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Pharmacokinetics of (glycolato-0,0′)-diammine platinum(II), a new platinum derivative, in comparison with cisplatin and carboplatin

Yasutsuna Sasaki[1], Tomohide Tamura[1], Kenji Eguchi[1], Tetsu Shinkai[1], Yasuhiro Fujiwara[1], Masaaki Fukuda[1], Yuichiro Ohe[1], Masami Bungo[2], Naoya Horichi[2], Shigeki Niimi[2], Koichi Minato[2], Kazuhiko Nakagawa[2], and Nagahiro Saijo[1]

National Cancer Center, [1]Department of Medical Oncology and [2]Pharmacology Division[2], 1-1, Tsukiji 5-Chome, Chuo-Ku, Tokyo 104, Japan

Summary. The pharmacokinetics of (glycolato-0,0′)-diammine platinum(II) (254-S; NSC 375101D), one of the new platinum analogues, was examined in a phase I study of this drug and compared with that of cisplatin and carboplatin. All drugs were given in short-term (30-min) i.v. drip infusions; the doses of 254-S, cisplatin, and carboplatin were 100, 80, and 450 mg/m^2, respectively. Platinum concentrations in whole plasma, plasma ultrafiltrate, and urine were determined by atomic absorption spectrometry. After the infusion, the plasma concentration of total platinum for the three agents decayed biphasically. Ultrafilterable platinum in plasma decreased in a biexponential mode after infusions of 254-S and carboplatin, whereas the free platinum of cisplatin showed a monoexponential disappearance. The peak plasma concentrations and AUC for free platinum were 5.31 μg/ml and 959 μg/min per ml for 254-S, 3.09 μg/ml and 208 μg/min per ml for cisplatin, and 19.90 μg/ml and 3446 μg/min per ml for carboplatin, respectively. The mean ratio of plasma ultrafilterable platinum to total platinum were calculated, and the results showed that the protein-binding abilities of 254-S and carboplatin were almost identical. More than 50% of the 254-S was excreted in the urine within the first 480 min after its administration. Thrombocytopenia was reported as a dose-limiting toxicity for both 254-S and carboplatin. This similarity in side effects may mainly be due to the comparable pharmacokinetic behavior of these two platinum compounds.

Introduction

During the 1970s, *cis*-diamminedichloroplatinum(II), (cisplatin; CDDP) was clinically established as a drug with broad use for the treatment of cancer [8, 9], in particular testicular [1, 2, 5], ovarian [18, 19], lung [3, 11], and bladder cancers [13, 20]. However its serious dose-limiting toxicities include, considerable renal toxicity, marked emesis, and neurotoxicity, especially hearing loss and peripheral neuropathy, although bone marrow toxicity is mild.

To find a platinum compound with less toxicity, a large number of platinum complexes have been synthesized and tested for antitumor activity. *cis*-Diammine-1,1-cyclobutane dicarboxylate platinum(II) (JM8 carboplatin; CBDCA) [4, 17] and (glycolato-0,0′)-diammine platinum(II) (NSC 375101D; 254-S) [12] are second-generation platinum-coordination complexes that show less nephrotoxicity and retain antitumor activity in animal models (Fig. 1). Carboplatin has been shown to be active against a variety of experimental tumors, including P388 and L1210 leukemia, B16 melanoma, and colon 26 carcinoma [4, 17]. 254-S, which was developed by Shionogi Pharmaceutical Company (Osaka, Japan), also exhibited superior anticancer activity against P388 leukemia, colon tumor 38, Lewis lung tumor, B16 melanoma, Walker 256 carcinosarcoma, MX-1 breast tumor, and Burkitt's lymphoma (DAUDI) in preclinical studies [12].

The pharmacokinetic study of new agents during phase I or II clinical trials is essential to the design of an optimal therapeutic protocol for further clinical use. In this study, the clinical pharmacokinetics of 254-S in plasma and urine was investigated and compared with that of cisplatin and carboplatin.

