

A Split Protocol of Cisplatinum (CDDP) Infusion in Outpatients: Examination of Pharmacokinetics

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ABSTRACT

We devised an outpatient therapy based on spreading the dose of Cisplatinum (CDDP) and evaluated its safety and the hydration regimen designed to be performed concurrently. We carried out a pharmacokinetic examination after the basic drip infusion schedule comprising administration of CDDP at 30 mg /m² with hydration at a volume of 2500 mL over 6 hours (the dose of CDDP was selected to be feasible for administration to outpatients, and 6 hours is the maximum time permitted for drip infusion) in patients with advanced cancer of digestive tract. The safety of the therapy was then evaluated. The pharmacokinetic values of free-platinum, non-protein bonding free-platinum, analyzed were AUC⁰⁻⁵ of 1.66 (mean) µg/mL/hr ± 0.203 (SD) and Cmax of 0.726 µg/mL (0.128). The serum creatinine (s-Cr) level, which is an index of renal function, showed no difference between the time points of before administration of CDDP, while the greatest aggravation of symptoms

was tested for within 1 month of administration and at 6 months after administration (*t* test: *P* = 0.0842, *P* = 0.1430). The Pearson correlation coefficients (*r*) were obtained between Cmax or AUC and the baseline serum creatinine level, patient age and the total dose of CDDP used in previous therapy, and were analyzed for significance. No correlation was observed between Cmax or AUC and any of these parameters. The present CDDP therapy is able to suppress Cmax to a low level, but a therapeutic effect can be expected from the AUC value. It was demonstrated that the present dosing regimen is a highly safe therapy that is not affected by baseline serum creatinine level, patient age or the total dose of CDDP used in previous therapy, and that long-term application of this dosing regimen does not influence renal function.

INTRODUCTION

The typical dosing method of CDDP in Japan is once every 3 to 4 weeks and is normally conducted on an inpatient basis.^{1,2} The primary reason for conducting the therapy on an inpatient basis is

the need for systemic hydration to treat the significant adverse drug reaction of renal toxicity caused by CDDP.

Chemoprotection is attempted to prevent renal toxicity in addition to systemic hydration, an example of which is the use of antidotes (STS, DDTC, WR-2721, GSH).³ However, these methods have not been used in general clinical practice yet, excluding some cases.

Cancer chemotherapy by concomitant administration of CDDP in inpatients requires a large volume of fluid infusion and long-term management of patients, which is expensive in terms of both time and cost. Some useful findings on renal toxicity were obtained by reports from clinical experience and clinical examinations: (1) administration by spreading the dose of CDDP over 2 to 5 days causes fewer renal disorders than by administration of the same dose over 1 day;⁴ (2) renal toxicity depends on C_{max}, and prolonged duration of CDDP administration can suppress C_{max} to a low value, thereby alleviating renal toxicity;^{5,6} (3) Oral hydration has the effect of alleviating renal toxicity comparable to that attained by systemic hydration;⁷ and (4) 5-HT₃ antagonist, an excellent antiemetic agent, is superior to metoclopramide in suppression of onset of renal toxicity.⁸

The anti-tumor effect of CDDP was depends on the area under the plasma concentration-time curve (AUC).⁹ Accordingly, if a certain AUC can be assured, successful anti-tumor effects of the CDDP therapy can be anticipated. Kobayashi et al reported that the AUC value of CDDP, a non-protein-binding free-platinum, was 1.80 µg/mL/hr after administration at 80 mg/m² and was 0.92 µg/mL/hr after administration at 33 mg/m², demonstrating that administration of CDDP at 33 mg/m² twice or more every 4 weeks has a comparable effect to that obtained by administration of CDDP at 80 mg/m² every 4 weeks.¹⁰

Accordingly, we modified¹¹ the concomitant therapy of CDDP¹² with TS-1, for which excellent therapeutic results have recently been reported for advanced and recurrent stomach cancer, devised an outpatient therapy by spreading the dose of CDDP over several days and evaluated the safety of the therapy by examining the pharmacokinetics.

