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ORIGINAL ARTICLE

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A formula for predicting optimal dosage of nedaplatin based on renal function in adult cancer patients

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Abstract *Purpose:* To predict the optimal dosage for nedaplatin (*cis*-diammineglycolatoplatinum), an anticancer drug and a platinum derivative like cisplatin and carboplatin, a simple formula was developed based on renal function in Japanese adult cancer patients. *Patients and methods:* Unbound platinum concentrations in plasma after intravenous infusion of nedaplatin were measured for 187 courses in 145 patients with lung, esophageal, and cervical and ovarian cancer undergoing clinical treatment. The data were divided into two sets, a model development data set of 94 courses and a validation data set of 93 courses. Regression analysis was applied to the relationship between the unbound platinum clearance (CL) of nedaplatin and the patients' renal function. The predictability and usefulness of this formula were assessed by validation using the external data set of 93 courses obtained from 75 patients. *Results:* A simple formula was obtained for predicting the platinum clearance using the creatinine clearance (CLcr): $CL = 0.0836 \times CLcr + 3.45$. Indices for the predictive performance for CL and the area under the plasma concentration curve (AUC) in the validation data were almost the same as those for the model development data. *Conclusions:* A formula for predicting the CL of unbound platinum after nedaplatin administration was developed, and only CLcr was found to be a significant covariate of the CL. This formula was useful for estimating the CL for the second as well as the first treatment with nedaplatin.

Keywords Nedaplatin · Platinum · Pharmacokinetics · Clearance

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Introduction

Nedaplatin (*cis*-diammineglycolatoplatinum) is an anticancer agent which is a platinum derivative like cisplatin (CDDP) and carboplatin (CBDCA) [17, 33]. In phase II clinical studies, high activities against head and neck cancer, non-small-cell lung carcinoma, esophageal cancer, testicular tumor, and cervical cancer have been reported [1, 9, 13, 14, 19, 21, 29]. Also, a higher antitumor activity of nedaplatin than of CDDP has been found in preclinical and in vitro studies [16, 31]. The plasma concentration profile of unbound platinum after nedaplatin infusion has been reported to be similar to that of total platinum, and the protein binding of nedaplatin to be lower than that of CDDP [23]. Nedaplatin has a short elimination half-life and a pharmacokinetic profile similar to that of CBDCA [24]. Nephrotoxicity often limits the clinical use of antitumor agents such as CDDP, but nedaplatin causes less nephrotoxicity than CDDP [15, 22, 27, 28], although its hematological toxicity can be a limiting factor at high dosages, as found with CBDCA [22].

In anticancer chemotherapy, it is usual to use the maximum tolerated dose with respect to side effects [5, 8, 10], and thus serious side effects often occur especially in patients exposed to high platinum concentrations. To minimize side effects, the optimum dosage regimen should be individualized by considering the pharmacokinetic variability of the patients. For CBDCA, studies on the optimum dosage regimens have been reported [3, 20, 32] and the relationships between the area under curve (AUC) of platinum and efficacy and toxicity after CBDCA administration have been investigated. Once we have information about the target AUC of an anticancer drug with the best efficacy and the least toxicity, we can determine the optimum dosage regimen to achieve the target AUC based on pharmacokinetic knowledge of the drug. For example, a formula for calculating the clearance (CL) of platinum has been reported for CBDCA [2, 4, 18].

In the case of nedaplatin, the precise pharmacokinetic properties of unbound platinum have not been adequately investigated in a large number of patients. In this study, we developed a simple formula that was able to explain the relationship between the CL of unbound platinum after nedaplatin administration and the renal function of patients based on plasma concentration data from 94 courses in Japanese adult patients. The resulting formula was validated by comparison with an external data set of 93 courses in 75 patients.

