Initial analysis of relationship between plasma platinum concentration and hematological adverse reaction associated with weekly chemotherapy using nedaplatin in combination with radiotherapy for cervical carcinoma

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Summary

Purpose: Established therapeutic guidelines for cervical carcinoma recommend concurrent chemo- and radiotherapy as standard treatment for locally advanced cervical carcinoma. Nedaplatin (CDGP) is a platinum agent developed in Japan that is less nephrotoxic than cisplatin (CDDP), but with equivalent antitumor potency. In the standard dosage regimen for cervical carcinoma, CDGP is administered once every four weeks (monthly regimen). We investigated the efficacy and safety of a new dosage regimen, in which CDGP was administered once weekly for five weeks (weekly regimen). *Methods:* We measured plasma platinum concentration of patients after administration of CDGP, and analyzed the relationship between plasma platinum concentration and hematological adverse reactions such as thrombocytopenia and leucopenia. *Results:* The relative rates of change in platelet and white blood cell counts tended to increase as the plasma concentration of platinum increased. Furthermore, the rate of change in platelet counts in relation to the area under the curve was greater for the monthly regimen as compared to weekly. On the other hand, the relative rates of change in WBC were nearly the same between the regimens. *Conclusions:* These findings indicate that when using chemotherapy with CDGP for a patient with a cervical carcinoma, a weekly regimen might reduce the severity of thrombocytopenia, while still exhibiting the same therapeutic efficacy as the monthly regimen.

Key words: Cervical carcinoma; Nedaplatin; Chemotherapy; Adverse reaction; Thrombocytopenia; Leucopenia.

Introduction

Nedaplatin (CDGP) is a platinum agent that was developed in Japan to reduce the severity of nephrotoxicity-related adverse reactions associated with cisplatin (CDDP) use. According to the package insert, CDGP should be administered once every four weeks (monthly regimen) and is indicated for various carcinomas, including cervical carcinoma. Severe bone marrow suppression is one of its important adverse effects, thus thorough analyses of efficacy and safety are needed for rational clinical usage. When treating cervical carcinoma with CDGP in combination with radiotherapy, a new dosage regimen of once weekly for five weeks (weekly regimen) was investigated [1, 2]. Past reports found no significant differences in efficacy between monthly and weekly regimens [1-3], though comparisons of safety between these regimens have not been reported. As for bone marrow suppression associated with CDGP, it was shown that the plasma concentration of platinum is correlated with the severity of hematological adverse reactions, such as thrombocytopenia and leucopenia, in patients receiving the monthly regimen [4]. In the present study, to assess the safety of a new dosage regimen of CDGP for cervical carcinoma, we investigated the pharmacokinetics of platinum after administration of CDGP, and the relationships between plasma platinum concentration and severity of thrombocytopenia or leukopenia. The present investigation accompanied the Kitasato Gynecologic Radiation Oncology Group 0501.

Study (KGROG0501) conducted at Kitasato University Hospital [5, 6] and was approved by the ethics review board of that institution. The expected 3-year overall survival rate is 40% and the threshold value is defined as 20%. The sample size was calculated as 45 (a. 0.05 and b. 0.1, non-compliance 10%). All patients will be followed up for three years. This study is an initial analysis.

Materials and Methods

Plasma platinum concentration after administration of CDGP

1) Measurement of plasma platinum concentration

Based on previously reported methods [7], the concentration of platinum in plasma was measured using graphite furnace atomic absorption spectrophotometry with the quantification procedure shown in Figure 1. Total platinum concentration was measured using a standard addition technique, in which the amount of extraction solvent (methyl isobutyl ketone) was adjusted to bring the final concentration of platinum to near 0.1 μg/ml.