PATIENTS AND METHODS

Patients

The present study was performed in a total of 10 cases, comprising 3 cases of non-resectable stomach cancer, 2 cases after resection of stomach cancer, 1 case of non-resectable pancreatic cancer, 3 cases after resection of pancreatic cancer and 1 case of colon cancer. The subjects were 4 males and 6 females aged 49 to 81 years old, with a mean age of 65. All patients had a medical history of CDDP at doses of 88 to 800 mg. The patients' background factors are shown in Table 1. Cases whose functions of the main organs were well preserved were selected as subjects for the study. The details of these values are as follows: WBC > 4,000/mL; PLT >100,000/mL; Hb > 9 g/dL; Renal function, BUN ≤ 25 mg/dL; Cr ≤1.3 mg/dL; Ccr ≥ 60 mL/min; Hepatic functions, bilirubin ≤ 1.5 mg/dL; and GOT and GPT, within twice the upper limit of the normal range. Cases presenting problems with therapy were excluded. All subjects were amenable to treatment on an outpatient basis and had submitted their written informed consent prior to the treatment.

Therapeutic Protocol

Subjects were orally administered TS-1 (tegafur-gimeracil-oteracil potassium) (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) daily at a dose of 80 mg/m² during the period from Day 1 to Day 21, and received intravenous drip infusion of CDDP at a dose of 30 mg/m² for 2 hours on Day 1 and Day 8. A three-

Table 1. Patient Characteristics*

No.	Age	Sex	Tumor type	Prior CDDP Administration		
				Dose	Course	Total
1	68	F	Colon	40 mg	5	200
2	67	M	Gastric	45 mg	7	315
3	81	F	Gastric	44 mg	2	88
4	74	M	Gastric	50 mg	4	200
5	50	F	Panc.	40 mg × 3 20 mg × 3	3	180
6	68	M	Panc.	50 mg	14	700
7	52	F	Panc.	40 mg	7	280
8	73	F	Panc.	40 mg	6	240
9	63	F	Gastric	40 mg	9	360
10	49	M	Gastric	50 mg	16	800

*Panc indicates pancreatic.

week administration period followed by a 2-week withdrawal period, making a total of 5 weeks, was set as 1 course and this course was then repeated. Pre-hydration was performed at a volume of 1000 mL for 2 hours with administration of an antiemetic agent and diuretic drug and then 400 mL of saline containing CDDP at 30 mg/m² was intravenously administered for 2 hours, followed by post-hydration at a volume of 1000 mL over 2 hours with administration of an antiemetic agent antagonist (ondansetron; 5-HT₃) and diuretic drug.

Analysis

Blood was sampled just before administration of CDDP, on the completion of administration (2 hours), at 1 hour after the completion of administration (3 hours) and at 3 hours after the completion of administration (5 hours). Five mL of blood was collected in a heparinized tube and immediately centrifuged at 4°C and 1000× for 10 minutes to separate the plasma. One mL of plasma thus obtained was ultrafiltrated at 4°C and 1000× g for 20 minutes using UltraFree with a fractional molecular weight of 30,000 (UFC3LTK00; Millipore Co., Ltd.). The ultrafiltrate and plasma were stored at -20°C and subject-

ed to measurement of free-platinum concentration by flameless atomic absorption spectrometry.

Pharmacokinetic Analysis

The pharmacokinetic parameters of free free-platinum (half-life, C_{max}, and AUC) were determined employing a one-compartment model using the MOMENT (EXCEL) computer program for pharmacokinetics.¹³ The AUC value was calculated using the trapezoidal method.

Statistics

The pharmacokinetic parameters determined were statistically analyzed. The renal function test values before and after administration of CDDP were compared and analyzed by paired *t*-test to detect any significant difference. For the relationship between each pharmacokinetic parameter and the baseline renal function test values (the baseline serum creatinine level), the total dose of CDDP used in previous therapy and patient age, Pearson's correlation coefficients (*r*) were calculated and analyzed for significance. Statistical processing was performed utilizing Statview v5.0 computer software.