Methods

Patients and data collection

Plasma unbound platinum concentration measurements were obtained from 187 courses in 145 Japanese adult patients with lung, esophageal, cervical and ovarian cancer treated with nedaplatin in the 14 institutions shown in Table 1. The patients were divided into two sets, the model development data set of 94 courses and the validation data set of 93 courses. Demographic data including gender, age, body weight (BWT), serum creatinine level (Scr), and creatinine clearance (CLcr) were also recorded for each patient. Data for plasma concentration of unbound platinum from 94 courses in 94 patients after the first administration of nedaplatin were used for regression analysis (data set D). The dose and infusion period varied among the patients, and the ranges of dose and infusion period were 20–107 mg/m^2 and 60–180 min, respectively. The numbers of data points for plasma unbound platinum concentration were three to seven per patient. The data were taken at the end of infusion and during a postinfusion phase at appropriate intervals. Although both total (bound and unbound) and unbound platinum concentrations were measured, we used only the data for unbound platinum in the present study because it has been reported to have a cytotoxic effect [11, 30]. To validate the formula obtained, new external data sets were used. They were as follows: (1) data after the second or later dosing from the same patients as those for model development (28 courses in 24 patients, data set V1); (2) data after the first dosing from a second group of patients (42 courses in 42 patients, data set V2); (3) data after the second dosing from a third group of patients (23 courses in 16 patients including 7 patients from data set V2, data set V3).

Assay methods

The concentrations of total and unbound platinum in plasma were measured by an atomic absorption spectrometry assay method at Shionogi Biomedical Laboratories (Osaka, Japan) [12]. The detection limit for this method was 0.2 μg/ml. The patients' demographic and clinical laboratory test data were obtained from each hospital.

Data analysis

Unbound platinum clearance (CL) was calculated according to Eq. 1 using the AUC of unbound platinum which was calculated by the trapezoidal method from zero time to the last sampling time. The pharmacokinetic analysis package WinNonlin Version 2.1 (Pharsight, Mountain View, Calif.) was used to calculate AUC.

$$\mathrm{CL} = \mathrm{Dose}/\mathrm{AUC} \tag{1}$$

The dependence of CL of unbound platinum on the patient characteristics was estimated by multiple linear regression analysis. The candidates tested for covariates of CL were Scr, CLcr, Age, BWT, infusion period (Tinf) and infusion rate (Rate). As well as the observed CLcr, the CLcr calculated according to the Cockcroft-Gault formula [6] (Eq. 2) was also tested. All variables were included in the regression model and the most significant variable was selected. The covariates were selected by a stepwise regression method based on the *F*-value at 5% of the significance level.

$$\mathrm{CLcr} = \frac{(140 - \mathrm{Age}) \cdot \mathrm{BWT}}{72 \cdot \mathrm{Scr}} \cdot 0.85^{\mathrm{Gender}} \tag{2}$$

In Eq. 2, Gender is a categorical value which is 0 for males and 1 for females.

To evaluate the goodness of fit by regression analysis, two indices, the mean prediction error (ME) as a measure of bias (Eq. 3) and root mean squared error (RMSE) as a measure of precision (Eq. 4) were used [26] to compare the predicted and observed values of CL and AUC. The relative values for these indices were also examined using Eqs. 5 and 6, respectively.

$$\mathrm{ME} = \frac{1}{\mathrm{N}}\sum (\mathrm{Pred} - \mathrm{Obs}) \tag{3}$$

$$\mathrm{RMSE} = \sqrt{\frac{1}{\mathrm{N}}\sum (\mathrm{Pred} - \mathrm{Obs})^2} \tag{4}$$

$$\mathrm{ME}(\%) = \frac{1}{\mathrm{N}}\sum \left(\frac{\mathrm{Pred} - \mathrm{Obs}}{\mathrm{Pred}}\right) \times 100 \tag{5}$$

$$\mathrm{RMSE}(\%) = \sqrt{\frac{1}{\mathrm{N}}\sum \left(\frac{\mathrm{Pred} - \mathrm{Obs}}{\mathrm{Pred}}\right)^2} \times 100 \tag{6}$$

In Eqs. 3–6, Pred is the predicted value of CL or AUC, Obs is the observed value of CL or AUC, and N is the number of patients.

