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

Pharmacokinetics and antitumor activity of a new platinum compound, *cis*-malonato[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl- 1, 3-dioxolane]platinum(II), as determined by ex vivo pharmacodynamics

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Abstract The pharmacokinetics and ex vivo pharmacodynamics studies on *cis*-malonato[(4*R*,5*R*)-4,5-bis (aminomethyl)-2-isopropyl-1, 3-dioxolane]platinum(II) (SKI 2053R, NSC D644591), cisplatin (CDDP), and carboplatin (CBDCA) were performed in beagle dogs. Equitoxic doses of SKI 2053R, CDDP, and CBDCA (7.5, 2.5, and 15.0 mg/kg, respectively) were given by i.v. bolus to three beagle dogs in a randomized crossover study. Plasma samples were analyzed for platinum by flameless atomic absorption spectrophotometry. Plasma concentrations of total and ultrafiltrable platinum for the three drugs declined in a biexponential fashion. The mean area under the concentration-time curve ($AUC_{0\rightarrow\infty}$) determined for ultrafiltrable platinum derived from SKI 2053R, as an active component, was 7.72 ± 2.74 μg h ml^{-1} (mean ± SD), with an initial half-life of 0.37 ± 0.20 h, a terminal half-life of 2.19 ± 0.93 h, a total clearance of 16.83 ± 4.76 ml min^{-1} kg^{-1}, and a steady-state volume of distribution of 1.57 ± 0.30 l/kg. The ex vivo antitumor activity of SKI 2053R was assessed using the ultrafiltrable plasma against two human lung-adenocarcinoma cell lines (PC-9 and PC-14) and five stomach-adenocarcinoma cell lines (MKN-45, KATO III, SNU-1, SNU-5, and SNU-16) by tetrazolium-dye (MTT) assay and was compared with that of CDDP and CBDCA using an antitumor index (ATI) determined from the ex vivo pharmacodynamic results of inhibition rates (%) versus time curves. The mean ATI value was shown to be ranked in the following order: SKI 2053R > CBDCA > CDDP. The mean ATI values recorded for SKI 2053R and CBDCA were significantly ($P < 0.05$) higher than that noted for CDDP; however, no statistically significant difference was observed between SKI 2053R and CBDCA, suggesting that the antitumor activity of SKI 2053R is superior to that of CDDP and is equivalent to that of CBDCA. These results suggest that SKI 2053R is a promising candidate for further development as a clinically useful anticancer drug.

Key words SKI 2053R · Pharmacokinetics · Antitumor activity

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

J.-G. Park
Cancer Research Institute, College of Medicine, Seoul National University, 28, Yongon-Dong, Chongno-Ku, Seoul 110–744, 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 potent anticancer drugs and is a major component of combination chemotherapy for a variety of human cancers [13]. However, its clinical usefulness has frequently been limited by undesirable side effects such as severe renal toxicity, nausea and vomiting, ototoxicity, and neurotoxicity [1, 3] and by the development of resistance [16]. Therefore, extensive efforts have been made to develop new CDDP analogues with higher or equivalent antitumor activity and lower toxicity [6, 11, 14]. Among them, *cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin, CBDCA) is now the only commercially available platinum derivative for clinical use. CBDCA has modified the problems of the renal and gastrointestinal toxicities of CDDP [6, 18]. CBDCA, however, has no enhanced therapeutic efficacy over CDDP and does not possess the property to overcome cross-resistance to CDDP [4].

In an attempt to develop a new, more potent antitumor platinum drug, we have recently prepared a series of 2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane platinum(II) complexes [8]. 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 on the basis of its high in vitro and in vivo antitumor activity against a number of murine and human tumor cell lines, including CDDP-resistant L1210 leukemia [8, 9], as well as its low nephrotoxicity in mice, rats, and dogs [7, 10, 12] and its sufficient solubility and stability in aqueous solution [8].

