Cancer Chemother Pharmacol (1995) 35: 441–445

SHORT COMMUNICATION

Dae-Kee Kim · Hun-Taek Kim · Yong-Baik Cho
Joo Ho Tai · Jae Suk Ahn · Taek-Soo Kim · Key H. Kim
Weon-Seon Hong

Antitumor activity of *cis*-malonato[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II), a new platinum analogue, as an anticancer agent

Received: 7 June 1994 / Accepted: 27 September 1994

Abstract The in vitro and in vivo antitumor activity of a new antitumor platinum complex, *cis*-malonato[(4*R*, 5*R*)-4, 5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2053R, NSC D644591), were evaluated and compared with those of cisplatin (CDDP) and carboplatin (CBDCA) using murine tumors. SKI 2053R was highly active in vitro against both L1210 murine leukemia and its CDDP-resistant subline, L1210/DDP; the relative resistances were 20.0-, 14.5-, and 2.7-fold for CDDP, CBDCA, and SKI 2053R, respectively. SKI 2053R showed activity comparable with or superior to either CDDP or CBDCA in mice implanted with L1210. In mice implanted with L1210/DDP, as compared with CBDCA, SKI 2053R showed high values for the percentage of treated survivors relative to controls and for numbers of cured mice, whereas CDDP had virtually no activity. In mice implanted with P388, all three drugs were highly active, but the intensity of activity was shown to be ranked in the following order: SKI 2053R > CDDP > CBDCA. The antitumor activity of SKI 2053R against Lewis lung carcinoma was comparable with that of both CDDP and CBDCA. The antitumor activity of SKI 2053R was further investigated against two human tumor xenografts, KATO III (stomach adenocarcinoma) and WiDr (colon adenocarcinoma), implanted s.c. in nude mice and was compared with that of CDDP. In SKI 2053R-treated groups, the time required for a mean tumor weight of 1,000 mg was 33.1 days in KATO III xenografts and 35.0 days in WiDr xenografts as compared with 30.2 and 27.2 days in CDDP-treated groups, respectively. SKI 2053R achieved growth-inhibition rates comparable with those of CDDP against KATO III (65% versus 59%) and WiDr xenografts (64% versus 54%) on day 35. These results indicate that SKI 2053R is an attractive candidate for further development as a clinically useful anticancer drug.

Key words SKI 2053R · Antitumor activity

D.-K. Kim (✉) · H.-T. Kim · Y.-B. Cho · J. H. Tai · J. S. Ahn
T.-S. Kim · K. H. Kim
Life Science Research Center, Sunkyong Industries, 600, Jungja-Dong, Changan-Ku, Suwon-Si, Kyungki-Do 440–745, Korea

W.-S. Hong
Department of Medicine, Asan Medical Center, College of Medicine, Ulsan University, Seoul 138–040, Korea

Introduction

cis-Dichlorodiammineplatinum(II) (cisplatin, CDDP) is one of the most widely used chemotherapeutic agents, either alone or, more often, in combination with other agents, in the treatment of various human cancers [14]. However, its clinical usefulness has frequently been limited by severe side effects, such as nephrotoxicity, gastrointestinal toxicity, ototoxicity, and neurotoxicity [3, 4], and by the emergence of cancer cells resistant to CDDP after an initial response [16].

To overcome these unfavorable drawbacks of CDDP, extensive efforts have been made to develop new CDDP analogues with equivalent or greater antitumor activity and lower toxicity [8, 12, 15]. Among them, *cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin, CBDCA) is now the only CDDP derivative commercially available for clinical use [2]. CBDCA has reduced renal and gastrointestinal toxicities as compared with CDDP [8, 17]. CBDCA, however, has no enhanced therapeutic efficacy over CDDP and has not circumvented acquired resistance to CDDP due to its cross-resistance with CDDP [7].

In an attempt to develop a new, potent antitumor platinum drug, we have recently synthesized a series of platinum complexes with a seven-membered ring structure between their carrier ligands and a platinum atom. Among them, *cis*-malonato[(4*R*, 5*R*)-4, 5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2053R) was selected for further development because of its high in vitro and in vivo antitumor activity, its low nephrotoxicity, and its sufficient solubility and stability in aqueous solution [10].