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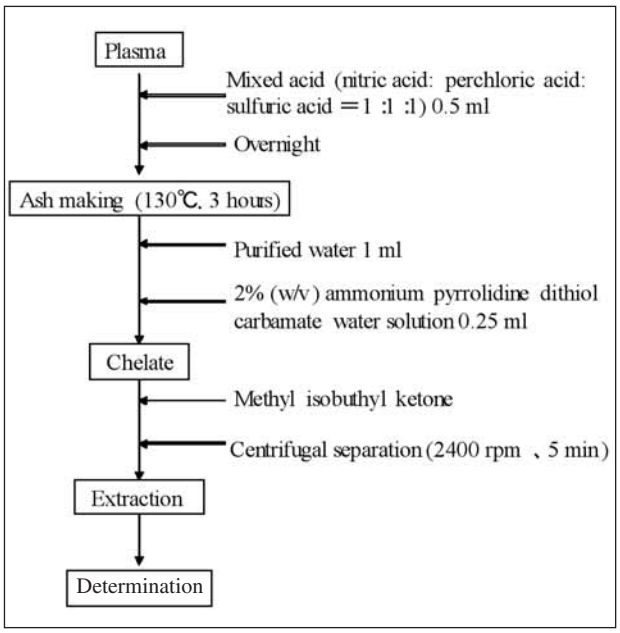


Figure 1. — Assay system used for nedaplatin.

2) Measurement of plasma platinum concentration after administration of CDGP and calculation of area under the curve (AUC)

Among patients enrolled in KGROG0501, the present subjects comprised those who consented to blood sampling. The subjects received chemotherapy with CDGP (single dose, 30 mg/m^2) with radiotherapy once weekly for 5 weeks. During one of those five courses, blood samples were collected at 1, 2, 3, 4, and five hours after the start of injection of CDGP, while they were collected at few points after the start of injection during the other four courses. The $AUC_{0-\infty}$ was calculated using the moment method based on five sampling points, with the moment analysis (MOMENT) macro in Microsoft Excel® (Microsoft Visual basic for application) used for analysis [8]. Since CDGP is a drug that is excreted renally, the influence of multiple injections on renal function was assessed by one-way analysis of variance based on the pre-administration values of serum creatinine (Scr) and blood urea nitrogen (BUN). The StatView® 5.0 (SAS Institute, Inc. Japan) software package was used for this analysis.

Relationship between plasma platinum concentration and hematological adverse reactions such as thrombocytopenia and leukopenia

The total $AUC_{0-\infty}$ for the weekly regimen and relative rates of changes in severity of thrombocytopenia and leukopenia were calculated using the following equations to assess these correlations.

Total $AUC_{0-\infty}$ = $AUC_{0-\infty}$ per administration × 5.

Relative rate of change in platelets (PLT) (%) = (PLTnadir - PLTpre)/PLTpre × 100.

Relative rate of change in white blood cells (WBC) (%) = (WBCnadir - WBCpre)/WBCpre × 100.

Next, we compared whether the data of the monthly regimen previously published was different from the data obtained although the total CDGP dosage. After that, we investigated the difference of the degree of thrombocytopenia and leukopenia against AUC for the weekly regimen and monthly regimen [4].

Results

Plasma platinum concentration after administration of CDGP

1) Measurement of plasma platinum concentration

The accuracy and reproducibility of the present method were investigated. In the present method, the relative error regarding the predicted value was about 5% with a RSD of 4.12%.

2) Measurement of plasma platinum concentration following CDGP and calculation of $AUC_{0-\infty}$

Patient characteristics

Five female patients served as subjects. Table 1 summarizes the number of plasma samples and number of courses with blood sampling, as well as values for dosage, age, body weight, Scr, BUN, AST, and ALT.

Table 1.