Recently, Sasaki et al. [19] reported a pharmacodynamic model to predict the clinical response of anticancer platinum drugs using the data obtained from a bioassay based on their ex vivo pharmacodynamics. They demonstrated that the antitumor index (ATI) values determined by ex vivo pharmacodynamics in humans showed better correlation with the clinical response than did the areas under the plasma concentration-time curve (AUCs) obtained by chemical assay.

In the present study, we determined the pharmacokinetic characteristics of SKI 2053R in beagle dogs in comparison with CDDP and CBDCA after i.v. administration of equitoxic doses of the three drugs and also compared the antitumor activity of SKI 2053R with that of both CDDP and CBDCA by determining the in vitro inhibitory activity of the beagle dogs' ultrafiltrable plasma against two human non-small-cell lung-cancer cell lines (PC-9 and PC-14) and five human stomach-cancer cell lines (MKN-45, KATO III, SNU-1, SNU-5, and SNU-16) on the basis of ex vivo pharmacodynamics.

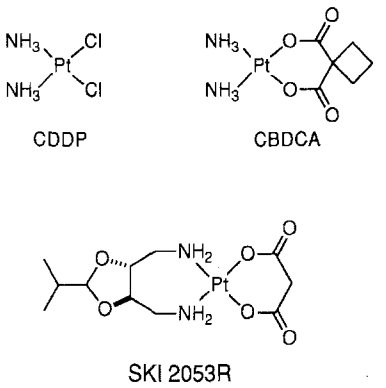

Fig. 1 Structures of SKI 2053R, CDDP, and CBDCA

Materials and methods

Cancer cells and animals

Two human lung-adenocarcinoma cell lines (PC-9 and PC-14) and five human stomach-adenocarcinoma cell lines (MKN-45, KATO III, SNU-1, SNU-5, and SNU-16) were used. PC-9, PC-14, MKN-45, and KATO III were kindly donated by Dr. N. Saijo, National Cancer Center Hospital, Japan. SNU-1, SNU-5, and SNU-16 were established at the Cancer Research Center, College of Medicine, Seoul National University, Korea [17], and were provided by Dr. J.-G. Park. All cell lines were propagated in RPMI-1640 medium (Gibco, Grand Island, N.Y.) supplemented with 10% heat-inactivated fetal bovine serum (Gibco), penicillin (100 units/ml), and streptomycin (100 μg/ml; RPMI-FCS) in a highly humidified incubator containing 5% CO_2 at 37°C. PC-9, PC-14, MKN-45, and SNU-16 grew as partially attached to the bottom of culture flask, and KATO III, SNU-1, and SNU-5 grew as suspension cultures. Male beagle dogs weighing 10–15 kg were purchased from Marshall Farms (USA).

Drug administration

SKI 2053R was synthesized at the Life Science Research Center of Sunkyong Industries, Korea, as previously described [8] (Fig. 1). CDDP and CBDCA were purchased from Sigma Chemical Co. (St. Louis, Mo., USA). The drugs were dissolved in sterile 0.9% NaCl solution just before experiments. A single dose of 7.5, 2.5, and 15.0 mg/kg of SKI 2053R, CDDP, and CBDCA dissolved in 0.9% NaCl solution, respectively, was given as a 3-min infusion to each dog in a volume of 3 ml/kg. Three beagle dogs were used in a randomized crossover study, which was performed three times, with a 4-week washout period for recovery being introduced between drug administrations. The delivered doses of SKI 2053R and CDDP were determined as the equitoxic doses in a previous toxicity study in beagle dogs [12], and the dose of CBDCA considered to be equitoxic to that of CDDP as based on their clinical doses [19] was employed. The preliminary toxicology study was performed to determine the levels of toxicity of the three drugs at the determined equitoxic doses in beagle dogs. Myelosuppression was the most common and severe toxicity for all three drugs: the percentage of the average maximal reductions in peripheral white blood cell and platelet counts, respectively, were 86.6 and 72.5 for SKI 2053R, 71.7 and 88.8 for CDDP, and 61.8 and 69.7 for CBDCA. Mild elevations of blood urea nitrogen, creatinine, glutamic oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) were observed for all three drugs, and slight body weight loss (approximately 11%) was observed in CDDP-treated beagle dogs only.