Table 1. Institutions where clinical data were obtained

Department of Thoracic Surgery, Asahikawa Medical University Hospital
Department of Obstetrics and Gynecology, Hiroshima City Hospital
Department of Obstetrics and Gynecology, Hyogo College of Medicine
Department of Obstetrics and Gynecology, Hyogo Prefectural Nishinomiya Hospital
Department of Obstetrics and Gynecology, Nara Prefectural Mimuro Hospital
Department of Obstetrics and Gynecology, National Mito Hospital
Department of Internal Medicine, National Shikoku Cancer Center Hospital
Department of Internal Medicine, Okayama Institute of Health and Prevention Hospital
Department of Internal Medicine, Okayama University
Department of Obstetrics and Gynecology, Osaka University, Faculty of Medicine
Department of Obstetrics and Gynecology, Saiseikai Tondabayashi Hospital
Department of Pulmonary Medicine, Saitama Cancer Center
Department of Radiology, Tokyo University
Department of Medicine I, Tokyo Women's Medical University

Validation

Validation of the estimated formula was performed by evaluating the predictive performance of CL and AUC for unbound platinum. The predicted CL and AUC values based on the estimated formula were compared with the observed values in the three validation data sets (V1, V2 and V3). The predictive performance of CL and AUC was evaluated with Eqs. 3–6.

Results

Table 2 summarizes the data and characteristics of the 94 patients (data set D) used to develop the formula to estimate unbound platinum CL, and those of the 75 patients used to validate the formula (data sets V1, V2 and V3). Concomitant therapy was applied in about 60% of the courses, and the numbers of courses for each combination regimen are listed. Figure 1 shows the dependence of the unbound platinum CL on Age, BWT and Scr in data set D. The CL showed a significant positive correlation with BWT ($CL = 0.096 \times BWT + 5.051$, $r = 0.279$, P-value for slope 0.006). CL showed a significant negative correlation with Age and Scr ($CL = -0.163 \times Age + 19.744$, $r = -0.433$, P-value for slope < 0.001; $CL = -7.442 \times Scr + 15.699$, $r = -0.365$, P-value for slope < 0.001). The relationships between CL and observed CLcr or CLcr calculated by the Cockcroft-Gault formula are shown in Fig. 2. CL showed a significant correlation with both the observed and the calculated CLcr ($CL = 0.066 \times CLcr + 4.825$,

Table 2. Characteristics of patients. Values are means ± SD with ranges shown in the adjacent column

	Data sets			
	D		V1, V2, V3	
Total number of patients (courses)	94 (94)		75 (93)	
Male	35 (35)		29 (29)	
Female	59 (59)		46 (64)	
Number of plasma samples				
Total	409		391	
Per course	4.4 ± 0.9	3–7	4.2 ± 1.2	2–7
Infusion time (min)	70.9 ± 24.8	60–180	112.5 ± 47.1	60–210
Dose (mg)				
Per patient	113.4 ± 30.8	33–180	102.3 ± 44.3	13–170
Per m^2	74.6 ± 17.8	20–107	67.9 ± 27.6	9–110
Concomitant therapy (no. of courses)				
Cyclophosphamide	5		10	
Ifosfamide	–		5	
Ifosfamide + bleomycin	10		10	
Ifosfamide + peplomycin	–		1	
Ifosfamide + vindesine	–		2	
Vindesine	41		5	
Gemcitabine	–		2	
Etoposide	4		3	
Vinorelbine	–		18	
None, cisplatin 1 week later	12		13	
None	22		24	
Age (years)	57.9 ± 10.2	32–77	57.9 ± 11.1	29–81
Body weight (kg)	54.8 ± 11.2	34–84	53.5 ± 8.7	36–76
Scr (mg/dl)	0.73 ± 0.19	0.4–1.2	0.74 ± 0.21	0.4–1.36
CLcr (ml/min)				
Observed	82.14 ± 25.64	43.0–165.6	79.56 ± 24.13	19.1–132.9
Calculated	81.96 ± 26.15	42.6–154.9	78.96 ± 27.12	19.7–178.8