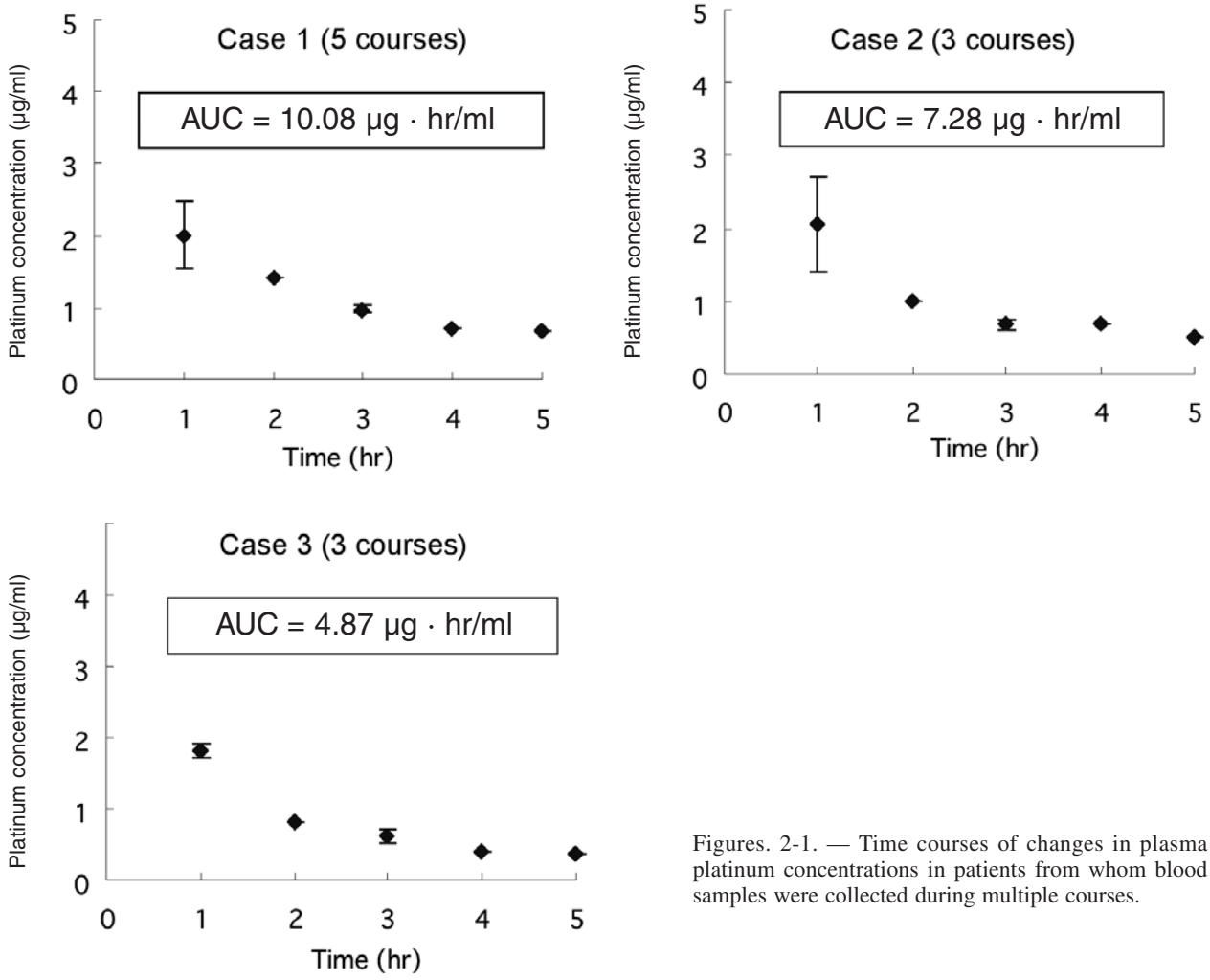
Total number of patients	5
Gender (male/female)	0/5
Number of plasma samples	40
Number of plasma course	13
Dose (mg/m^2)	30
Age (years old)	52.6 ± 15.3 [30-69]
Body Weight (kg)	52.4 ± 9.8 [49.7-69.5]
Scr (mg/dl)	0.67 ± 0.15 [0.5-0.87]
BUN (mg/dl)	12.2 ± 2.4 [9-15]
AST (IU/l)	15.6 ± 6.0 [10-25]
ALT (IU/l)	13.4 ± 10.7 [6-32]