Blood–sample preparation

Blood was sampled from beagle dogs through an indwelling i.v. cannula placed in the cephalic vein into a heparin-containing syringe prior to drug administration and at 5, 10, 15, and 30 min as well as 1, 1.5, 2, 4, 6, 8, 12, and 24 h after the end of infusion. Plasma was immediately separated by centrifugation at 600 *g* for 10 min. As soon as plasma had been prepared, a part of it was passed through an Amicon CF 4104 filter (Amicon Corporation, Danvers, Mass., USA) by centrifugation at 1500 *g* for 20 min at 4°C to remove protein. The protein-free ultrafiltrates for platinum analysis and bioassay and aliquots of whole plasma for platinum analysis were stored at − 70°C until analysis.

Pharmacokinetic analysis

Total and ultrafiltrable platinum in plasma were quantitatively analyzed at 265.9 nm with a flameless atomic absorption spectrophotometer (Varian SpectrAA 300, Zeeman, USA). The detection limit of platinum was 0.02 μg/ml. The concentrations of total and ultrafiltrable platinum for the three drugs in plasma were best characterized by a biexponential decline; thus, a biexponential equation was fitted to the plasma platinum levels. The pharmacokinetic parameters calculated by a two-compartment model using the computer program RSTRIP were as follows; initial half-life ($t_{1/2}$ α), terminal half-life ($t_{1/2}$ β), total clearance (CL_T), area under the

plasma concentration-time curve from time 0 to 24 h ($AUC_{0\to 24}$) or extrapolated to infinity ($AUC_{0\to\infty}$), and steady-state volume of distribution (Vd_{ss}).

Antitumor activity test based on ex vivo pharmacodynamics

The in vitro antitumor activity of the ultrafiltrable plasma obtained from beagle dogs treated with equitoxic doses of the three platinum drugs was evaluated against seven human cancer cell lines by tetrazolium-dye (MTT) assay. In brief, single-cell suspensions were prepared by mechanical disaggregation for PC-9 and PC-14 and by treatment with trypsin and ethylenediamine tetraacetic acid (EDTA) followed by mechanical disaggregation for MKN-45, KATO III, SNU-1, SNU-5, and SNU-16. Seeding numbers and incubation periods were determined after confirmation of the linear relationship between the absorbance (optical density, OD) and number of cells plated in standard and the growth curve generated for each cell line. After viability was confirmed as being over 95% by trypan blue dye exclusion, cells were counted using a hemocytometer, diluted with RPMI-FCS, and plated in 96-well plates at final concentrations (135 µl/well) of 2.0×10^3, 2.5×10^3, 2.5×10^3, 2.5×10^3, 1.5×10^3, 1.5×10^3, and 1.0×10^3 cells/well for PC-9, PC-14, MKN-45, KATO III, SNU-1, SNU-5, and SNU-16, respectively. Cells were then treated with 15 µl of ultrafiltrable plasma of SKI 2053R, CDDP, and CBDCA sampled at each time point.

After incubation for 4 days at 37°C in a humidified incubator containing 5% CO_2, 15 µl of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma) dissolved in phosphate-buffered saline (5 mg/ml) was added to each well and the plates were incubated for an additional 4 h. To solubilize the formazan crystals that formed, 150 µl of acidified 2-propanol was added to each well and the contents of each well were subjected to repeated pipetting, about 20 times, resulting in good solubilization. The OD was measured at 540 nm using an enzyme-linked immunosorbent assay (ELISA) reader (Dynatech, MR 5000, USA). Each experiment was performed in triplicate and repeated three times. The inhibition rate (IR, expressed in percent) was calculated by the formula *[1–(mean OD in 3 test wells –OD in background well)/(mean OD in 3 control wells –OD in background well)] × 100.* The biological antitumor activity was determined in terms of the ATI, which was defined as the area under the IR versus time curve plotted from 0 to 120 min by bioassay and calculated by the trapezoidal rule.

Statistical analysis

Statistically significant 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.

