinical trials. CDMP and related complexes warrant further investigation.

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(Received 14 November 1991; accepted 5 December 1991)