Time-course of plasma platinum concentration in each patient

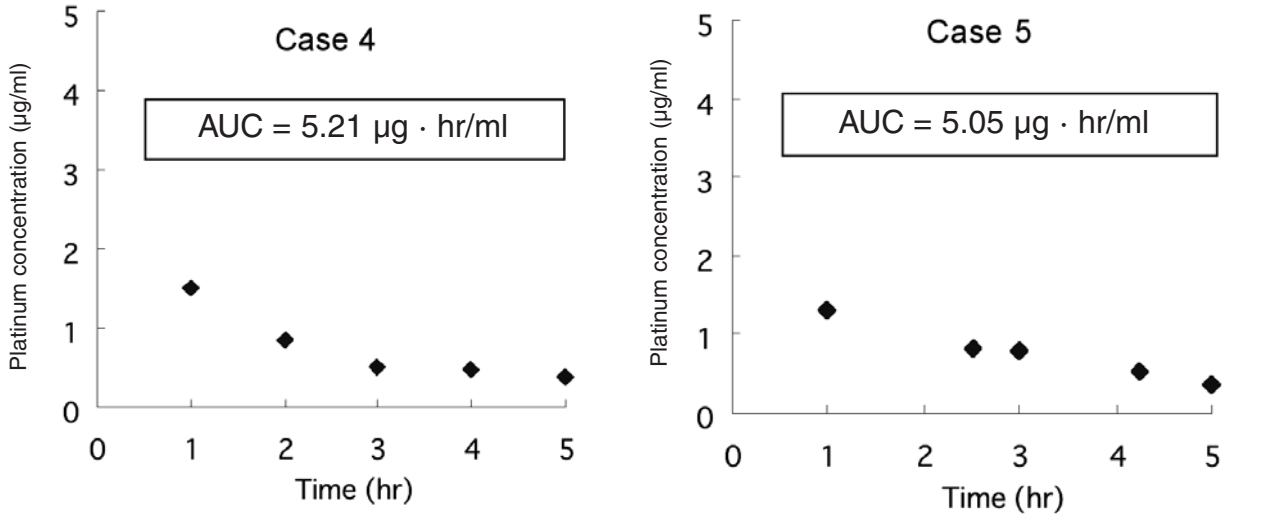
Figure 2-1 shows the time-courses of plasma platinum concentration changes in the patients from whom blood samples were collected during multiple courses, while Figure 2-2 shows those in patients from whom blood samples were collected during only one course. In case 1, blood samples were collected during all five courses, while they were collected during three courses in cases 2 and 3. None of the patients displayed marked changes in plasma platinum concentration during any of the courses after the start of CDGP administration.

Relationship between renal function and plasma platinum concentration

None of the five patients showed significant increases in the values for Scr or BUN among the courses, and repeated administrations did not cause marked influences on renal function (Figure 3). In the figure, the dotted lines indicate the upper and lower limits of normal. All values for Scr and BUN in the patients were within a normal range.



Figures. 2-1. — Time courses of changes in plasma platinum concentrations in patients from whom blood samples were collected during multiple courses.



Figures 2-2. — Time courses of changes in plasma platinum concentrations in patients from whom blood samples were collected from only 1 course.

Relationships between plasma platinum concentration and severity of thrombocytopenia and leukopenia.

Tables 2 and 3 show relative rates of change in total $AUC_{0-\infty}$, and PLT and WBC counts in the five patients. Total $AUC_{0-\infty}$ in all patients ranged from 24.35 to 50.40 · g h/ml. The relative rates of change ranged from -42% to -81% for platelet counts and from -36% to -93% for WBC counts.

Table 2.

Case	Total AUC (μg · hr/ml)	PLT_{pre} (10^4/μl)	PLT_{nadir} (10^4/μl)	Relative change in PLT (%)
1	50.4	22.9	4.4	-81
2	36.4	21.8	6.9	-68
3	24.35	27.1	7.7	-72
4	26.05	35.2	7.3	-79
5	25.25	20.4	11.8	-42

Table 3.