Patients and methods

Patients and materials. A total of 15 patients were entered in the study, and 5 patients each were given cisplatin, carboplatin, or 254-S. To be eligible for this study, patients must either have failed to respond to conventional chemotherapy or have received no prior conventional chemotherapy; none of the patients had previously received platinum compounds. The performance status of all patients was 0, 1, or 2 on the Eastern Cooperative Oncology Group

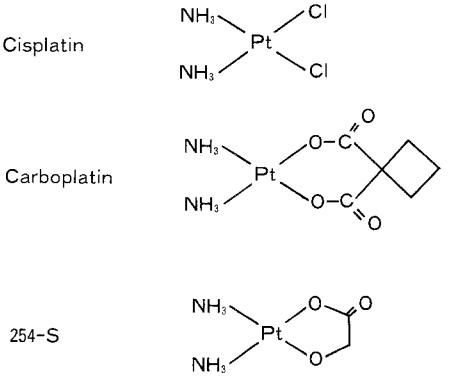

Fig. 1. Structures of cisplatin, carboplatin, and 254-S

Offprint requests to: Yasutsuna Sasaki

scale. All patients had adequate bone marrow function (WBC count of >3000 cells/μl and platelet count of >100,000/μl), liver function (bilirubin level of <2.0 mg/dl), and renal function (serum creatinine level of <1.5 mg/ml). Informed consent was obtained from all patients before treatment.

Either 100 mg/m^2 254-S, 80 mg/m^2 cisplatin, or 450 mg/m^2 carboplatin was given in 150 ml 5% glucose solution to each of five patients by i.v. drip infusion over 30 min. The dose of 254-S was that recommended for a phase II study, and those of cisplatin and carboplatin were standard doses in clinical use. The patients who received cisplatin were also given 3000 ml electrolyte-containing solution as well as antiemetic and diuretic agents before and after administration of the drug. Cisplatin and carboplatin were obtained from Bristol-Meyers Company (Tokyo, Japan) and 254-S, an investigational agent, was supplied by the Shionogi Pharmaceutical Company.

Sampling and analysis. An indwelling i.v. cannula was placed in the patient's arm opposite that receiving the drug. Blood samples were obtained before and just after the end of the drug infusion and at 5, 15, 30, 60, 120, 240, and 480 min after the infusion. Blood was collected in a heparin-containing syringe, and plasma was immediately separated by centrifugation at 600 *g* for 10 min. Part of the plasma was immediately passed through an Amicon CF 25 filter (cutoff, 25,000 daltons; Amicon Corporation, Danvers, Mass, USA) by centrifugation at 2000 *g* for 15 min at 4° C to remove protein. Both the ultrafiltered protein-free plasma and whole plasma were then stored at −70° C until analysis. Urine samples were collected at the time of voiding and stored at −20° C as pooled 4-h collections. Platinum concentrations in plasma (total platinum), plasma ultrafiltrate (free platinum), and urine were determined with a Hitachi (Tokyo) model 170-50A flameless atomic absorption spectrometer as previously reported [6, 15].

Pharmacokinetic data analysis. After the infusion, a biexponential equation of the form

$$C = Ae^{-\alpha t} + Be^{-\beta t},$$

where C is the concentration at time t and A, B and α, β are the concentration and rate constants, respectively, was fitted to all plasma platinum levels except the plasma free-platinum level for cisplatin using a computerized non-linear least-squares technique by the computer program APAS (Automated Pharmacokinetic Analysis System of Yamaoka, Nankodo, Tokyo). A monoexponential equation was applied to the protein free-platinum level in plasma for cisplatin. Concentration times the time (C × T) for the curve of platinum in plasma was estimated by calculating AUC; AUCs were determined from the computer-generated fit and corrected for the period of the infusion (0–30 min) by the trapezoidal rule.

Results

Pharmacokinetics of the platinum analogues

After the infusion, the plasma concentrations of total platinum for the three agents declined in a biexponential fashion. The alpha and beta half-lives of cisplatin, carboplatin, and 254-S were 31 and 2880, 57 and 840, and 43 and 768 min, respectively (Fig. 2 and Table 1). As expected, the peak plasma concentration was highest for carboplatin,

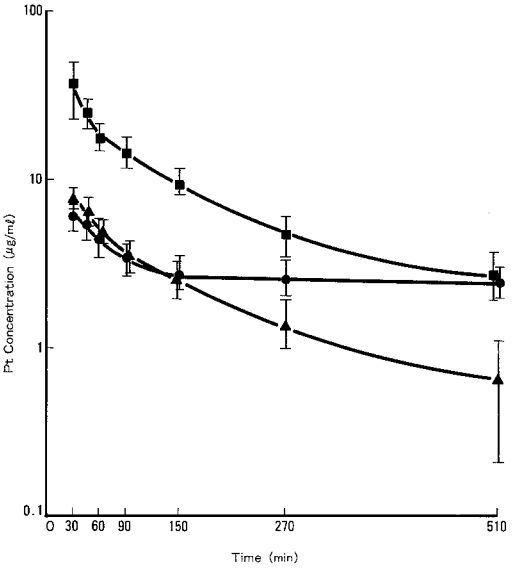

Fig. 2. Plasma level of total platinum in five patients treated with 80 mg/m^2 cisplatin (●), 450 mg/m^2 carboplatin (■), or 100 mg/m^2 254-S (▲). Each drug was given in a 30-min drip infusion. The points represent means ± SD of five patients