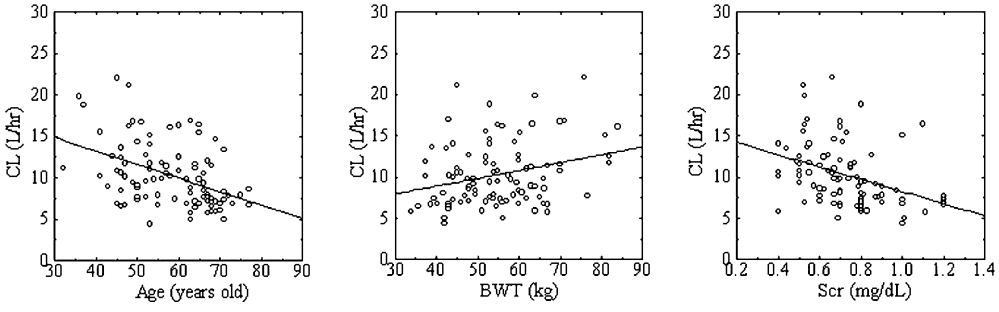

Fig. 1. Relationship between CL of unbound platinum and Age, body weight (*BWT*) and Scr in data set D (model development data)

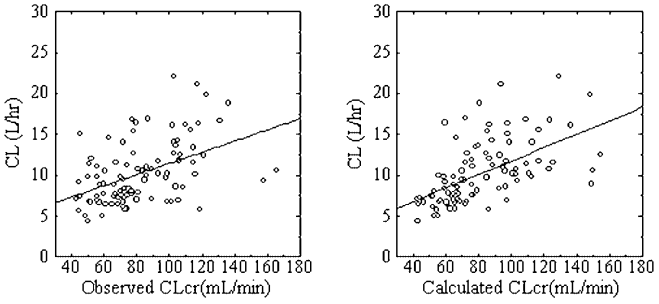

Fig. 2. Relationship between CL of unbound platinum and observed and calculated CLcr in data set D (model development data)

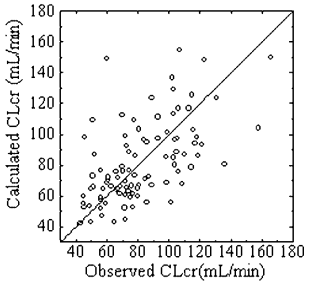

Fig. 3. Relationship between observed CLcr and calculated CLcr in data set D (model development data). The line is the line of unity

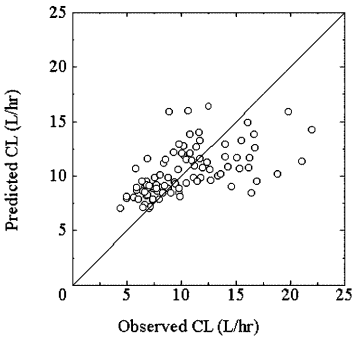

Fig. 4. Relationship between observed CL and calculated CL in data set D (model development data). The line is the line of unity

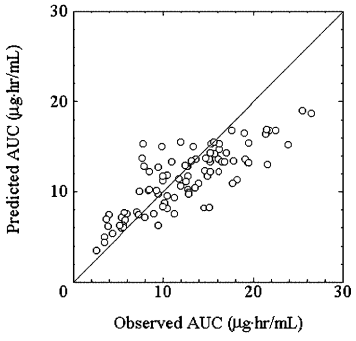

Fig. 5. Relationship between observed AUC and calculated AUC in data set D (model development data). The line is the line of unity

Table 3. Multiple coefficient of determination (R^2) and P-value for significance

Covariate	R^2	P-value
Age	0.188	< 0.001
BWT	0.078	0.006
T_{inf}	0.001	0.726
Rate	0.008	0.380
Scr	0.133	< 0.001
1/Scr	0.112	0.001
CLcr observed	0.195	< 0.001
CLcr calculated	0.325	< 0.001

$r = 0.441$, P-value for slope < 0.001; CL = 0.084×calculated CLcr + 3.450, $r = 0.570$, P-value for slope < 0.001). The relationship between the observed and the calculated CLcr is shown in Fig. 3. The observed and the calculated CLcr showed a significant correlation (observed CLcr = 0.566×calculated CLcr + 36.100, $r = 0.575$, P-value for slope < 0.001).

