Phase I Study and Pharmacological Analysis of cis-Diammine(glycolato)platinum (254-S; NSC 375101D) Administered by 5-Day Continuous Intravenous Infusion

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ABSTRACT

A phase I study of cis-diammine(glycolato)platinum (254-S; NSC 375101D) was conducted in 15 patients with refractory or relapsing malignancy by 5-day continuous i.v. infusion. Three to 5 patients per dose were given 50, 75, 87.5, or 100 mg/m²/120 h (10-20 mg/m² daily for 5 days). Toxicity evaluation and pharmacokinetic analysis were performed in 15 and 14 patients, respectively. Thrombocytopenia and neutropenia were the dose-limiting toxicities at the maximum tolerated dose of 87.5 mg/m²/120 h (17.5 mg/m²/day); however, nonhematological toxicities including renal toxicity, nausea and vomiting, and peripheral neuropathy were mild and well tolerated. The nadir of platelets and neutrophils was observed 4 and 5 weeks, respectively, after the initiation of drug infusion. Plasma and urine samples were obtained during and after infusion for quantification by atomic absorption spectrophotometry of total and free platinum levels derived from 254-S. The maximum level of total platinum was obtained after 120 h of infusion, whereas the steady state concentration of free platinum in the patients given 75 mg/m² or more was over 0.1 μg/ml. Free platinum levels declined monophasically, with half-lives of 0.65-2.56 h/100 mg/m² dose. The mean area under the concentration versus time curve (AUC) in the patients treated with 75 mg/m² was 1069 μg/ml min, which was similar to that obtained in the patients receiving 100 mg/m² of 254-S by i.v. drip infusion over 30 min. There was a direct correlation between the dose administered and the AUC of platinum (R = 0.757, P = 0.002) or the steady state plasma concentration of free platinum (R = 0.763, P = 0.002). The percentage of platinum excreted in urine 144 h after the initiation of infusion ranged from 73.1 to 100% for each dose level. No significant relationship was established between creatinine clearance in patients before treatment and the AUC or steady state concentration of free platinum. The plasma platinum AUC showed a linear correlation with the percentage of change in leukocytes

100 × Pretreatment count − nadir Pretreatment count

(R = 0.736, P = 0.003). In conclusion, the recommended phase II dose for a continuous infusion of 254-S is 75.5 mg/m²/120 h every 6 weeks.

INTRODUCTION

cis-Diaminedichloroplutnum(II) (cisplatin) is one of the key drugs in the treatment of solid tumor such as germ cell of the testis, ovarian cancer, bladder cancer, head and neck cancer, and lung cancer (1-9). Various toxicities, however, including gastrointestinal toxicity, renal toxicity, neurotoxicity, and cumulative myelosuppression, are sometimes dose limiting in its clinical use. Among several methods which have been developed to prevent such toxicities, continuous infusion of cisplatin can not only reduce the incidence of renal injury but also elevate the AUC (10-13). In addition, in vitro studies show that prolonged exposure of human lymphoma cells to a low concentration of cisplatin can result in a killing effect similar to that obtained by short-time exposure to a concentration 10-fold greater (14). Although a definite conclusion has not been reached, recent clinical trials indicate promising anticancer activity of cisplatin when a continuous regimen is used (12, 13).

Various derivatives of platinum compounds such as carboplatin have been produced in order not only to reduce the adverse effect but also to increase the antitumor effect. 254-S, as one of the second-generation platinum coordination compounds, showed less nephrotoxicity and retained better activity against a variety of cancer cell lines than cisplatin in preclinical studies (15, 16). In addition, the pharmacokinetic behavior of 254-S is strikingly different from that of cisplatin. Cisplatin easily binds to serum protein, with the result that a smaller percentage of unbound platinum with anticancer activity is detected in the serum of patients treated with cisplatin. In the case of 254-S, however, almost 80% of the platinum was detected as the free form and the AUC of the free platinum was larger than that in the case of cisplatin, when the agents were administered as an i.v. drip infusion (17). These pharmacokinetic characteristics were almost the same as those for carboplatin (17).

