Optimum Schedule of Selenium Administration to Reduce Lethal and Renal Toxicities of *cis*-Diamminedichloroplatinum in Mice

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(Received October 14, 1988)

The optimum conditions of selenium administration to reduce the side effects of a single dose of *cis*-diamminedichloroplatinum (*cis*-DDP) in mice were examined. The best effects against lethal toxicity of *cis*-DDP was obtained when sodium selenite was administered subcutaneously (s.c.) to mice simultaneously with s.c. injected *cis*-DDP at a molar ratio of 1 to 3.5 (sodium selenite to *cis*-DDP) on the first day and the same amount of selenite was given daily for four subsequent days. This coadministration of selenite completely depressed not only lethal toxicity of *cis*-DDP but also its renal toxicity (indicated by increased blood urea nitrogen values) and intestinal toxicity (indicated by the incidence of diarrhea) which were usually observed in the mice treated with *cis*-DDP alone. Furthermore, coadministration of selenite did not compromise the antitumor activity of *cis*-DDP against several transplantable tumors in mice. Therefore, the administration schedule of selenite with *cis*-DDP described above may be useful for cancer chemotherapy.

Keywords — *cis*-diamminedichloroplatinum; selenium; optimum condition; toxicity; antitumor activity

Introduction

cis-Diamminedichloroplatinum (*cis*-DDP) has demonstrated its clinical activity in a broad spectrum of malignancies.^{1,2)} Its application is, however, associated with a number of serious side effects, including nephrotoxicity, gastrointestinal toxicity (diarrhea, nausea) and ototoxicity.³⁾ The nephrotoxicity is a major dose limiting factor.³⁾ Although development of dosing regimens utilizing intravenous hydration and diuresis have made *cis*-DDP a valuable drug for cancer chemotherapy,¹⁾ a better method for prevention of its toxic side effects is required.

It is well known that selenium shows potent protective effects against toxicity of heavy metals such as mercury⁴⁾ and cadmium.⁵⁾ This effect of selenium is explained by interaction with metals to form a stable selenium-metal complex in animals.⁶⁾ Selenium appears to interact with many metals, including platinum, other than mercury and cadmium.⁷⁾ Recently, the protective effects of selenite, a selenium compound, against toxicity of *cis*-DDP in mice was reported.⁸⁻¹⁰⁾ These studies revealed that selenite specifically inhibits expression of the lethal and

renal toxicity of *cis*-DDP without affecting its antitumor activity.⁸⁻¹⁰⁾

In the present study, we investigated the optimum condition for selenium administration to prevent *cis*-DDP toxicity effectively and its application in cancer chemotherapy using tumor bearing mice.

Materials and Methods

Chemicals — *cis*-DDP was kindly supplied by Nippon Kayaku Co., Ltd., Tokyo. Sodium selenite and sodium selenate were obtained from Nakarai Chemicals Ltd., Kyoto. Selenocystine and selenomethionine were purchased from Sigma Chemical Co., St. Louis. The chemicals were dissolved in saline prior to use.

Animals — Male ICR mice were purchased from Charles River Japan Inc., Atsugi. BALB/c, C57BL/6, DBA/2, CDF₁ and BDF₁ male mice were purchased from Shizuoka Laboratory Animal Center, Hamamatsu, Japan.

Tumors — Ehrlich carcinoma cells were kindly donated by Nippon Kayaku Co., Ltd. and passaged by i.p. transplantation in male ICR mice. P388 leukemia cells, cells of colon adeno-

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carcinomas 26 and 38 were kindly supplied by Dr. T. Tsuruo, Japanese Foundation for Cancer Research, Tokyo. P388 leukemia cells were passaged by i.p. transplantation in male DBA/2 mice. Colon 26 and 38 cells were maintained in male BALB/c mice and male C57BL/6 mice, respectively, by s.c. transplantation in the left flank. The viability of tumor cells was tested by trypan blue exclusion.

Evaluation of Protective Effects of Selenium Compounds — Male ICR mice (4–5 weeks old) were injected s.c. with a single dose of *cis*-DDP (35 $\mu\text{mol/kg}$) on day 0. Sodium selenite or other selenium compounds were administered s.c. at a dose of 10 $\mu\text{mol/kg/d}$ once a day for 5 d. Administration of selenium compounds on the day of *cis*-DDP administration was performed 1 min after *cis*-DDP injection. The protective effects of selenium were assessed by changes in the body weights and number of surviving mice.