Table 1. Pharmacokinetic parameters of total platinum in plasma of patients treated with platinum compounds

Drug	Dose (mg/m^2)	A (μg/ml)	α (min^{-1})	$T_{1/2\alpha}$ (min)	B (μg/ml)	β (min^{-1})	$T_{1/2\beta}$ (min)	AUC (μg/min per ml)
Cisplatin	80	3.62	0.024	31	2.46	0.0002	2880	1545
Carboplatin	450	24.67	0.050	57	10.50	0.0036	840	4337
254-S	100	5.31	0.035	43	2.38	0.0041	768	1144

Table 2. Pharmacokinetic parameters of ultrafilterable platinum in plasma of patients treated with platinum compounds

Drug	Dose (mg/m^2)	A (μg/ml)	α (min^{-1})	$T_{1/2\alpha}$ (min)	B (μg/ml)	β (min^{-1})	$T_{1/2\beta}$ (min)	AUC (μg/min per ml)
Cisplatin	80	3.09	0.021	33	–	–	–	208
Carboplatin	450	19.90	0.018	34	7.78	0.0047	145	3446
254-S	100	5.31	0.035	43	2.38	0.0041	261	959

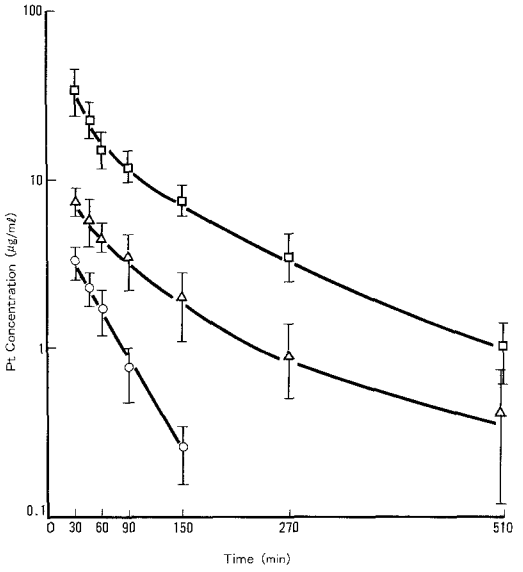

Fig. 3. Plasma level of free platinum in five patients treated with 80 mg/m^2 cisplatin (○), 450 mg/m^2 carboplatin (□), or 100 mg/m^2 254-S (△). Each drug was given in a 30-min drip infusion. The points represent means ± SD of five patients

followed by 254-S and cisplatin. However, although 254-S had a higher peak plasma concentration than cisplatin, the AUC of the latter was higher because of the longer $t_{1/2\beta}$ of cisplatin.

The plasma concentration of ultrafilterable platinum declined in a biexponential mode after the infusion of carboplatin and 254-S, whereas the free platinum level of cisplatin fit a monoexponential equation by the APAS system, as reported in the previous section (Fig. 3 and Table 2). The peak plasma concentrations and AUCs of free platinum as an active component were 19.90 and 3446 for carboplatin, 5.31 and 959 for 254-S, and 3.09 μg/ml

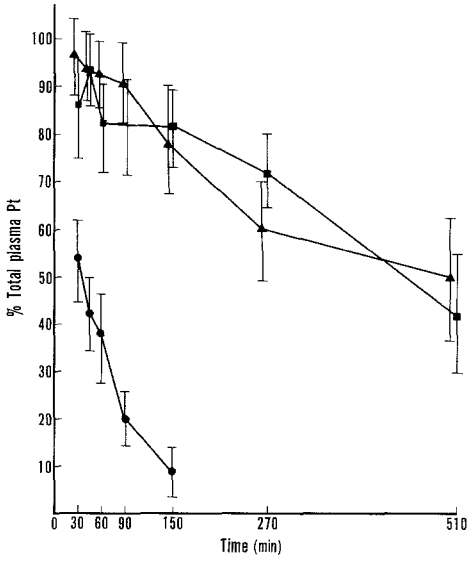

Fig. 4. Percentage of plasma platinum that was ultrafilterable in five patients treated with 80 mg/m^2 cisplatin (●), 450 mg/m^2 carboplatin (■), or 100 mg/m^2 254-S (▲). Each drug was given in a 30-min drip infusion. The points represent means ± SD of five patients