Results

Pharmacokinetics of the platinum compounds

The concentration versus time curves generated for total and ultrafiltrable platinum in plasma obtained from beagle dogs receiving SKI 2053R, CDDP, and CBDCA are shown in Fig. 2. The pharmacokinetic parameters derived from these curves are presented in Table 1. The plasma concentration of total and ultrafiltrable platinum for the three drugs declined in a biexponential fashion. The binding of platinum to plasma protein at the initial phase, until 1 h after administration, was minimal to moderate for CBDCA (17%) and SKI 2053R (35%) but was great for CDDP (83%). In contrast to the initial phase, by 24 h postadministration the majority of the platinum for SKI 2053R (97%) and CBDCA (95%) was bound to plasma protein. The $t_{1/2}\ \alpha$ and $t_{1/2}\ \beta$ values recorded for ultrafiltrable platinum of SKI 2053R (mean ± SD) were

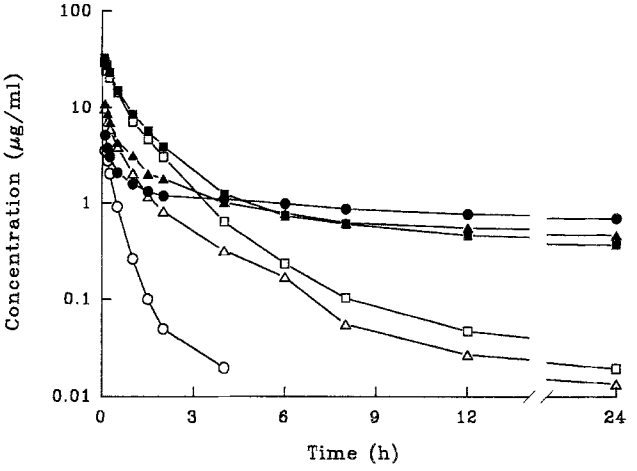

Fig. 2 Concentration versus time curves generated for total and ultrafiltrable platinum (Pt) in the plasma of beagle dogs given a single 3-min i.v. infusion of 7.5, 2.5, and 15.0 mg/kg of SKI 2053R, CDDP, and CBDCA, respectively. Each point represents the mean value for three independent crossover experiments (*Black triangles* total Pt of SKI 2053R, *white triangles* ultrafiltrable Pt of SKI 2053R, *black circles* total Pt of CDDP, *white circles* ultrafiltrable Pt of CDDP, *black squares* total Pt of CBDCA, *white squares* ultrafiltrable Pt of CBDCA)

Table 1 Pharmacokinetic parameters of total and ultrafiltrable platinum derived from SKI 2053R, CDDP, and CBDCA after i.v. administration of 7.5, 2.5, and 15.0 mg/kg, respectively, to dogs[a]

Drugs	Total platinum		Ultrafiltrable platinum				
	$t_{1/2}\alpha$ (h)	$AUC_{0\to 24}$ (µg h ml^{-1})	$t_{1/2}\alpha$ (h)	$t_{1/2}\beta$ (h)	CL_T (ml min^{-1} kg^{-1})	$AUC_{0\to\infty}$ (µg h ml^{-1})	Vd_{ss} (l/kg)
SKI 2053R	0.53 ± 0.10[b]	21.91 ± 8.25	0.37 ± 0.20	2.19 ± 0.93	16.83 ± 4.76	7.72 ± 2.74	1.57 ± 0.30
CDDP	0.28 ± 0.07	22.08 ± 3.27	0.22 ± 0.03	1.89 ± 0.51	25.96 ± 3.68	1.63 ± 0.21	1.06 ± 0.25
CBDCA	0.59 ± 0.23	39.68 ± 13.30	0.57 ± 0.19	2.39 ± 0.64	10.38 ± 3.27	25.17 ± 9.25	0.67 ± 0.06

[a] Three beagle dogs were used in a randomized crossover study
[b] Each value indicates the mean value ± SD for three independent experiments