Case	Total AUC (μg · hr/ml)	WBC_{pre} (10^3/μl)	WBC_{nadir} (10^3/μl)	Relative change in WBC (%)
1	50.4	9	0.6	-93
2	36.4	6.1	3.9	-36
3	24.35	7.8	1.8	-77
4	26.05	5.2	0.7	-87
5	25.25	3.7	1.8	-51

Next, the weekly and monthly regimens were compared. Figure 4 shows the relationships between the $AUC_{0-\infty}$ and severity of thrombocytopenia and leukopenia with the regimens. Our results showed that the relative rates of change in PLT and WBC counts tended to increase as AUC increased. Furthermore, the rate of change in PLT count in relation to AUC was greater for the monthly regimen as compared to the weekly regimen. On the other hand, the relative rates of change in WBC were nearly the same between the regimens.

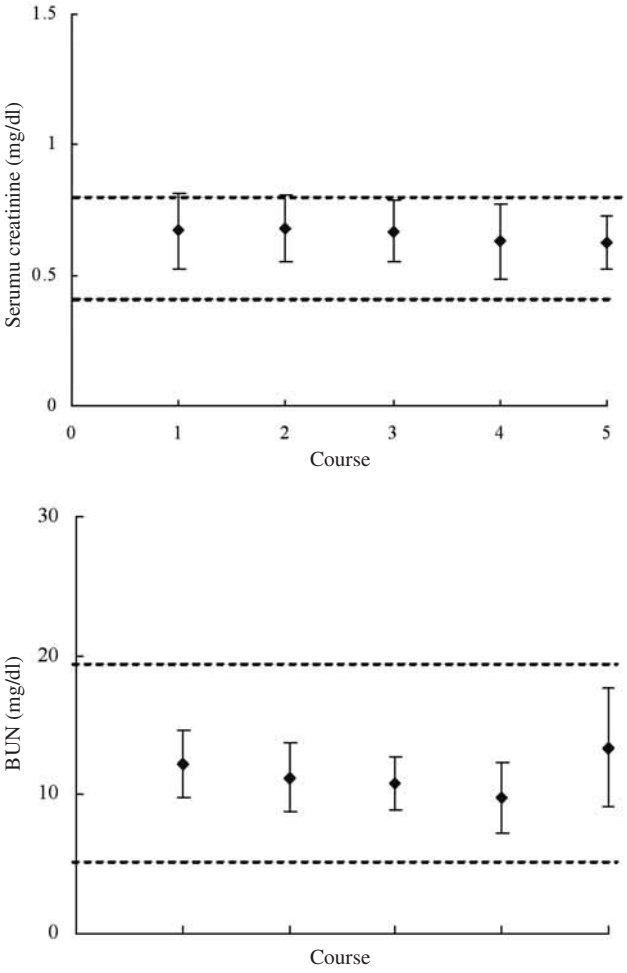


Figure 3. — Serum creatinine and blood urea nitrogen (BUN) before administration of nedaplatin in each case. Dotted lines indicate the upper and lower limits of the normal range.

Discussion

Since the subjects satisfied the inclusion criteria for KGROG0501, the present study displayed minimal bias in regard to patient characteristics. However, all subjects were women with cervical carcinoma.

In the results of the population analysis for the monthly regimen, it was shown that creatinine clearance was a significant variable for clearance, while body weight was a significant variable for the distribution volume of CDGP [9]. In the present study, the dosage of CDGP was based on body surface area. Since individual differences in distribution volume were taken into account and individual differences in clearance were not, individual differences in the pharmacokinetics of CDGP were observed. When a dosage of 30 mg/m^2 of CDGP per course was administered in the present study, slight individual differences were seen in the $AUC_{0-\infty}$ values (range, 4.87-10.08 μg·h/ml), which has been reported previously. Idei *et al*. [1] noted that the average value of AUC after administration of 30 mg/m^2 of CDGP was about 5 μg ·h/ml, while Oguma *et al*. [10] reported that the value of $AUC_{0-\infty}$ after administration of 20-40 mg/m^2 of CDGP was 9.49-16.22 μg · h/ml. In the present study, CDGP was administered once weekly at 30 mg/m^2 for five weeks. Since the half-life of CDGP was reported to range from 2-13 hours [10], it was considered to be completely eliminated after one week. No marked differences were found in regard to the time-course of plasma platinum concentration among the five courses in each patient, suggesting that those concentrations were nearly the same among all the courses. This was also supported by the finding of no changes in Scr and BUN values among all five courses. Based on these findings, it was considered reasonable to calculate the total AUC in the weekly regimen by multiplying the AUC for a single administration by five. Two points should be considered when comparing the degrees of thrombocytopenia and leukopenia in relation to the AUC between the weekly and monthly regimens. First, CDGP therapy was combined with radiotherapy in the weekly regimen, but was not combined