On the other hand, we previously reported that the IC50 was influenced by prolonged drug exposure (18). The IC50 after 24 h exposure to 254-S was decreased from one-tenth to one-hundredth, of the IC50 observed within 1 h depending upon the cell line. From these observations, a clinical phase I trial by 5 days CI was conducted in order not only to determine the MTD but also to determine the pharmacokinetic and pharmacodynamic relationship in this administration schedule. The pharmacological differences among cisplatin, carboplatin, and 254-S are discussed.

MATERIALS AND METHODS

Patients. Fifteen patients were entered in this phase I study. All patients had to have histological or cytological evidence of advanced malignancy for which routine treatments were not or had not been effective. Patient requirements included: (a) life expectancy of at least 8 weeks; (b) age of 21-70 years; (c) performance status by the ECOG criteria (19) of 2 or better; (d) no major surgery within 14 days and no radiotherapy or chemotherapy within 28 days of the beginning of treatment; (e) adequate bone marrow function (WBC of 4,000/μl, platelet count of 100,000/μl, hemoglobin of > 11.0 g/100 ml), renal...
emission spectrometry according to the previously published method.

No antiemetic agents were given on days 1–7. No antiemetic agents were given before or during chemotherapy except if the patient experienced gastrointestinal toxicity over grade 3 in the ECOG criteria (19).

During the course of this phase 1 study, each patient received one dose level of continuous 5-day infusion of 254-S and the total dose of 254-S ranged from 50 to 100 mg/m². The starting dose was 10 mg/m²/day (50 mg/m²/course, which is the 50% dose for phase II study of i.v. bolus infusion of 254-S) (17, 20). Three to five patients received each dose level. The first three patients received the lowest dose, the next group the next dose, etc. There was no dose escalation in any of each patient. The MTD was defined as the dose at which 50% grade 3 and/or 20% grade 4 toxicity was observed.

Study Parameters. Toxicity was evaluated on the basis of the ECOG criteria (19) and clinical toxicity was carefully monitored by daily interviews and examinations throughout the study. The patients were evaluated for toxicity at least 6 weeks after administration of the drug. The ECOG criteria were also used for evaluating the tumor response (19). Briefly, complete response was defined as a disappearance of all evidence of the tumor for at least 4 weeks, partial response was defined as decrease by at least 50% in the sum of the products of the longest perpendicular diameters of all measurable lesions; no change meant a decrease within 50% or an increase of less than 25% in any measurable lesions; progressive disease was defined as an increase of more than 25%. Appearance of a new lesion in any other response category was also considered as progressive disease. If clinical response was obtained during the phase I study, the patient was allowed to receive further courses of CI of 254-S at the same dose level as the initial treatment.

Sample Collection and Preparation. Blood samples for the pharmacokinetic evaluation of CI of 254-S were drawn in heparinized tubes at 0 (just before administration), 3, 6, 12, 24, 48, 72, 96, and 120 h using centrifugation at 1500 x g for 15 min and plasma ultrafiltrates were prepared by centrifugation of the plasma at 1500 x g for 30 min in CF 25 Centriflow membrane cones (Amicon Corp., Danvers, MA) at 1°C. All plasma, plasma ultrafiltrate, and urine samples were stored at -70°C until analyzed.

Analytical Procedures. Plasma samples were diluted 5-fold with distilled water, whereas the filtrate portions were tested without dilution. These samples were analyzed directly at 265.9 nm in a Hitachi Z8000 Polarized Zeeman atomic absorption spectrophotometer (Hitachi, Ltd., Tokyo, Japan) as described previously (21). Calibration standards (0.0, 0.5, 1.0, 1.5, 2.0 μg of platinum/ml) were made up in normal saline and these standards were also diluted with distilled water. The limits of detection of platinum in unfiltered plasma and the filtrate portion were 0.1 and 0.002 μg of platinum/ml, respectively.

Urine samples were analyzed by inductively coupled plasma atomic emission spectrometry according to the previously published method.