0.37 ± 0.20 and 2.19 ± 0.93 h, respectively. The mean $AUC_{0\to\infty}$ values obtained for ultrafiltrable platinum of SKI 2053R, CDDP, and CBDCA were 7.72 ± 2.74, 1.63 ± 0.21, and 25.17 ± 9.25 μg h ml^{-1}, respectively. The mean CL_T of ultrafiltrable platinum of CDDP (25.96 ± 3.68 ml min^{-1} kg^{-1}) was higher than that of both SKI 2053R (16.83 ± 4.76 ml min^{-1} kg^{-1}) and CBDCA (10.38 ± 3.27 ml min^{-1} kg^{-1}) and, consequently, the $AUC_{0\to\infty}$ determined for ultrafiltrable platinum of CDDP was smaller than that obtained for either SKI 2053R or CBDCA. The mean Vd_{ss} values recorded for ultrafiltrable platinum of SKI 2053R, CDDP, and CBDCA were 1.57 ± 0.30, 1.06 ± 0.25, and 0.67 ± 0.06 l/kg, respectively.

Comparison of antitumor activity of the platinum compounds based on ex vivo pharmacodynamics

The antitumor activity of SKI 2053R was compared with that of CDDP and CBDCA using the ATI determined from the ex vivo pharmacodynamic results of IR versus time curves (Table 2). Figure 3 shows IRs found for the ultrafiltrable platinum of SKI 2053R, CDDP, and CBDCA in plasma from 0 to 120 min after drug administration. Maximal IRs for the three drugs were observed after 5 min in all cancer cell lines tested except for PC-14 and were shown to be ranked in the following order: CDDP > SKI 2053R > CBDCA in the two lung-cancer cell lines and SKI 2053R > CDDP > CBDCA in the five stomach-cancer cell lines. The IR of CDDP decreased rapidly as compared with that of both SKI 2053R and CBDCA; consequently, the antitumor activity of CDDP was not detected after 120 min against all seven cancer cell lines. The mean ATI value noted for SKI 2053R was 2.3- and 1.5-fold higher than those obtained for CDDP and CBDCA, respectively, and the mean ATI values recorded for SKI 2053R and CBDCA were significantly ($P < 0.05$) higher than that found for CDDP; however, no statistically signifcant difference was observed between SKI 2053R and CBDCA. SKI 2053R showed the highest ATI value against SNU-5 cells, which was 4.5-fold higher than that of CDDP.

Table 2 Comparison of the antitumor activity of SKI 2053R, CDDP, and CBDCA against seven human cancer cell lines by ATI[a]

Cell line	ATI[b]		
	SKI 2053R	CDDP	CBDCA
PC-9[c]	1521	1274	1778
PC-14[c]	3640	2411	3099
MKN-45[d]	3753	1379	2173
KATO III[d]	3190	1601	1861
SNU-1[d]	2673	1692	2280
SNU-5[d]	7343	1647	3964
SNU-16[d]	4563	1376	2462
Mean ±SD	3812 ± 1826*	1626 ± 381	2517 ± 773*

* Significantly different from the value obtained for CDDP ($P < 0.05$)

[a] Comparison of the antitumor activity of ultrafiltrable plasma obtained from beagle dogs treated with 7.5, 2.5, and 15.0 mg/kg of SKI 2053R, CDDP, and CBDCA, respectively, was made using ATI, which was defined as the area under the % IR versus time curve plotted from 0 to 120 min as obtained by ex vivo pharmacodynamic assay and was calculated by the trapezoidal rule

[b] Each value indicates the mean value for three independent crossover experiments

[c] Human non-small-cell lung cancer cells

[d] Human stomach-cancer cells

Discussion

This study was designed to characterize the pharmacokinetics and determine the antitumor activity of SKI 2053R using ex vivo pharmacodynamics in comparison with that of CDDP and CBDCA. The pharmacokinetics of platinum complexes concerns ultrafiltrable platinum as well as total platinum. Ultrafiltrable platinum, being the parent compound and non-protein-bound metabolites, has been considered to be the biologically active platinum species with antitumor and toxic properties [2, 5].