Evaluation of Antitumor Activity — The effect of selenium treatment on the antitumor activity of *cis*-DDP against ascites tumors was examined using mice inoculated with Ehrlich carcinoma or P388 leukemia cells. On day 0, Ehrlich tumor (10^6 cells) or P388 (10^6 cells)

cells were injected i.p. to ICR mice aged 6 weeks or BDF₁ mice aged 8 weeks, respectively. These mice received a single dose of *cis*-DDP (30, 35 or 45 $\mu\text{mol/kg}$, s.c.) with or without selenite (10 or 12.9 $\mu\text{mol/kg/d}$, s.c.) on day 1. Selenite was administered s.c. once a day for 5 d (on day 1 to 5). The first administration of selenite (on day 1) was performed 1 min after *cis*-DDP injection. The antitumor activity was evaluated by the mean survival time of a group of mice. Effects of selenite on the antitumor activity of *cis*-DDP against ascites tumor cells were also evaluated by the number of Ehrlich ascites tumor cells in mice. In a separate experiment to examine the effect of therapy on the growth of tumor cells, Ehrlich tumor cells (10^6 cells) were injected i.p. in ICR mice on day 0, and the drug treatments described above were started on day 3. Then, the number of living ascites tumor cells and blood urea nitrogen (BUN) values of the mice were determined on day 8 (5 d after administration of *cis*-DDP).

Mice s.c. transplanted with Ehrlich carcinoma, colon 26 or colon 38 cells were used for evaluation of the effects of selenite on antitumor activity of *cis*-DDP against solid tumors. Ehrlich carcinoma, colon 26 or colon 38 cells were in-

TABLE I. Effect of a Single Administration of Selenite on Lethal Toxicity of *cis*-DDP in Mice

Dose of selenite ($\mu\text{mol/kg}$)	Interval (h)	Number of surviving mice									
		Days after <i>cis</i> -DDP injection									
		0	3	4	5	6	7	8	9	10	15
0	—	7	7	6	2	0	0	0	0	0	0
5	0 <i>a)</i>	7	7	7	3	2	0	0	0	0	0
10	0 <i>a)</i>	7	7	4	2	2	0	0	0	0	0
25	0 <i>a)</i>	7	7	7	3	2	2	2	2	2	2
35	0 <i>a)</i>	7	7	7	3	3	3	3	3	3	3
45	0 <i>a)</i>	7	7	7	7	7	5	4	3	3	3
35	–24 <i>b)</i>	7	7	6	4	2	2	2	1	1	1
35	–4 <i>b)</i>	7	7	7	4	2	2	2	2	2	2
35	–1 <i>b)</i>	7	7	7	4	2	2	2	2	2	2
35	1 <i>c)</i>	7	7	7	5	3	3	3	3	3	3
35	4 <i>c)</i>	7	6	5	4	3	3	3	3	3	3
35	24 <i>c)</i>	7	7	7	3	1	1	1	1	1	1

A single dose of *cis*-DDP (35 $\mu\text{mol/kg}$) was administered s.c. to mice. Selenite was injected s.c. at a dose of 5, 10, 25, 35 or 45 $\mu\text{mol/kg}$. *a)* Selenite was administered with *cis*-DDP simultaneously. *b)* Selenite was administered to mice 1, 4 or 24 h before *cis*-DDP injection. *c)* Selenite was administered to mice 1, 4 or 24 h after *cis*-DDP injection.

jected s.c. into the back of ICR mice (6 weeks old), BALB/c mice (8 weeks old) or C57BL/6 mice (8 weeks old), respectively, on day 0 as reported previously.¹¹⁾ The drug treatments described above were started on day 3 after tumor transplantation. The antitumor activity was evaluated by the tumor weight on days 8 and 15 (5 and 12 d after *cis*-DDP administration) and BUN values were measured spectrophotometrically using a BUN assay kit (Urea-N-test; Wako Pure Chemicals, Tokyo) on day 8.

Statistical Calculation — Student's *t*-test was used for evaluating statistical significance.

Results and Discussion

Effect of a Single Administration of Selenite

The effect of a single administration of selenite on lethal toxicity of *cis*-DDP (35 $\mu\text{mol/kg}$, s.c.) in male ICR mice is shown in Table I. A dose-dependent protective effect of simultaneously administered selenite was observed. However, the lethal toxicity of *cis*-DDP was not completely prevented even when the dose of selenite was increased to 45 $\mu\text{mol/kg}$. Pre- or post-administration of selenite (35 $\mu\text{mol/kg}$, s.c.) was less effective against *cis*-DDP toxicity

than simultaneous administration.