Table 2. Serum Creatinine Before and After Therapy

No.	Before	After 1 Month	After 6 Months	Status
1	0.77	0.84	-	Alive
2	0.73	0.76	0.77	Alive
3	1.02	0.96	0.96	Alive
4	0.70	0.66	0.70	Alive
5	0.83	0.73	0.47	Alive
6	1.34	1.31	1.09	Alive
7	0.58	0.59	-	Alive
8	0.59	0.53	-	Dead
9	0.65	0.57	-	Alive
10	0.71	0.64	0.67	Alive
mean	0.792 (± 0.231)	0.759 (± 0.234) [*]	0.777 (± 0.221) [†]	Alive

^{*}Before vs after 1 Month, $P=0.0842$. [†]Before vs after 6 Months, $P=0.1430$.

RESULTS

Pharmacokinetics of CDDP

Changes in the blood concentration of the non-protein bound free-platinum of cisplatin are shown in Figure 1. The blood concentration decreased monophasically and exponentially after the completion of administration and at 5 hours after the start of administration had almost reached the limit of measurement sensitivity. The pharmacokinetic values analyzed were AUC^{0-5} of $1.66 \mu\text{g/ml/hr}$ (mean) ± 0.203 (S.D.) and C_{max} of $0.726 \mu\text{g/mL}$ (0.128). Yamamoto et al reported that the $AUC^{0-\infty}$ of free-free-platinum was $3.05 \mu\text{g/mL/hr}$ (0.92) after administration of CDDP at a dose of 80 mg/m^2 for 1 hour.¹⁴ The AUC value obtained in the present study was attained by CDDP administration at a dose of 30 mg/m^2 until 5 hours after administration but was one half the AUC value reported by Yamamoto et al. The C_{max} obtained in the present study was $0.726 \mu\text{g/mL}$, which was sufficiently lower than the reference level of C_{max} to prevent the renal toxicity reported by Nagai et al.⁵

Clinical Laboratory Values Before and After Administration of CDDP

The serum creatinine level, an index of renal function, was measured before

administration of cisplatin and at the timepoint when the greatest aggravation of symptoms was observed within 1 month after administration and analyzed by t -test. The s-Cr level was $0.792 \mu\text{g/dL}$ (mean) ± 0.231 (S.D.) and $0.795 \text{ mg/dL} \pm 0.234$ at each timepoint without elevation of the serum creatinine level. Also, no significant difference was observed in the values by t -test ($P = 0.0842$) (Table 2). The serum creatinine level of the 6 patients (outpatients) in whom it had been possible to measure before administration and at 6 months after the start of administration showed no difference ($0.777 \text{ mg/dL} \pm 0.221$ ($P = 0.1430$)).

Correlation of Pharmacokinetic Values with Clinical Laboratory Values, Patient Age and Total Dose of CDDP Used in Previous Therapy

To confirm the effect of cisplatin administration on the renal function, the Pearson correlation coefficients were obtained between C_{max} or AUC and the baseline serum creatinine level, patient age, and the total dose of CDDP used in previous therapy, and analyzed for significance. No correlation was observed between C_{max} or AUC and the baseline s-Cr level, patient age or the total dose of CDDP used in previous therapy (Table 3).