The plasma levels of total and ultrafiltrable platinum measured for the three drugs declined very rapidly in the α-phase, the order of rapidity being CDDP > SKI 2053R > CBDCA. The initial half-lives of total and ultrafiltrable platinum recorded for each drug were shown to be similar. This result indicates that the elimination of total platinum in the α-phase is mostly associated with the fate of ultrafiltrable platinum. The long terminal half-life of total platinum derived from SKI 2053R is also comparable with that of both CDDP and CBDCA, probably due to the drugs' common property of irreversible binding of platinum to plasma protein [20].

The plasma clearance observed for ultrafiltrable platinum of SKI 2053R was higher than that seen for CBDCA but was lower than that noted for CDDP. Therefore, the $AUC_{0\to\infty}$ values calculated for ultrafiltrable platinum of the three drugs were ranked in the following order: CBDCA > SKI 2053R > CDDP. The high $AUC_{0\to\infty}$ value obtained for total platinum of CDDP could be explained by the high extent of plasma protein binding, even though a lower dose of CDDP was given as compared with those of SKI 2053R and CBDCA.

For evaluation of the antitumor activity of new compounds under investigational status, a number of in vitro and in vivo test systems have been developed. These evaluation systems, however, have some limitations in predicting the clinical antitumor activity. When an antitumor drug is given to humans, the response to the drug is thought to be influenced by two major