Effect of Consecutive Administration of Selenite

Daily consecutive s.c. administration of selenite at a dose of 10 $\mu\text{mol/kg/d}$ for 4 or 5 d completely prevented the lethal toxicity of *cis*-DDP (Table II). When selenite was administered once a day for 5 d (day 0–4), a 10 $\mu\text{mol/kg/d}$ of dose gave the best results among various daily dosages examined with respect to its protective effects against mortality and body weight loss in mice receiving *cis*-DDP on day 0 (Table II).

To depress the lethal toxicity of *cis*-DDP (35 $\mu\text{mol/kg}$) completely, simultaneous administration of selenite with *cis*-DDP on day 0 was essential (Fig. 1). When the consecutive administration of selenite for 5 d was started 2 d before *cis*-DDP administration (Fig. 1e) or simultaneously with *cis*-DDP administration (Fig. 1f), complete prevention of lethal toxicity of *cis*-DDP and a substantial decrease in the rate of body weight loss induced by *cis*-DDP were observed in both cases (Fig. 1). It has been reported that simultaneous administration of selenite significantly reduced the toxicity of heavy metals, but its preadministration induced undesirable effects.¹²⁾ Therefore, the first administra-

TABLE II. Effect of Daily Consecutive Administration of Selenite on Body Weight and Survival of Mice Receiving a Single Dose of *cis*-DDP

Treatment with selenite ($\mu\text{mol/kg/d}$)	Number of surviving mice									Body weight of surviving mice on day 20 (%) <i>a)</i>
	Days after <i>cis</i> - DDP injection									
	0	3	4	5	6	7	8	10	20	
Control	7	7	7	7	7	7	7	7	7	145 $\pm$ 6
0 (<i>cis</i> - DDP alone)	7	7	7	4	3	2	1	1	0	—
10 ($\times$ 1: day 0)	7	7	7	4	3	3	3	3	3	125 $\pm$ 8 <i>c)</i>
10 ($\times$ 3: day 0—2)	7	7	7	6	4	4	4	4	4	128 $\pm$ 5 <i>c)</i>
10 ($\times$ 4: day 0—3)	7	7	7	7	7	7	7	7	7	129 $\pm$ 7 <i>b)</i>
10 ($\times$ 5: day 0—4)	7	7	7	7	7	7	7	7	7	135 $\pm$ 10
Control	7	7	7	7	7	7	7	7	7	133 $\pm$ 5
0 (<i>cis</i> - DDP alone)	7	6	6	6	3	1	1	0	0	—
5 ($\times$ 5: day 0—4)	7	7	7	7	6	6	6	5	5	101 $\pm$ 2 <i>c)</i>
10 ($\times$ 5: day 0—4)	7	7	7	7	7	7	7	7	7	132 $\pm$ 1
15 ($\times$ 5: day 0—4)	7	7	7	7	7	7	7	7	7	126 $\pm$ 4
20 ($\times$ 5: day 0—4)	7	7	7	7	7	7	7	7	7	115 $\pm$ 8 <i>c)</i>

Mice were administered with *cis*-DDP (35 $\mu\text{mol/kg}$, s.c.) on day 0. Selenite was administered s.c. to the mice once a day for 0–4 d. ^{a)} % of initial body weight (mean $\pm$ S.D.). ^{b)} ^{c)} Significantly different from control (^{b)} $p < 0.005$, (^{c)} $p < 0.001$).

Fig. 1. Effect of the Administration Schedule of Selenite on Growth and Survival Rates of Mice Receiving a Single Dose of *cis*-DDP

Mice were administered *cis*-DDP (35 μ mol/kg, s.c.) on day 0. Selenite (10 μ mol/kg) was administered s.c. once a day for 5 d.

tion of selenite was given simultaneously with *cis*-DDP in the subsequent experiments.