Briefly, 1 ml of urine was put into a 5-ml volumetric flask; then 0.5 ml of yttrium solution (20 μg of yttrium/ml) as an internal standard was added, and the mixture was diluted by adding distilled water to the mark. Standard solutions of platinum and yttrium were individually diluted with distilled water from atomic absorption standard solutions containing 1000 μg of platinum or yttrium/ml. The emission intensities of platinum and yttrium in standard and sample solutions were measured simultaneously at analytical lines of platinum 214.423 nm and yttrium 371.029 nm, respectively, by means of main and reference monochromators under operational conditions by a Shimadzu ICPS-1000 sequential scanning spectrometer (Shimadzu, Kyoto, Japan). Platinum concentrations were obtained from a calibration curve. The limit of detection for urine samples was 0.5 μg of platinum/ml.

Pharmacokinetic Analysis. The plasma concentrations of total and free platinum were determined by the noncompartmental method. The natural logarithms of the filterable platinum concentration versus time data from the postinfusion phase were fitted to a single-kinetic elimination term by a linear least squares method by the computer program MULTI (23). The steady state plasma level of free platinum (C(f)) was calculated as the mean concentration of C24, C48, C72, C96, and C120 which represent the plasma concentration of free platinum at 24, 48, 72, 96, and 120 h during infusion of 254-S, respectively. The volume of distribution at steady state (V(d)) was determined by the administered platinum dose of 254-S within first 24 h divided by C(f). The AUC was calculated by the trapezoidal method, and the systemic clearance (Cl) was calculated from the relationship Cl = dose/AUC. Renal clearance for 254-S (Clr) was calculated from the product of each total clearance term by the fraction of the 254-S dose excreted unchanged in the urine. Nonrenal clearance of the drug (Cl(n)) was the difference between the corresponding total clearance and renal clearance. All pharmacokinetic and toxicity data were obtained from the first course of chemotherapy.

Results

Patien Characteristics. Fifteen patients were enrolled in this study and received 15 courses of CI 254-S. The dose was increased in 4 steps from the entry dose of 50 mg/m² to a maximum dose of 100 mg/m² (Table 1). Most of the patients were in good performance status. Inadequate blood sampling was performed in one patient. A total of 15 courses were evaluable for toxicity and 14 courses were examined for pharmacokinetics and a pharmacokinetic pharmacodynamic relationship. None of the patients had non-small cell lung cancer and the remaining patients had a variety of solid malignancies. All patients had previously received chemotherapy, radiotherapy, surgery, or 2 or more of these 3 treatments.

Hematological Toxicity. Hematological toxicities of the first treatment course are detailed in Table 2. Dose-related leukopenia and thrombocytopenia were observed. No hematological toxicities were observed in the three patients who were given 50 mg/m². Although the 4 patients given 75 mg of 254-S/m² tolerated the dose well, all of the 3 patients treated with 100 mg/m², as the next step, had grade 3 or 4 leukopenia and were moved back to 87.5 mg/m². Most of the patients who received 75 mg of 254-S/m² also developed grade 3 or more serious thrombocytopenia and leukopenia. We set this dose level as the MTD. The dose-limiting toxicity (DLT) of this regimen proved to be leukopenia and thrombocytopenia. The nadirs of platelets and neutrophils were observed 4 and 5 weeks, respectively, after the initiation of drug infusion and the counts were recovered within 6 weeks in the patients who received 87.5 mg of 254-S/m² or more (Fig. 1). Platelets were administered to two patients...
who developed grade 4 thrombocytopenia. Only one patient who was treated with doses of 75 mg/m² received antibiotic support for an episode of fever and documented infection during the period of neutropenia.

Nonhematological Toxicity. Unlike hematological toxicity, the nonhematological toxicity shown in Table 3 was mild and well tolerated. The elevation of blood urea nitrogen was observed in one patient with ECOG grade 1. Elevation of serum creatinine was observed in two patients and it was reversible. Peripheral neuropathy was also mild and no clinical problems were observed. Dose-related nausea and vomiting appeared in the patients who received 75 mg/m² or more per course; however, grade 3 gastrointestinal toxicity which required antiemetic agents was observed in only one patient who received 100 mg of 254-S/m². Transient arrhythmia was observed in one patient given 75 mg/m². No hepatic or pulmonary toxicity was encountered in this regimen.