In this study, we investigated the antitumor activity of SKI 2053R against murine tumors in mice, examined its cross-resistance in L1210/DDP, a CDDP-resistant subline of

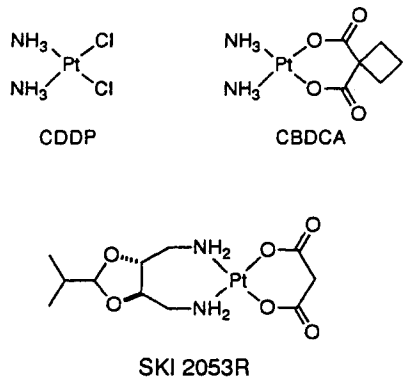

Fig. 1 Structures of CDDP, CBDCA, and SKI 2053R

L1210, and compared these parameters with those of CDDP and CBDCA. We also evaluated the antitumor activity of SKI 2053R against two human tumor xenografts, KATO III and WiDr, in nude mice and compared it with that of CDDP.

Materials and methods

Drugs

CDDP and CBDCA were purchased from Sigma Chemical Co. (St. Louis, Mo., USA). SKI 2053R was synthesized at the Life Science Research Center of Sunkyong Industries (Korea) as previously described [10] (Fig. 1). The drugs were either dissolved in sterile 0.9% NaCl solution or suspended in 0.5% carboxymethyl cellulose solution immediately before use for i.p. injection.

Animals and tumor cells

DBA/2 mice weighing 19–22 g were used for the maintenance of L1210 leukemia, L1210/DDP leukemia, and P388 leukemia, and C57BL/6J mice weighing 19–22 g were used for the maintenance of Lewis lung carcinoma (LL/2). Male C57BL/6J × DBA/2 F_1 (BDF_1) mice weighing 19–22 g were used for the experiments involving L1210, L1210/DDP, P388, and LL/2. BALB/c-nu/nu nude mice aged 4 weeks were used for the maintenance of human tumor xenografts and for the antitumor evaluation test. All mice were purchased from Charles River Japan, Inc. (Sekyo, Japan) and were fed with a sterilized pellet diet and autoclaved water ad libitum. Nude mice were housed in autoclaved filter-capped cages (Nalgene, Rochester, N.Y., USA). All housing cages were kept in laminar air-flow units in our laboratory (Flufrance 94230, France).

L1210 leukemia, P388 leukemia, and LL/2 carcinoma were obtained from the American Type Culture Collection (Bethesda, Md., USA). L1210/DDP, a CDDP-resistant subline of L1210, was developed by continuously exposing L1210 cells to stepwise increasing concentrations of CDDP as previously described [5]. L1210 and L1210/DDP were propagated in RPMI 1640 medium (Gibco, Grand Island, N.Y., USA) supplemented with 10% fetal bovine serum (Gibco), 100 units penicillin/ml, and 100 μg streptomycin/ml in an incubator under a highly humidified atmosphere containing 5% CO_2 at 37 °C. The resistance of L1210/DDP to CDDP was maintained by the treatment of DBA/2 mice with i.p. injections of 5 mg/kg CDDP every 4 days after implantation as described elsewhere [1]. L1210 and P388 were maintained by serial passage in the i.p. cavities of DBA/2 mice. LL/2 was maintained by serial passage in the right subaxillary region of C57BL/6J mice. KATO III (human stomach adenocarcinoma) xenografted in nude mice was kindly provided by Dr. N. Saijo (National Cancer Center Hospital and Research Institute, Japan). WiDr (human colon adenocarcinoma) was purchased from the American Type Culture Collection (Bethesda, Md., USA) and was xenografted s.c. into nude mice (10^7 cells). These human tumor xenografts were maintained by serial s.c. transplantation of 2- to 3-mm^3 fragments into the right subaxillary region of nude mice.