Table III shows effects of selenite on lethal toxicity of *cis*-DDP at a dosage of 50 μ mol/kg which exceed the minimum 100% lethal dose (35 μ mol/kg). The effective dose of selenite which reduced *cis*-DDP-induced lethal toxicity was found to be 15 μ mol/kg/d (Table III). From

these results (Tables II and III, Fig. 1), we decided that the optimal administration schedule was as follows: sodium selenite was administered s.c. to mice simultaneously with s.c. injected *cis*-DDP at a molar ratio of 1 to 3.5 (sodium selenite to *cis*-DDP) on the first day and the same amount of selenite was given daily for the subsequent 4 days. This administration schedule com-

TABLE III. Effect of Selenite on Survival of Mice Receiving *cis*-DDP at a Single Dose of 50 μ mol/kg

Dose of selenite (μ mol/kg/d)	Number of surviving mice						
	Days after <i>cis</i> -DDP injection						
	0	3	4	5	6	10	15
0	7	7	4	0	0	0	0
10 ($\times 5$)	7	7	6	6	3	3	3
15 ($\times 5$)	7	7	7	6	6	6	6
20 ($\times 5$)	7	7	6	5	4	4	4

Mice were administered with *cis*-DDP (50 μ mol/kg, s.c.) on day 0. Selenite was administered s.c. daily from day 0 to 4.

Fig. 2. Effect of Selenite on BUN Values and Frequency of Diarrhea in Mice Receiving *cis*-DDP

The results are presented as the means $\pm$ S.D. for four ICR mice. ■, *cis*-DDP (30 μmol/kg) alone; ▲, *cis*-DDP (35 μmol/kg) alone; ●, *cis*-DDP (35 μmol/kg) + selenite (10 μmol/kg). *a*, *b*, Significantly different from BUN values on day 0 (*a*) $p < 0.01$, (*b*) $p < 0.001$).

pletely depressed not only the lethal toxicity of *cis*-DDP (35 μmol/kg) but also its renal toxicity, indicated by increases in BUN values, and intestinal toxicity, indicated by the incidence of diarrhea, which are usually observed in mice treated with *cis*-DDP alone (Fig. 2). By coadministration of selenite according to the fixed schedule described above, the LD₅₀ value of *cis*-DDP was elevated from 31.6 to 58.0 μmol/kg.

Table IV shows the effects of various selenium compounds on lethal toxicity of *cis*-DDP in mice. All of the selenium compounds tested sig-

nificantly reduced the lethal toxicity of *cis*-DDP in the same way as selenite, suggesting that the protective effect may be a common property of many selenium compounds.

Effects of the administration route of selenite on the lethal toxicity of *cis*-DDP were also investigated (Table V). Even when selenite was administered orally, the same protective effect was observed as in the cases administered *via* other routes. Selenite selenium has been reported to be readily absorbed gastrointestinally.¹³⁾ Thus, the oral administration of selenite may be

TABLE IV. Effect of Various Selenium Compounds on Survival and Body Weight of Mice Receiving *cis*-DDP

Treatment	Survival rate of mice on day 15 (%)	Body weight of surviving mice on day 15 ^{a)} (%)
Control	100	132 $\pm$ 8
<i>cis</i> -DDP alone	0	—
+ sodium selenite	100	111 $\pm$ 7 ^{b)}
+ sodium selenate	100	102 $\pm$ 11 ^{b)}
+ selenocystine	86	88 $\pm$ 15 ^{b)}
+ selenomethionine	100	104 $\pm$ 5 ^{b)}

Mice were administered with *cis*-DDP (35 μmol/kg, s.c.) on day 0. Selenium compounds (10 μmol/kg/d) were administered s.c. daily from day 0 to 4. Each group consisted of 7 animals. *a*) % of initial body weight (mean $\pm$ S.D.). *b*) Significantly different from control (*b*) $p < 0.001$).

TABLE V. Effect of Administration Route of Selenite on Survival and Body Weight of Mice Receiving *cis*-DDP

Treatment	Survival rate of mice on day 15 (%)	Body weight of surviving mice on day 15 ^{a)} (%)
Control	100	124 $\pm$ 3
<i>cis</i> -DDP alone	0	—
+ selenite; s.c.	100	105 $\pm$ 5 ^{b)}
+ selenite; i.p.	100	103 $\pm$ 6 ^{b)}
+ selenite; i.v.	100	114 $\pm$ 5 ^{b)}
+ selenite; p.o.	100	108 $\pm$ 6 ^{b)}

Mice were administered *cis*-DDP (35 μmol/kg, s.c.) on day 0. Selenite (10 μmol/kg/d) was administered daily from day 0 to 4. Each group consisted of 7 animals. *a*) % of initial body weight (mean $\pm$ S.D.). *b*) Significantly different from control (*b*) $p < 0.001$).