Pharmacokinetic Studies. Fourteen treatment courses were evaluable for pharmacokinetic analysis. The pharmacokinetic parameters determined by the noncompartmental method in 14 patients are summarized in Table 4 and the plasma pharmacokinetic changes in both total and free platinum are presented in Fig. 2. During the 120-h period of infusion, the plasma concentration of total platinum did not reach a steady state and the plasma level gradually increased until infusion was completed. However, the free platinum concentration reached a steady state level within 24 h of initiation of the infusion. The steady state concentration of free platinum in the patients given 75 mg/m² or more was over 0.1 μg/ml. Elimination of free platinum was rapid and fit the monoexponential model with elimination half-lives between 0.65 and 2.56 h. However, a prolonged excretion phase for total platinum was observed. The volumes of distribution at steady state were relatively high, between 69.4 and 182.8 liters.

The percentages of platinum excreted in the urine for a 6-day period were 73.1–100% of the dose and daily excretion of platinum was almost constant (Table 4, Fig. 3). There was no
correlation between $C_r$ and percentage of the dose excreted in the urine. The AUC increased approximately linearly with the dose over the range of 50–100 mg/m$^2$. The mean AUC in the patients given 75 mg of 254-S/m$^2$ reached 1069.4 ± 257.7 (SD) µg/ml/min (data not shown). There was a significant correlation between the dose of 254-S and the AUC of platinum (Fig. 4) ($R = 0.757$, $P = 0.002$) or steady state platinum concentration (Fig. 5) ($R = 0.767$, $P = 0.002$). No correlation was observed between the amount of platinum excreted in the urine during 6 days and $C_r$ before treatment (data not shown).

**Pharmacokinetic Pharmacodynamic Relationship.** We defined the percentage of change in leukocyte or platelet count, which indicates the degree of myelosuppression after treatment by this regimen, as

\[
\frac{100 \times \text{Pretreatment leukocyte count or platelet count} - \text{nadir}}{\text{Pretreatment leukocyte count or platelet count}}
\]

The percentage of change in leukocytes in the 14 patients has a significant relationship to the AUC of free platinum ($R = 0.736$, $P = 0.003$) (Fig. 6) or the percentage of change in platelets ($R = 0.818$, $P = 0.001$) (Fig. 7). However, no correlation was observed between pretreatment Ccr and percentage of change in leukocytes or platelets (data not shown).