In vitro growth-inhibition test

The in vitro growth-inhibitory activity of SKI 2053R, CDDP, and CBDCA was assessed by the trypan blue dye-exclusion method against L1210 and L1210/DDP. Prior to the experiments with L1210/DDP, the cells were cultured in drug-free medium for 2 weeks. L1210 and L1210/DDP cells in exponential growth were placed in 24-well multidish plates (Nunc, Denmark) at a density of 1×10^5 cells/well, and various concentrations of SKI 2053R, CDDP, and CBDCA in culture medium were added to each well in duplicate. After incubation for 48 h at 37 °C in an incubator containing 5% CO_2, cells were stained with trypan blue and the number of viable cells were counted. The growth-inhibitory activity was expressed as the concentration (IC_{50}) that reduced cell numbers in untreated controls by 50% in dose-response curves plotted with probit analysis and was determined in three independent experiments. Relative resistance was defined as the ratio of the IC_{50} value of L1210/DDP to that of L1210.

In vivo antitumor-activity test

In vivo antitumor activity on murine tumors was evaluated as previously described [6]. Briefly, BDF_1 male mice were implanted i.p. with 1×10^6 viable (those excluding trypan blue) cells of L1210, L1210/DDP, P388, and LL/2, respectively, on day 0. The drugs were given i.p. according to two treatment schedules: three intermittent injections on days 1, 5, and 9 (q4d × 3) and 9 daily consecutive injections (qd × 9) beginning on day 1 after tumor implantation. Three doses were used and the highest dose of each drug was determined as the dose lethal to 10% of the animals (LD_{10}) for each compound as previously estimated in non-tumor-bearing mice. Six mice were used for treatment groups and 15 mice, for control groups. Antitumor activity was evaluated by comparing the mean survival time (MST) of treated groups (T) with that of control groups (C) and was expressed as % T/C (the percentage of the MST of T relative to the MST of C). All experiments were terminated on day 60. Mice alive on day 60 were considered to be cured and were included in calculations of the MST of treated mice. When mice were dead, necropsy was performed and drug-induced death was judged if neither ascites nor splenomegaly was found.

In the experiments performed on the human tumor xenografts, mice bearing xenografts were randomized into treated or control groups, with six mice being used for treatment groups and 10 mice, for control groups. Chemotherapy was initiated at approximately 2 (for KATO III) or 3 (for WiDr) weeks after transplantation, when each tumor had reached a weight of approximately 100 or 300 mg, respectively. SKI 2053R and CDDP were given i.p. on a q4d × 3 schedule at a dose of 100 and 5 mg/kg per injection, respectively (previously determined as the maximum tolerated doses). Antitumor activity was evaluated by comparing the days required for a mean tumor weight (MTW) of 1,000 mg. Tumor volume (V) was calculated weekly using the equation $V = 1/2 \times a \times b^2$, in which a and b are the length (in millimeters) and width (in millimeters), respectively, measured with Vernier calipers of tumors grown in the subaxillary region. On day 35 after the start of treatment, the MTW, relative tumor growth (RTG), and inhibition rate (IR,%) were determined. RTG was calculated by dividing the tumor weight on day 35 (MTW_{35}) by that on day 0 (MTW_0). IR was obtained from the equation $(1 - RTG \text{ in } T/RTG \text{ in } C) \times 100$.

Statistical analysis

Statistical difference was determined by analysis of variance (ANOVA) with Duncan's multiple-range test and Tukey's studentized range test using a statistical analysis system (SAS). P values of < 0.05 were considered statistically significant.