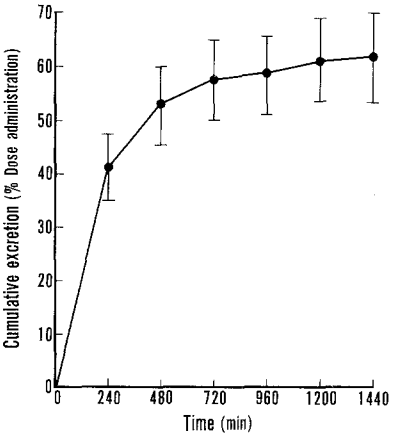

Fig. 5. Urinary excretion of platinum by patients given 100 mg/m^2 254-S. All urine voided by the patients was collected and stored as pooled 4-h specimens. The points represent means ± SD of five courses of 254-S therapy given to five patients

and 208 μg/min per ml for cisplatin, respectively. However, it is difficult to compare the clinical anticancer activity of these three platinum compounds from their AUC values and peak plasma concentrations.

The mean ratios of plasma ultrafilterable-to-total platinum are presented in Fig. 4, which shows that the free form of platinum disappeared around 150 min after the infusion of cisplatin. However, the protein-binding abilities of carboplatin and 254-S were almost the same in vivo, and the levels of free platinum were almost 50% for carboplatin and 254-S, even 510 min after the infusion.

The kidney was the major platinum excretion route in patients receiving 254-S, with more than 50% eliminated within the first 480 min after administration of the drug. By 1440 min, 59.6% ± 9.4% of the infused platinum had been excreted in the urine (Fig. 5).

Discussion

The results of this pharmacological analysis of platinum compounds show that the pharmacokinetic behavior of 254-S is similar to that of carboplatin, which in turn is strikingly different from that of cisplatin. Regardless of the different peak plasma concentrations of the two analogues, the free as well as protein-bound platinum infused as 254-S or as carboplatin showed similar biexponential disappearance. The pharmacological differences between 254-S or carboplatin and cisplatin reflect the differences in binding to plasma protein. Cisplatin easily binds with serum protein, with the result that a smaller percentage of platinum is excreted in the urine after cisplatin infusion than in the case of 254-S or carboplatin. The present analysis shows that more than 50% of the 254-S platinum was excreted in the urine within 8 h after drug infusion. Although urinary excretion data for carboplatin was not available in this study, the percentage of urinary excretion of 254-S was very similar to that of carboplatin, which has previously been reported [16]. The dose-limiting toxicity of 254-S was myelosuppression, especially thrombocytopenia, and its gastrointestinal toxicity was milder than that induced by cisplatin. No renal toxicity was observed with 254-S despite the absence of hydration. The adverse effects induced by 254-S were similar to those induced by carbo-

platin, which may be reflected by the same pharmacokinetic patterns in plasma for 254-S and carboplatin. No patient with impaired renal function was entered in the present study, but when 254-S is given to patients with decreased renal plasma flow, the retention of free platinum and AUC level increase, which may induce severe thrombocytopenia [10, 14]. Pharmacokinetics as well as side effects of 254-S must also be studied in patients with impaired renal function.

The clinical antitumor activity of 254-S has not been compared with that of cisplatin and carboplatin. Shiratori and co-workers compared 254-S and cisplatin using chemotherapeutic index values. They demonstrated that 254-S had stronger antineoplastic activity than cisplatin against i.p. implanted P388 leukemia and B16 melanoma and s.c. implanted colon tumor 38, Lewis lung tumor, MX-1 breast cancer, DAUDI, and Walker 256 carcinosarcoma [12]. We have compared the cytotoxic effects of 254-S, cisplatin, and carboplatin against five human non-small-cell lung-cancer cell lines by continuous exposure to the same drug concentration in an in vitro colony assay. The results showed that 254-S had the same or a little less anticancer activity than cisplatin but 5–10 times stronger activity than carboplatin after the cells were exposed continuously to each drug and their IC_{50} values were compared [10]. The present study showed that the AUC values of free platinum for 254-S and carboplatin were 959 and 3446 μg/min per ml, respectively, that is, and AUC value for carboplatin 4 times higher than that for 254-S, although the potential anticancer activity of the former at the same concentration is lower than that of 254-S. These findings show that clinical phase II and III studies must be conducted to evaluate the clinical usefulness of 254-S compared with that of cisplatin and other platinum derivatives.

As yet, no administration method for 254-S other than i.v. drip infusion has been reported, whereas daily i.v. bolus carboplatin-administration trials [7] and continuous-infusion studies of cisplatin have been carried out. On the basis of pharmacological analysis, daily administration or continuous i.v. drip infusion are also warranted for 254-S because of the longer retention of the active form of this drug. Further pharmacological and clinical evaluation of 254-S in combination with other anticancer agents should also be conducted.

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