Table 3. Correlation Between Pharmacokinetic Parameters and Baseline s-Cr, Total CDDP Dose or Patients Age

		Baseline s-Cr	Total CDDP dose	Age
C _{max}	n	10	10	10
	r	0.358	0.425	-0.222
	P	0.3211	0.2294	0.55
AUC ⁰⁻⁵	n	10	10	10
	r	0.406	0.462	-0.182
	P	0.2545	0.1862	0.6270

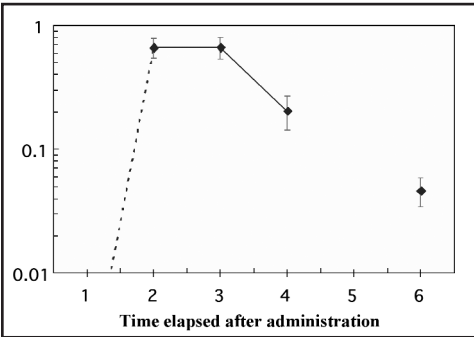


Figure 1. Changes in blood concentration of free-platinum (n=10).

The above findings suggest that the present dosing regimen may not be affected by the baseline serum creatinine level, patient age or the total dose of CDDP used in previous therapy and may not influence renal function even after long-term application of this regimen.

DISCUSSION

Nausea and vomiting, which are main adverse drug reactions of CDDP, occurred frequently, even on the day following administration of CDDP and thereafter. Patients are expected to develop hypovolemia due to the above adverse drug reactions of nausea and vomiting with intestinal symptoms of diarrhea, etc. Accordingly, they were at high risk of developing renal disorders unless long-term hydration was performed, even after administration of CDDP. It has therefore been assumed

up to now that cancer chemotherapy with drugs such as CDDP needed to be conducted on an inpatient basis.

5-HT₃ antagonist, a new antiemetic agent, is highly effective in preventing emesis and causes no renal toxicity of the type that is observed after administration of metoclopramide.⁸ Thus, the use of 5-HT₃ could allow a reduction of the hydration volume needed on the day following CDDP administration and thereafter. Oral hydration is highly convenient for hydration on the day following CDDP administration and thereafter, and is reported to have the effect of causing fewer renal function disorders than observed with systemic hydration.⁷ Although there is no standard theory dictating the ideal volume for oral hydration, D. J. Stewart et al⁸ conducted hydration with 6 to 8 cups of drinking water daily for several days after administration of CDDP. The minimum required volume of hydration is possibly less than those routinely used by many institutions. There are reports that support the use of CDDP therapy on an outpatient basis^{15,16} and attempts to administer it in outpatients have been occasionally performed.^{17,18} However, these reports are rare and there are no reports that confirm the safety of this outpatient therapy based on long-term observation of renal and other functions.

We carried out an examination of pharmacokinetics after a basic drip infusion schedule of administration of

CDDP at 30 mg/m² plus hydration at the volume of 2500 mL over 6 hours (the dose of CDDP was selected to be feasible for administration to outpatients, and 6 hours is the maximum time permitted for drip infusion) and the safety of the therapy was evaluated. The pharmacokinetic values analyzed were AUC⁰⁻⁵ of 1.66 µg/mL/hr ± 0.203 and Cmax of 0.726 µg/mL (0.128), making therapeutic effect highly likely from the AUC value in spite of Cmax being suppressed to a low value. Our results confirmed that the present dosing regimen is not affected by the baseline serum creatinine level, patient age or the total dose of CDDP, as was the case in the previous therapy, and does not influence renal function. Other than nausea and vomiting, there were no adverse drug reactions such as peripheral nervous disorders or hearing disorders, which commonly result from a high CDDP Cmax.

An extremely good therapeutic effect on intestinal cancer was obtained by this dosing regimen, as previously reported,¹¹ and no therapeutically problematic adverse drug reactions, such as renal disorders, peripheral nervous disorders or hearing disorders were observed in 100 or more patients receiving this therapy. Spreading the dose used in this therapy is practical, since it can prevent the onset of adverse drug reactions by suppressing the peak plasma concentration of platinum but can be expected to have a marked therapeutic effect by maintaining the AUC value.

If the serum creatinine level before the therapy is within the normal range, this therapy is highly useful, since it is not affected by patient age or the total dose of CDDP received in previous therapies. It does not influence renal function, even if carried out in the long term, and can thus be conducted repeatedly.

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