Table 1 Antitumor activity of SKI 2053R, CDDP, and CBDCA against L1210, L1210/DDP, P388, and LL/2 cells in mice[a]

Drug	Treatment schedule (days)	Dose (mg/kg)	% T/C[b]			
			L1210	L1210/DDP	P388	LL/2
SKI 2053R	q4d × 3	100.0	440 (2/6)[c], (1/6)[d]	213 (1/6)[c], (1/6)[d]	452 (5/6)[c]	295 (3/6)[c]
	(1, 5, 9)	77.0	386 (2/6)[c]	283 (1/6)[c]	476 (6/6)[c]	198
		60.0	250	320 (2/6)[c]	387 (3/6)[c]	169 (1/6)[c]
	qd × 9	30.0	307 (1/6)[c]	300 (2/6)[c]	426 (5/6)[c]	212 (2/6)[c]
	(1–9)	23.0	239	140	476 (6/6)[c]	181 (1/6)[c]
		17.0	278 (1/6)[c]	155	435 (5/6)[c]	197 (2/6)[c]
CDDP	q4d × 3	6.0	320 (1/6)[c], (1/6)[d]	122	336 (3/6)[c], (1/6)[d]	287 (4/6)[c]
	(1, 5, 9)	4.6	307	121	476 (6/6)[c]	216 (1/6)[c]
		3.5	278 (1/6)[c]	124	375 (1/6)[c]	215
	qd × 9	3.0	313 (1/6)[c], (1/6)[d]	111 (3/6)[d]	175 (1/6)[c], (5/6)[d]	294 (5/6)[c], (1/6)[d]
	(1–9)	2.3	447 (2/6)[c]	121	476 (6/6)[c]	315 (5/6)[c]
		1.7	213	119	452 (5/6)[c]	262 (3/6)[c]
CBDCA	q4d × 3	100.0	303 (1/6)[c], (1/6)[d]	79 (3/6)[d]	323 (3/6)[c]	243 (2/6)[c]
	(1, 5, 9)	77.0	158	241	238 (1/6)[c]	250 (1/6)[c]
		60.0	194	140	273 (2/6)[c]	224 (2/6)[c]
	qd × 9	40.0	184	153	369 (3/6)[c]	286 (2/6)[c]
	(1–9)	30.0	303 (1/6)[c]	236 (1/6)[c]	331 (3/6)[c]	218 (2/6)[c]
		23.0	157	143	281 (1/6)[c]	275 (4/6)[c]

[a] Male BDF_1 mice (6 mice/treatment group and 15 mice/control group) were implanted i.p. with 1×10^6 cells of L1210, L1210/DDP, P388 or LL/2 on day 0. The MSTs of control mice bearing L1210, L1210/DDP, P388, or LL/2 tumors were 8.8, 12.1, 12.4, or 17.0 days, respectively

[b] MST of the treated group/MST of the control group ×100

[c] Values in parentheses represent numbers of 60-day survivors/numbers of animals tested

[d] Values in parentheses represent numbers of toxic deaths/numbers of animals tested

Results

In vitro growth-inhibitory activity against L1210 and L1210/DDP

The growth-inhibitory activity of platinum complexes was evaluated against L1210 and L1210/DDP. IC_{50} values in L1210 tumors obtained for SKI 2053R, CDDP, and CBDCA were 0.33, 0.12, and 3.18 μM, respectively. IC_{50} values in L1210/DDP tumors recorded for SKI 2053R, CDDP, and CBDCA were 0.89, 2.42, and 46.0 μM, respectively. L1210/DDP was 20.0– and 14.5–fold more resistant to CDDP and CBDCA, respectively, than was L1210, while this resistant subline was 2.7–fold more resistant to SKI 2053R.

Antitumor activity against L1210 , L1210/DDP, P388, and LL2

The antitumor activity of SKI 2053R in mice inoculated i.p. with L1210, L1210/DDP, P388, and LL2 was examined in comparison with those of CDDP and CBDCA (Table 1). Following a q4d × 3 schedule, the maximal % T/C values obtained for SKI 2053R, CDDP, and CBDCA in L1210 tumors were 440%, 320%, and 303%, respectively. The numbers of cured mice were also higher in groups treated with SKI 2053R as compared with CDDP and CBDCA. In L1210/DDP, the % T/C values obtained in mice treated with SKI 2053R were higher than those recorded for CDDP and CBDCA, and 4 of 18 mice were cured in groups treated with SKI 2053R, whereas no mouse was cured in groups treated with CDDP or CBDCA. On a qd × 9 schedule against L1210, a maximal % T/C value of 447% and 3 cured mice were observed among 18 animals treated with CDDP, whereas % T/C values of 303% and 307% and 1 and 2 cured mice were found in groups treated with CBDCA and SKI 2053R, respectively. In mice implanted with L1210/DDP, the maximal % T/C value recorded for SKI 2053R was higher than those obtained for either CDDP or CBDCA.