All variables were first included in the regression model and the significance of each variable was examined. Table 3 shows the summary of the regression analysis. Most of the variables except Tinf and Rate were found to be significantly related to CL. Considering that the correlation between CL and calculated CLcr was the best ($r = 0.570$), we decided to use the calculated CLcr as a covariate. Because the calculated CLcr and the observed CLcr displayed a significant correlation as shown in Fig. 3, the observed CLcr was excluded from the candidates in subsequent analyses. Moreover, Age, BWT and Scr are included in the Cockcroft-Gault formula, and therefore these variables were also excluded. A stepwise regression method gave the final formula to estimate CL as Eq. 7. Only the calculated CLcr was found to be a significant covariate for the CL of unbound platinum. The multiple coefficient of determination (R^2) adjusted for degrees of freedom was 0.317.

$$CL = 0.0836 \times CLcr + 3.45 \quad (7)$$

Figure 4 shows the relationship between the CL predicted by Eq. 7 and the observed CL. Figure 5 shows the relationship between the AUC calculated using the predicted CL and the observed AUC. Table 4 shows the values of the indices for the goodness of fit (ME and RMSE). There seemed to be a tendency to underestimate the CL at higher values over about 15 l/h, and also to underestimate the AUC over about 20 μg·h/ml. However, overall, a practically acceptable prediction was achieved for both CL and AUC.

Validation was performed using the external data set from the patients listed in Table 2. Figure 6 shows the relationship between the CL predicted by Eq. 7 and the observed CL in the patients for the validation. Figure 7 shows the relationship between the AUC calculated using the predicted CL and observed AUC. Table 5

Table 4. Summary of predictive performance for CL and AUC in the model development process. The percentage values are relative indices given by Eqs. 5 and 6 (*ME* mean prediction error, *RMSE* root mean squared error)

	ME		RMSE	
CL (l/h)	0.002	0.3%	3.134	29.6%
AUC (μg·h/ml)	–1.175	–8.3%	3.470	29.7%

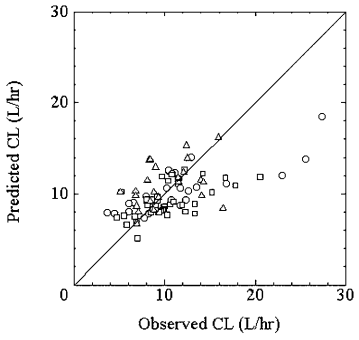

Fig. 6. Relationship between observed and predicted CL in the validation data, data set V1 (*circles*), data set V2 (*squares*) and data set V3 (*triangles*). The line is the line of unity

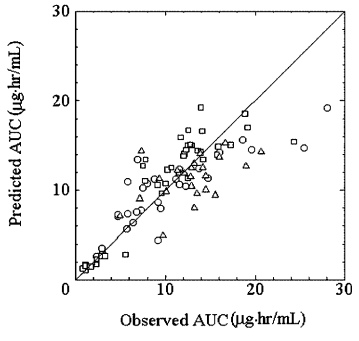

Fig. 7. Relationship between observed and predicted AUC in the validation data, data set V1 (*circles*), data set V2 (*squares*) and data set V3 (*triangles*). The line is the line of unity

shows the values of the indices for predictive performance. Profiles for the correlation of the CL and AUC in the validation data seem to display the same patterns as those in the data set used for model development. In both the validation and the model development data sets, CL and AUC tended to be underestimated at higher values. The values of ME and RMSE for CL and AUC in the validation data were almost the same as those in the model development data, but the value of ME for the CL in the validation data was slightly larger.