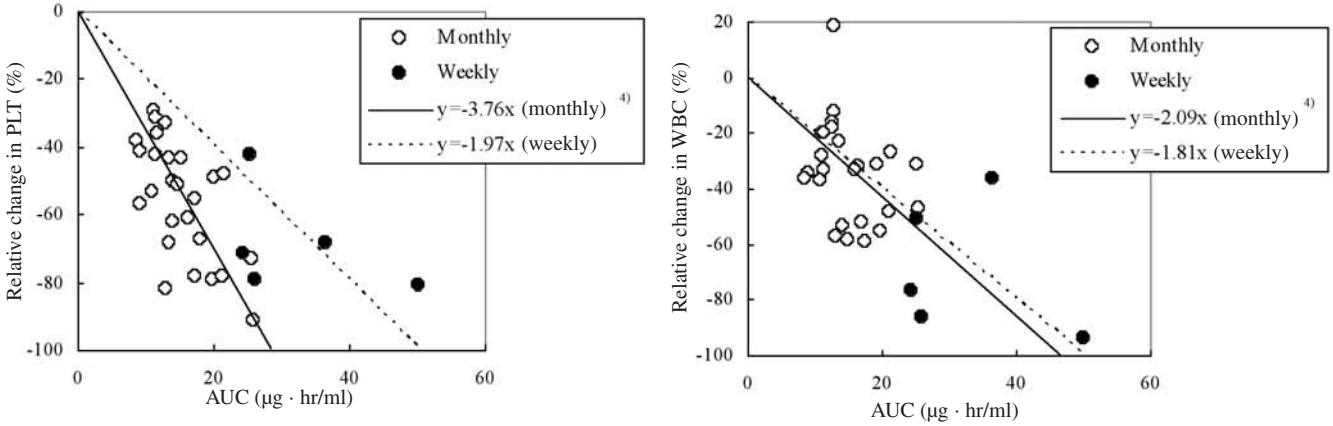


Figure 4. — Relationships among relative changes in values for PLT, WBC, and AUC of platinum.

with radiotherapy in the monthly regimen. Bone marrow suppression is one of the adverse reactions caused by radiotherapy [11].

However, since combining CDGP with radiotherapy does not exacerbate adverse reactions [3], the effects of radiotherapy were not taken into account in the present study. Second, the AUC was calculated based on total plasma platinum concentration in the weekly regimen, whereas it was calculated based on the plasma unbound platinum concentration in the monthly regimen. In general, plasma unbound platinum is responsible for antitumor action and adverse reactions, however, since CDGP exists mostly as unbound platinum in blood [10], we considered that calculation of the AUC based on total plasma platinum concentration did not impact the results of this study.

When compared to the monthly regimen, the slope of the regression line for the relative rates of change in thrombocytopenia in relation to the AUC was less than that for the weekly regimen, suggesting that a divided administration of CDGP may lessen its effects on platelets. Regarding leukopenia, no marked differences were observed, suggesting that the influences of the monthly and weekly regimens on WBC are comparable.

Together, our findings indicate that when using CDGP for cervical carcinoma, a weekly regimen might reduce the severity of thrombocytopenia, while exhibiting the same therapeutic efficacy as a monthly regimen [1-3]. Due to the relatively few cases considered in the population phramacokinetics study, we recommend analysis based on a larger statistical sample.

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