Although all three drugs tested were highly active against P388, SKI 2053R showed activity higher than or equal to that of CDDP and greater than that of CBDCA. T/C values of more than 400% and cures of more than 5 of 6 mice were observed more frequently in groups treated with SKI 2053R as compared with CDDP, whereas the % T/C values and numbers of cured mice recorded for CBDCA were lower than those obtained for either SKI 2053R or CDDP. In mice treated with CDDP, six drug-induced deaths were observed, although mortality was dependent upon the schedule used.

Although the % T/C values recorded for SKI 2053R against LL/2 were lower in general than those obtained for CDDP and CBDCA on a qd × 9 schedule, SKI 2053R achieved the highest % T/C value (295%) on a q4d × 3 schedule. The numbers of cured mice among animals treated with the highest dose on the q4d × 3 schedule were greatest in groups treated with CDDP, followed in rank order by SKI 2053R and CBDCA.

Antitumor activity against human tumor xenografts

The antitumor activity of SKI 2053R was evaluated against two human xenografts, KATO III and WiDr, in nude mice

Table 2 Antitumor activity of SKI 2053R and CDDP against KATO III and WiDr xenografts in nude mice[a]

Drug	Dose (mg/kg)	KATO III					WiDr				
		Days to 1,000 mg[b]	MTW_0[c] (mg)	MTW_{35}[c] (mg)	RTG[c]	IR (%)	Days to 1,000 mg[b]	MTW_0[c] (mg)	MTW_{35}[c] (mg)	RTG[c]	IR (%)
Control	–	18.2	111±13	3,173±1,220	28.4±9.9	–	16.3	359±98	2,841±850	8.3±3.2	–
SKI 2053R	100	33.1	111±10	1,101±628**	10.0±6.1**	65	35.0	361±94	1,000±309**	3.0±1.5*	64
CDDP	5	30.2	110±11	1,295±781**	11.9±7.5**	59	27.2	368±93	1,379±398**	3.8±1.1*	54

* Significantly different from control ($P < 0.05$)
** Significantly different from control ($P < 0.01$)
[a] Six mice were used for treatment groups and 10 mice for control groups. Chemotherapy was initiated at approximately 2 (for KATO III) or 3 (for WiDr) weeks after tumor transplantation. SKI 2053R and CDDP were given i.p. on a q4d × 3 schedule at a dose of 100 and 5 mg/kg per injection, respectively. MTW, RTG, and IR were evaluated on day 35
[b] Number of days required for a mean tumor weight of 1,000 mg
[c] Data represent mean values ±SD

and compared with that of CDDP (Table 2). In mice transplanted with KATO III, the time required for a MTW of 1,000 mg was 33.1 and 30.2 days in SKI 2053R- and CDDP-treated mice, respectively; these values were greater than that observed in untreated mice. IR values were 65% and 59% in SKI 2053R- and CDDP-treated mice, respectively, on day 35.

In mice transplanted with WiDr, no difference in MTW and RTG was observed between SKI 2053R- and CDDP-treated groups. The time required for a MTW of 1,000 mg was 35.0 and 27.2 days in SKI 2053R- and CDDP-treated mice, respectively, as compared with 16.3 days in untreated mice. IR values were 64% and 54% in SKI 2053R- and CDDP-treated mice, respectively, on day 35.

Discussion

The major interests in the field of new platinum-based antitumor drug development are whether the new drug exhibits an enhanced antitumor activity and spectrum as well as reduced toxicity, whether it overcomes acquired resistance, and whether it has improved physicochemical properties, such as water solubility and stability, in comparison with the parent drug. The main purpose of this study was to evaluate the antitumor activity of SKI 2053R in vivo against the murine tumors L1210, P388, and LL/2, in comparison with that of CDDP and CBDCA. We also investigated the effects of SKI 2053R in vitro and in vivo in overcoming the acquired resistance of L1210/DDP cells, because the development of acquired resistance after initial therapeutic effectiveness has been a serious clinical problem in chemotherapeutic failure.