Discussion

We developed a simple formula for calculating the optimal dosage of nedaplatin. A formula relating the unbound platinum CL after CBDCA administration with the renal function of patients has already been reported [2]. It relates CL to the glomerular filtration rate (GFR), but CLcr or Scr are usually measured rather than GFR as an index of renal function in the present Japanese clinical situation. We therefore decided to use CLcr as a measure of renal function.

Multiple regression analysis showed that the relationship between CL and the calculated CLcr gave the best correlation. Therefore we omitted the variables Age, BWT and Scr which were included in the Cockcroft-Gault formula prior to the covariate selection procedure. For reference, multiple regression analysis was performed using Eq. 8 including Age, BWT and Scr:

$$CL = a \times Age + b \times BWT + c \times Scr + d \quad (8)$$

where a, b, c and d are coefficients for the linear regression model. The multiple coefficient of determination (R^2) adjusted for degrees of freedom was 0.377 and the indices for the goodness of fit were: ME = –0.014 (–0.3%) and RMSE = 2.960 (28.8%), which were almost the same as those for Eq. 7. However, in the case of the validation data set ($N = 93$), ME and RMSE were 0.629 (–32.0%) and 3.469 (242%), respectively. The predictive performance was poorer for Eq. 8 than for Eq. 7. From these results, we decided to use Eq. 7, which is also simpler to use in clinical practice.

It has been reported that CL decreases following the second dose of cisplatin [7], but no clear differences were observed in the predictive performances of Eq. 7 with any of the validation data sets (V1, V2 and V3), leading to the conclusion that Eq. 7 is useful not only for the first treatment with nedaplatin but also for the second and later courses of treatment. In order to clarify the change in platinum clearance during nedaplatin treatment, differences in platinum clearance in identical

Table 5. Summary of predictive performance for CL and AUC in the validation data. The percentage values are relative indices given by Eqs. 5 and 6 (*ME* mean prediction error, *RMSE* root mean squared error)

	Data set	ME		RMSE	
CL (l/h)	V1	–1.008	–6.2%	4.118	34.4%
	V2	–1.040	–11.4%	2.819	29.4%
	V3	0.924	6.4%	3.280	31.7%
	All (V1, V2, V3)	–0.545	–5.4%	3.370	31.5%
AUC (μg·h/ml)	V1	–0.624	–4.0%	3.714	34.7%
	V2	0.723	4.3%	2.597	26.4%
	V3	–1.576	–17.0%	3.570	37.4%
	All (V1, V2, V3)	–0.251	–3.5%	3.217	32.0%

patients were tested by a paired *t*-test. The differences in the mean values between the CL on the first cycle and those on the second or later cycles in the same patients were tested. The mean values of CL were 11.0 l/h and 11.6 l/h in the first cycle and the second or later cycles, respectively, and the SDs of the CL values were 3.8 and 5.7, respectively. The *P*-value obtained from the paired *t*-test was 0.507, indicating no significant difference. It was supposed that nedaplatin was less nephrotoxic than cisplatin and it was considered that CL did not change with the second dose of nedaplatin.

For individualizing the dosage regimen for nedaplatin, as well as the prediction method of AUC, as shown here, the relationship between AUC and efficacy or toxicity should also be examined. It has been reported that the change in the number of leukocytes is related to the AUC of unbound platinum [25]. Thus it must be meaningful to adjust dosage based on the target AUC related to the toxicity, and our formula would be helpful for determining the optimum dosage regimen to achieve the target AUC after infusion.

In conclusion, we developed a new formula for predicting the CL of unbound platinum after nedaplatin administration. Only CLcr was found to be a significant covariate of CL. The CL was not affected by either the infusion period or the infusion rate. This formula for estimating CL was found to be useful for the second treatment with nedaplatin as well as for the first treatment.

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