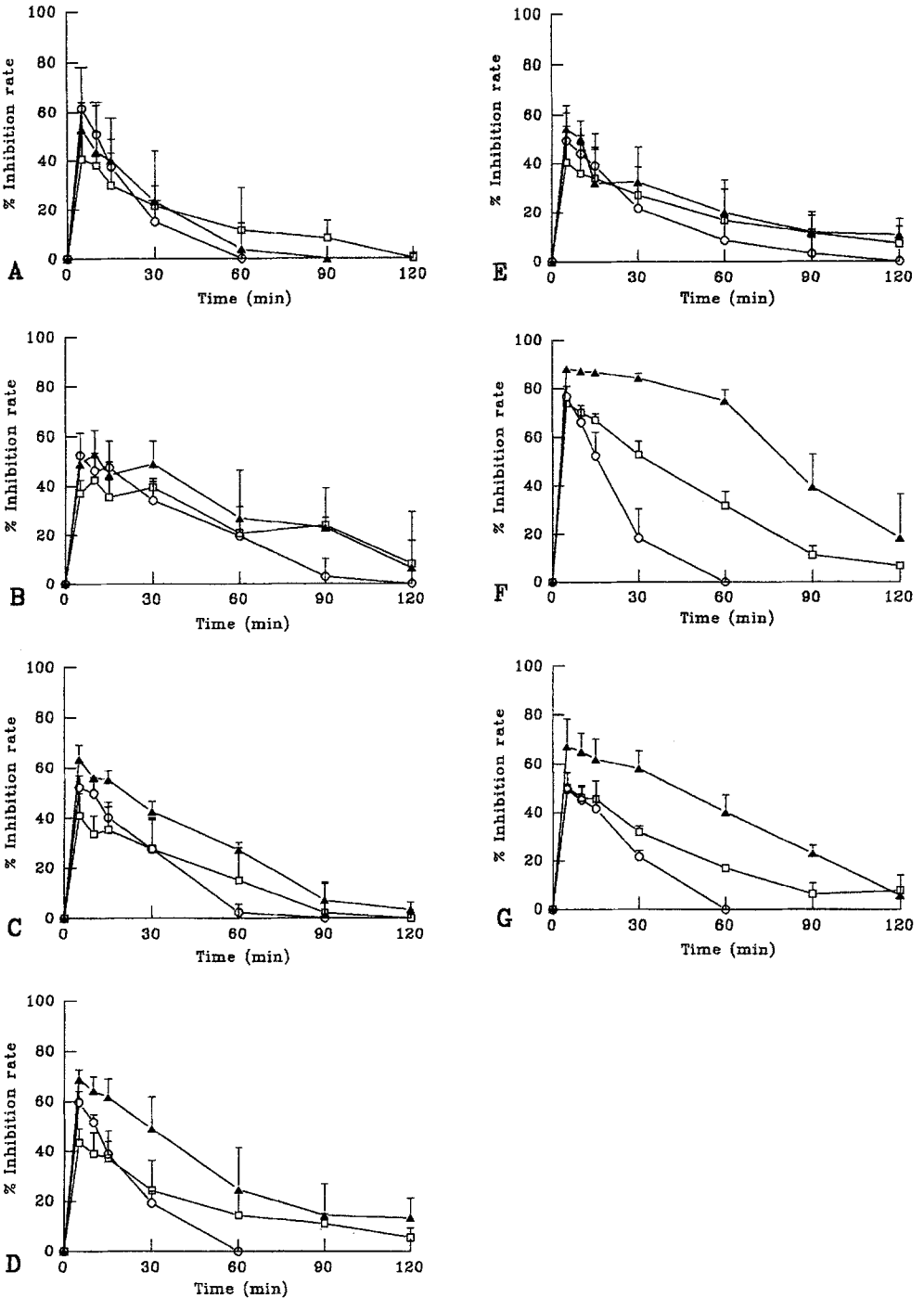

Fig. 3A–G Comparison of the antitumor activity of ultrafiltrable plasma obtained from beagle dogs treated with SKI 2053R (7.5 mg/kg, *black triangles*), CDDP (2.5 mg/kg, *white circles*), and CBDCA (15.0 mg/kg, *white squares*), respectively, as determined by ex vivo pharmacodynamic assay. Human lung-cancer cell lines PC-9 (**A**) and PC-14 (**B**) and human stomach-cancer cell lines KATO III (**C**), MKN-45 (**D**), SNU-1 (**E**), SNU-5 (**F**), and SNU-16 (**G**) were used as target cells. Each point represents the mean value ± SD for three independent crossover experiments

factors: one is the amount of the active form of the drug in vivo, which is usually determined by its concentration and duration, and the other is the sensitivity of tumor cells to the drug. Concerning platinum-based anticancer drugs, the AUC of the active form, ultrafiltrable platinum, is regarded as a major determinant of the antitumor activity.

There has been a discrepancy between in vitro chemosensitivity and clinical response, which is usually caused by differenes in the pharmacokinetic behavior of the drugs. Therefore, it is not suitable to compare the 50% inhibitory concentrations (IC_{50} values) obtained from the in vitro chemosensitivity test to predict the clinical response directly. We have thought it desirable to predict the clinical response of new antitumor compounds in the preclinical stage with reliable parameters. Therefore, in this study the antitumor activity of SKI 2053R was investigated according to the concept described by Sasaki et al. [19] and was compared with that of CDDP and CBDCA.

In a previous study [8], the in vitro cytotoxicity of SKI 2053R against the above mentioned seven human

cancer cell lines was about 2.5 times lower than that of CDDP and was 4.9 times higher than that of CBDCA; the mean IC_{50} values obtained for SKI 2053R, CDDP, and CBDCA were 3.59 ± 2.89, 1.45 ± 0.99, and 17.75 ± 13.17 μg/ml, respectively. However, in contrast to the in vitro cytotoxicity, the mean ATI value recorded for SKI 2053R against seven human cancer cell lines was significantly higher than that observed for CDDP in this study.

Since the clinically achievable dose of CDDP can be increased if CDDP is given with pre- and posthydration [15], we do not exclude the possibility that, given the condition of employing a dose determined in beagle dogs without such modifications, the antitumor activity of CDDP predicted in this study from the ATI value might be estimated to be lower than the actual activity. Considering the previous report [19] that the ATI values determined by ex vivo pharmacodynamics in humans showed a good correlation with the clinical response, the high mean ATI value recorded for SKI 2053R in this study suggests that this drug would show encouraging antitumor activity and pharmacokinetic behavior in a clinical study. These results suggest that SKI 2053R is a promising new anticancer drug for further clinical evaluation.

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