The growth-inhibitory activity of platinum complexes against L1210 was evaluated in terms of the IC_{50} value, demonstrating the order of activity to be CDDP > SKI 2053R > CBDCA. The rank order of the IC_{50} value, however, is not thought to be that of the clinical antitumor activity predicted, because the dose of administration and subsequent plasma concentrations differ among the drugs.

In the in vitro evaluation of a new investigational antitumor drug, a common problem is that the accurate platinum concentration of the active form of the drug is not known until the phase I study has been finished. Although a model system to calculate the peak plasma concentration from the LD_{50} value for the drug in mice has been reported [18], the calculated value does not always reflect the actual value in humans. Therefore, in this study the in vivo antitumor activity was evaluated after administration of the equitoxic doses determined in mice. The highest dose of each drug was approximately the LD_{10} estimated in non-tumor-bearing mice under the corresponding schedules of the antitumor-activity test. On the other hand, in the evaluation of the capacity of a drug to overcome CDDP resistance, the value for relative resistance is thought to have the most validity, because the effects of delivered doses are eliminated in the determination of relative resistance. SKI 2053R showed a relative resistance of 2.7-fold, which was much lower than those of CDDP and CBDCA. The resistance-overcoming effect of SKI 2053R was also evaluated in an in vivo model. In mice implanted with L1210/DDP, SKI 2053R showed high % T/C values and numbers of cured mice, which were similar to those obtained in mice implanted with L1210. On the other hand, the % T/C values recorded for CDDP and CBDCA against L1210/DDP were lower than those obtained for SKI 2053R. Moreover, six mice were cured by the treatment with SKI 2053R, whereas no mouse was cured by the treatment with CDDP or CBDCA except for one mouse among the animals treated with CBDCA on the qd × 9 schedule. From these in vitro and in vivo results, we conclude that SKI 2053R may be active against CDDP-resistant tumors.

The mechanisms by which the lack of cross-resistance develops between SKI 2053R and CDDP are not yet clear. Although there is no direct evidence at present, we suspect that a new 1,3-dioxolane-4,5-bis(aminomethane) carrier ligand may be responsible for this lack of cross-resistance. In mice implanted with P388, all three drugs were active, but the intensity of activity was shown to be ranked in the order of SKI 2053R > CDDP > CBDCA. The antitumor activity of SKI 2053R against LL/2 was comparable on the q4d × 3 schedule but lower than those of CDDP and CBDCA on the qd × 9 schedule.

Since human tumor xenograft models have been used to predict the chemotherapeutic response of tumors in humans to anticancer agents [19], we investigated the antitumor activity of SKI 2053R against KATO III and WiDr. In the present study, although the parameters used to evaluate the antitumor activity, such as the time in days required for a

MTW of 1,000 mg as well as the MTW, RTG, and IR on day 35, were similar between the SKI 2053R-treated group and the CDDP-treated group, the former achieved more delayed growth and higher IR values than the latter against two human tumor xenografts.

Toxicology studies of SKI 2053R in mice, rats, and dogs have shown that it has a toxicity profile different from that of CDDP [9, 11, 13]. The results demonstrating that SKI 2053R has a resistance-circumventing activity against CDDP-resistant tumors, superior or comparable in vivo antitumor activity as compared with CDDP and CBDCA, and a toxicity profile different from that of CDDP strongly suggest that SKI 2053R is an attractive candidate for further development as a clinically useful anticancer drug. SKI 2053R is currently undergoing phase 1 clinical trials in Korea.