TABLE VI. Effect of Selenite on Antitumor Activity and Renal Toxicity of *cis*-DDP in Mice Inoculated i.p. with Ehrlich Ascites Tumor Cells

Drug and dose		Living tumor cells in ascites ($\times 10^5$ cells) ^{a)}	BUN (mg/100 ml) ^{a)}
<i>cis</i> -DDP (μ mol/kg)	Selenite (μ mol/kg/d)		
0	0	26300 $\pm$ 6500	24.4 $\pm$ 5.5
0	10	23500 $\pm$ 4700	30.9 $\pm$ 6.0
25	0	1630 $\pm$ 960 ^{b)}	38.2 $\pm$ 11.6
30	0	91 $\pm$ 99 ^{b)}	75.5 $\pm$ 14.6 ^{b)}
35	0	34 $\pm$ 38 ^{b)}	149.5 $\pm$ 29.3 ^{b)}
35	10	34 $\pm$ 20 ^{b)}	29.5 $\pm$ 3.1

Mice were inoculated i.p. with Ehrlich ascites tumor cells on day 0. *cis*-DDP was administered s.c. on day 3. Selenite was given daily from day 3 to 7. Each group consisted of 5 animals. ^{a)} Determined on day 8 (mean $\pm$ S.D.). ^{b)} Significantly different from control (^{b)} $p < 0.001$).

TABLE VII. Effect of Selenite on Antitumor Activity of *cis*-DDP in Mice Inoculated i.p. with P388 Leukemia or Ehrlich Ascites Tumor Cells

Drug and dose		Survival time (d) <i>a)</i>	Lifespan (%)
<i>cis</i> - DDP (μ mol/kg)	Selenite (μ mol/kg/d)		
[P388; i.p.]			
0	0	12.3 $\pm$ 2.1	100
0	10	13.3 $\pm$ 1.2	108
30	0	21.9 $\pm$ 3.3 <i>b)</i>	178
35	0	5.7 $\pm$ 1.3 <i>b)</i>	46
35	10	24.7 $\pm$ 4.3 <i>b)</i>	201
45	12.9	27.7 $\pm$ 5.6 <i>b)</i>	225
[Ehrlich; i.p.]			
0	0	14.0 $\pm$ 1.9	100
0	10	15.0 $\pm$ 3.7	107
30	0	18.9 $\pm$ 2.7 <i>b)</i>	135
35	0	4.6 $\pm$ 0.7 <i>b)</i>	33
35	10	21.2 $\pm$ 4.7 <i>b)</i>	151
45	12.9	28.2 $\pm$ 7.3 <i>b)</i>	201

Mice were inoculated i.p. with P388 leukemia or Ehrlich ascites tumor cells on day 0. *cis*-DDP was administered s.c. on day 1, and selenite was administered s.c. daily from day 1 to 5. Each group consisted of 10 animals. ^{a)} Mean $\pm$ S.D. ^{b)} Significantly different from control (^{b)} $p < 0.001$).

applicable for clinical use to depress *cis*-DDP toxicity.

Effect of Selenite on Antitumor Activity of *cis*-DDP

Table VI shows the effect of selenite on antitumor activity of *cis*-DDP in mice inoculated i.p. with Ehrlich tumor cells. Twenty five micromoles per kilogram of *cis*-DDP appeared to be the maximum dose applicable without raising

the BUN values, the indicator of renal damage, when *cis*-DDP was administered alone. However, coadministration of selenite almost completely depressed the renal toxicity of *cis*-DDP without compromising its antitumor activity even when the dose of *cis*-DDP was elevated to 35 μ mol/kg. The antitumor activity of *cis*-DDP indicated by prolongation of the survival time of mice inoculated i.p. with Ehrlich tumor cells

TABLE VIII. Effect of Selenite on Antitumor Activity and Renal Toxicity of *cis*-DDP in Mice Inoculated s.c. with Ehrlich Ascites Tumor, Colon Adenocarcinoma 26 or 38 Cells