**DISCUSSION**

Continuous i.v. infusion of an anticancer agent is one of the promising strategies to enhance cytotoxic activity and/or to reduce side effects (24). Several reports on continuous infusion of cisplatin have documented better response rates and lower side effects as compared with intermittent drug infusion (12, 13). Dominici et al. administered high-dose cisplatin (40 mg/m$^2$/day) for 5 days as a CI in children with solid tumors, without serious toxicity (25). After i.v. drip infusion over 30 min, the ultrafilterable platinum in plasma decreased in a monoexponential mode after cisplatin but in a biexponential mode after infusion of 254-S or carboplatin (17). The protein-binding abilities of 254-S and carboplatin were almost identical and the thrombocytopenia was reported as a dose-limiting toxicity for 254-S and carboplatin. Only one paper has reported the continuous infusion of carboplatin (26). However, it is difficult to...
make a comparison of pharmacokinetic behavior between 254-S and carboplatin in continuous infusion, because the phase I study by Shea et al. was conducted with high dose carboplatin with autologous bone marrow support. The pharmacokinetic curve of total and ultrafilterable plasma platinum in one patient who was treated with high dose carboplatin was similar to that obtained in our study. The ultrafilterable platinum concentration of both 254-S and carboplatin reached a steady-state level by 24 h and did not vary markedly from the level over the remainder of the infusion, whereas there was a continued increase in total plasma platinum concentration between the early and later stages of drug administration. In the present study, we could not escalate the dose of 254-S given by 5-day CI above 87.5 mg/m²/course, whereas the standard dose of i.v. bolus infusion of 254-S is reported to be 100 mg/m² (17, 20). Regarding cisplatin, renal toxicity, which is dose limiting in i.v. bolus infusion and which may be related to the peak plasma concentration, is reduced by continuous i.v. infusion. Myelosuppression appears to be dose limiting in CI of cisplatin. However, myelosuppression, especially thrombocytopenia, was observed as the dose-limiting toxicity in both i.v. bolus and continuous i.v. infusion of 254-S. The reason why we could not administer more than 87.5 mg of 254-S/m² without serious toxicity might be that the AUC with a dose of 75 mg/m² by CI and that of 100 mg/m² in i.v. bolus infusion are the same, as we reported previously (1069 µg/ml/min versus 959 µg/ml/min) (17). This suggestion is supported by the significant relationship between AUC and the myelosuppressive effect (Figs. 6 and 7). The determination of the AUC value is crucially important for the prediction of side effects of anticancer agents, but in the continuous regimen, the incidence of leukopenia was almost the same as that of thrombocytopenia and it appeared 5 weeks after administration of 254-S. This delayed myelosuppression was not observed with the intermittent infusion. The pharmacokinetic data suggested that the elimination phase of total platinum was prolonged. In addition, there exists probability of contribution of toxic metabolite for prolonged myelosuppression.

On the basis of “dose intensity,” (27) this CI regimen has less intensity than conventional i.v. bolus infusion owing to the smaller dose and delayed myelosuppressive effect. Shea et al. conducted a phase I clinical trial of carboplatin by 4-day CI with autologous bone marrow support and found that the MTD was 2000 mg/m², which was about 5 times higher than the dose in conventional infusion of carboplatin (26). In the future, an approach such as the use of autologous bone marrow support and/or granulocyte-colony stimulation factor might be an effective method for increasing not only the dose but also the AUC in CI of 254-S.

In the present study, Vd∞ were relatively high, which might be due to increased fraction unbound to protein in plasma in this administration method of 254-S.

Egorin et al. (28) found that the percentage of reduction in platelet counts was proportional to the C∞ before treatment in
patients treated with carboplatin (28). We reported a similar observation in patients treated by i.v. bolus infusion of 254-S (29). In the present analysis, however, we did not find any significant relationship between the Cr and AUC or percentage of change in platelet count. This may be in part due to the small number of patients entered in this phase I study and that all of them had relatively good Cr (≥52.5 ml/min). However, further investigation is necessary to define the pharmacokinetic pharmacodynamic relationship in the CI regimen.

We empirically chose the starting dose of CI 254-S as 50 mg/m², which was 50% of the dose in i.v. bolus infusion, and then we escalated the dose to 75 and 100 mg/m². The escalation rate at each step was 50 and 33% of the previous dose, respectively. Retrospective analysis of the AUC suggests that the escalation was rather too rapid because the mean AUC with the initial dose was 620 µg/ml/min which was 64.4% of the AUC in the patients who received bolus infusion of 100 mg of 254-S/m². The concept of pharmacokinetically guided dose escalation of Collins et al. (30) is one of the scientific approaches to dose escalation study; however, no general rule of dose escalation applies for when the method of administration is changed. Our study suggests that an AUC of more than 1000 µg/ml/min was the “maximum tolerated systemic exposure (MTSE)” (31) of 254-S in both i.v. bolus infusion and CI and also suggests that the AUC or other pharmacokinetic parameters could play an important role not only in conducting a dose escalation study but also in changing an administration method.

Clinical response was observed in 3 patients with uterine cervix cancer of 12 patients evaluable for response and none of them had been given cisplatin or other platinum coordination compounds.

In conclusion, the recommended dose for a phase II study of 254-S by CI is 75.5 mg/m² 120 h every 6 weeks.

REFERENCES


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