References

1. Burchenal JH, Kalaher K, O'Toole T, Chisholm J (1977) Lack of cross-resistance between certain platinum coordination compounds in mouse leukemia. Cancer Res 37: 3455
2. Calvert AH, Harland SJ, Newell DR, Siddik ZH, Jones AC, McElwain TJ, Raju S, Wiltshaw E, Smith IE, Baker JM, Peckham MJ, Harrap KR (1982) Early clinical studies with *cis*-diammine-1,1-cyclobutanedicarboxylate platinum(II). Cancer Chemother Pharmacol 9: 140
3. Carter SK (1984) Cisplatin – past, present and future. In: Hacker MP, Douple EB, Krakoff IH (eds) Platinum coordination complexes in cancer chemotherapy. Martinus Nijhoff, Boston, p 359
4. Durant JR (1980) Cisplatin: a clinical overview. In: Prestayko AW, Crooke ST, Carter SK (eds) Cisplatin, current status and new developments. Academic Press, New York, p 317
5. Eastman A, Illenye S (1984) Murine leukemia L1210 cell lines with different patterns of resistance to platinum coordination complexes. Cancer Treat Rep 68: 1189
6. Geran RI, Greenberg NH, McDonald MM, Schumacher AM, Abbott BJ (1972) Protocols for screening chemical agents and natural products against animal tumors and other biological systems. Cancer Chemother Rep 3: 1
7. Gore M, Fryatt I, Wiltshaw E, Dawson T, Robinson B, Calvert A (1989) Cisplatin/carboplatin cross-resistance in ovarian cancer. Br J Cancer 60: 767
8. Harrap KR (1985) Preclinical studies identifying carboplatin as a visible cisplatin alternative. Cancer Treat Rev 12 [Suppl A]: 21
9. Kang K-S, Shin D-J, Cho J-J, Kim H-O, Kim B-H, Lee Y-S (1992) Acute toxicity of *cis*-malonato[(4*R*,5*R*)-4, 5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2053R) in rats and mice. Korean J Toxicol 8: 205
10. Kim D-K, Kim G, Gam J, Cho Y-B, Kim H-T, Tai J-H, Kim KH, Hong W-S, Park J-G (1994) Synthesis and antitumor activity of a series of [2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) complexes. J Med Chem 37: 1471
11. Kim H-O, Kang K-S, Shin D-J, Cho J-J, Kim B-H, Seo K-W, Nam K-H, Lee Y-S (1992) Subacute toxicity of *cis*-malonato[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2053R) in rats. Korean J Toxicol 8: 217
12. Kracker AJ, Hoeschele JD, Elliott WL, Showalter HDH, Sercel AD (1992) Anticancer activity in murine and human tumor cell lines of bis(platinum) complexes incorporating straight-chain aliphatic diamine linker groups. J Med Chem 35: 4526
13. Lee Y-S, Kang K-S, Shin D-J, Cho J-J, Kim H-O, Kim B-H, Lim Y-K (1992) Subacute toxicity of *cis*-malonato[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2053R) in beagle dogs. Korean J Toxicol 8: 235
14. Loeher PJ, Einhorn LH (1984) Cisplatin. Ann Intern Med 100: 704
15. Mellish KJ, Kelland LR, Harrap KR (1993) In vitro platinum drug chemosensitivity of human cervical squamous cell carcinoma cell lines with intrinsic and acquired resistance to cisplatin. Br J Cancer 68: 240
16. Ozols RF, Ostechega Y, Myers CE, Young RC (1985) High-dose cisplatin in hypertonic saline in refractory ovarian cancer. J Clin Oncol 3: 1246
17. Rose WC, Schurig JE (1985) Preclinical antitumor and toxicologic profile of carboplatin. Cancer Treat Rev 12 [Suppl A]: 1
18. Scheithauer W, Clark GM, Salmon SE, Dorda W, Shoemaker RH, Von Hoff DD (1986) Model for estimation of clinically achievable plasma concentrations for investigational anticancer drugs in man. Cancer Treat Rep 70: 1379
19. Steel GG, Peckham MJ (1988) The therapeutic response of a variety of human tumor xenografts. In: Winograd B, Peckham MJ, Pinedo HM (eds) Human tumour xenografts in anticancer drug development. Springer, Berlin Heidelberg New York, p 3