Drug and dose		Tumor weight (g)		BUN
<i>cis</i> -DDP ($\mu\text{mol/kg}$)	Selenite ($\mu\text{mol/kg/d}$)	on day 8	on day 15	on day 8 (mg/100 ml)
[Ehrlich; s.c.]				
0	0	0.46 ± 0.19	2.30 ± 1.21	19.4 ± 2.0
0	10	0.15 ± 0.04	2.02 ± 0.68	23.8 ± 4.1
25	0	0.06 ± 0.01 <i>b)</i>	0.57 ± 0.19	33.2 ± 8.6
30	0	0.03 ± 0.01 <i>c)</i>	0.49 ± 0.03	67.0 ± 39.5
35	0	0.02 ± 0.01 <i>c)</i>	Died	153.0 ± 10.8 <i>d)</i>
35	10	0.02 ± 0.005 <i>c)</i>	0.17 ± 0.03	25.9 ± 1.1 <i>c)</i>
45	12.9	0.02 ± 0.004 <i>c)</i>	0.05 ± 0.009 <i>b)</i>	26.6 ± 5.2
[Colon 26; s.c.]				
0	0	0.36 ± 0.05	2.43 ± 0.53	21.4 ± 3.7
0	10	0.23 ± 0.07	1.87 ± 0.67	19.7 ± 1.2
25	0	0.16 ± 0.04 <i>d)</i>	0.78 ± 0.20 <i>c)</i>	40.8 ± 2.9 <i>d)</i>
35	0	0.04 ± 0.02 <i>d)</i>	(0.52)	83.4 ± 5.6 <i>d)</i>
45	0	0.02 ± 0.004 <i>d)</i>	Died	103.7 ± 29.6 <i>d)</i>
35	10	0.03 ± 0.01 <i>d)</i>	0.38 ± 0.06 <i>d)</i>	29.0 ± 5.0
45	12.9	0.02 ± 0.004 <i>d)</i>	0.29 ± 0.06 <i>d)</i>	27.7 ± 7.4
[Colon 38; s.c.]				
0	0	0.20 ± 0.04	1.14 ± 0.33	27.0 ± 2.5
0	10	0.17 ± 0.04	0.72 ± 0.23	26.4 ± 3.3
25	0	0.12 ± 0.09	0.55 ± 0.11	43.5 ± 4.3 <i>d)</i>
30	0	0.09 ± 0.02 <i>c)</i>	0.41 ± 0.05 <i>c)</i>	70.0 ± 3.2 <i>d)</i>
35	0	0.03 ± 0.01 <i>d)</i>	Died	89.6 ± 6.5 <i>d)</i>
45	0	0.02 ± 0.002 <i>d)</i>	Died	124.7 ± 20.7 <i>d)</i>
35	10	0.02 ± 0.009 <i>d)</i>	0.23 ± 0.08 <i>c)</i>	31.0 ± 4.5
45	12.9	0.02 ± 0.003 <i>d)</i>	0.04 ± 0.02 <i>d)</i>	32.0 ± 4.7

Mice were inoculated s.c. with Ehrlich ascites tumor, colon adenocarcinoma 26 or 38 cells on day 0. *cis*-DDP was administered s.c. on day 3, and selenite was administered s.c. daily from day 3 to 7. Values are means $\pm$ S.D. (4 animals). *a)* The value from one surviving mouse. *b*–*d)* Significantly different from control (*b*) $p < 0.01$, (*c*) $p < 0.005$, (*d*) $p < 0.001$.

(Table VII) and by growth inhibition of solid tumors inoculated s.c. (Table VIII) was also unaffected by the coadministration of selenite. These results suggest that the coadministration of selenite with *cis*-DDP efficiently depresses the lethal and renal toxicities of *cis*-DDP without affecting its antitumor activity against several transplantable tumors in mice and allows the administration of a relatively high dose of *cis*-DDP.

The administration schedule of selenite with *cis*-DDP established in the present study may be applicable for clinical cancer chemotherapy. The mechanism of the protective effects of selenite against the *cis*-DDP toxicity can not be ex-

plained at present. In the case of inorganic mercury, selenite has been found to reduce the renal toxicity of mercury by inhibiting the uptake of mercury by the kidneys.^{14,15)} However, renal accumulation of platinum was not significantly affected by coadministration of selenite in the present experiment (data not shown). Further studies on the mechanism of the selective effects of selenite on the toxicity of *cis*-DDP are in progress in our laboratory.

Acknowledgement This study was supported by a Grant-in-Aid for Special Project Research, Cancer-Bioscience, from the Ministry of Education, Science and Culture, Japan (No.

61210030).

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