

## Determination of Optimal Dosage for Nedaplatin Based on Pharmacokinetic and Toxicodynamic Analysis

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**Abstract.** Nedaplatin is a platinum derivative anticancer drug. To determine its target AUC in cancer patients, the relationship between platinum AUC and hematological toxicity after administration of nedaplatin was analyzed. The data for plasma unbound platinum concentration, platelet (PLT) and white blood cell (WBC) counts were retrospectively obtained from 108 courses administered to 74 Japanese adult cancer patients. PLT and WBC decreased significantly after nedaplatin administration. The results of linear regression analysis suggested that the relative reduction ratio of PLT significantly correlated with AUC after nedaplatin administration and the relationship was not affected by the dosing course of nedaplatin nor the combination of other cancer drugs. From these findings, it became possible to determine the target AUC based on the pre-dose value of PLT and the tolerable or target nadir of PLT after nedaplatin administration. By using a simple formula to predict the individual platinum clearance of nedaplatin from a patient's renal function, it is possible to determine the optimal dose for individuals by taking into consideration the adequate maximum tolerable AUC and individual platinum clearance.

Nedaplatin, cis-diammineglycolatoplatinum (1), is an anticancer drug that was developed to reduce nephrotoxicity, which is often a dose-limiting factor of cisplatin (2, 3), and also to offer higher antitumor activity than carboplatin (4). In phase II clinical studies, high efficacy against head and neck cancer, non-small cell lung carcinoma, esophageal cancer, testicular tumor and cervical cancer has been reported (5). The dose-limiting factor for nedaplatin is said to be its hematological toxicity, which is also the case with carboplatin (2, 3, 6, 7).

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In anticancer chemotherapy, the maximum tolerance dose (MTD) with respect to side-effects is usually used to achieve the optimal effect (8-10), and therefore serious adverse effects often occur, especially in patients exposed to a high drug concentration. To minimize the frequency of adverse effects, the optimal dosage regimen should be individualized by taking the inter-individual pharmacokinetic variability into consideration. For this purpose, it is important to predict individual platinum clearance. We previously reported a simple formula for predicting platinum clearance based on individual renal function, *i.e.*, creatinine clearance, after nedaplatin administration (11), like the Calvert formula for carboplatin (12). We also reported the population pharmacokinetic parameters of nedaplatin (13), which offer useful information for constructing nomograms to set up appropriate dosing regimens and also for Bayesian forecasting. Such pharmacokinetic information is useful for individual control of the optimal plasma concentration and area under the curve of plasma concentration (AUC).

To determine the optimal dosage regimen, it is necessary to combine pharmacodynamic and toxicodynamic data with pharmacokinetic information, as has been done for other platinum derivatives. The relationship of the AUC of plasma unbound platinum with efficacy and toxicity after carboplatin administration has been investigated, and the target AUC for the optimal dosage regimen has been proposed (14-16). Because the pharmacokinetic profile and hematological toxicity of carboplatin are similar to those of nedaplatin (6, 17, 18), the dosage regimen of nedaplatin can be determined based on AUC as in the case of carboplatin.

The aim of the present study was to evaluate the relationship between platinum AUC and nephrotoxicity and/or hematological toxicity after nedaplatin administration, and to determine the optimal dosage regimen in cancer patients based on the toxicodynamic data.

### Patients and Methods

**Patients.** Plasma unbound platinum concentration data (474 points), platelet (PLT) and white blood cell (WBC) counts were retrospectively collected from 108 courses administered to 74 Japanese adult patients with lung, esophageal, cervical or ovarian

cancer. The patients had been given clinical treatments with nedaplatin once a month at 12 institutions. All data were collected as a part of a post-marketing surveillance of nedaplatin in multi-centers, and informed consent and ethical approval were obtained at each institution. Demographic data including gender, age, body weight (BWT), serum creatinine level (Scr) and creatinine clearance (CLcr) were also collected. The dose level and the infusion duration varied among the patients, with ranges of 40-110 mg/m<sup>2</sup> and 1-5 hours, respectively. The number of data points for plasma unbound platinum concentration were 2-8 per patient. Plasma samples were taken at the end of the infusion and during the post-infusion phase at appropriate intervals. All the plasma platinum concentrations before the start of nedaplatin infusion were under the detection limit. Although both the total (sum of bound and unbound) and unbound platinum concentrations were measured, we used only the data for unbound platinum in the present study because it is related to the cytotoxic effects (19, 20). In each treatment course, PLT and WBC counts were measured before and after nedaplatin administration. The data with concomitant dosing of cisplatin or carboplatin were excluded from the analysis. Data obtained after arterial infusion, and from patients with dialysis or radiation treatment, were also excluded.

*Assay methods.* The plasma unbound fraction was separated by an ultrafiltration method. Total and unbound plasma platinum concentrations were measured by a validated atomic absorption spectrometry assay method (21) in Shionogi Biomedical Laboratories (Osaka, Japan). The lower determination limit of this method is 0.2 µg/mL. Demographic data and values from clinical laboratory tests were obtained from each hospital where the treatment was administered.

*Calculating AUC.* Unbound platinum AUC was used. The number of data points per patient for plasma unbound platinum concentration was 2-8, and AUC calculated by the trapezoidal method may have included a large calculation error especially when there were few points for the concentration data. Therefore, AUC was calculated using  $AUC = \text{dose} / CL$ , where individual clearance (CL) was estimated by an empirical Bayesian method using the population pharmacokinetic parameters of nedaplatin that we had reported previously (13), using NONMEM Version 5 (22) with a *post hoc* option.

*Pharmacokinetic and toxicodynamic analysis.* In order to clarify the possible effect of nedaplatin on nephrotoxicity and hematological toxicity, the differences of mean values for Scr, CLcr, PLT and WBC before and after nedaplatin administration were examined using the paired *t*-test at a 5% significance level. The test was performed separately for both cases of nedaplatin monotherapy and combination therapy with other anticancer drugs. As shown in the Results, there were no significant changes in both Scr and CLcr in the case of nedaplatin monotherapy, and there were only small changes in both Scr and CLcr in the case of combination therapy. No further assessments for nephrotoxicity were performed.

The number of courses at each grade of hematological toxicity, based on the National Cancer Institute Common Toxicity Criteria (23, 24), is summarized with the values of unbound platinum AUC, pre-dose counts and nadir of PLT or WBC. The dependence of possible changes of PLT or WBC on platinum AUC and pre-dose counts of PLT or WBC were evaluated by a linear regression

analysis. Considering that some previous reports regarding carboplatin had shown a linear relationship between PLT and platinum AUC on using the relative change in PLT, we also used the relative change of PLT or WBC from the pre-dose values as dependent variables as given by Eq.(1), which uses the case of PLT as an example (25-31).

$$\frac{(PLT_{nadir} - PLT_{pre})}{PLT_{pre}} \times 100 (\%) = \theta_1 \times AUC \quad (1)$$

In Eq.(1), PLT<sub>pre</sub> is the pre-dose count of PLT, and PLT<sub>nadir</sub> is the nadir of PLT after administration of nedaplatin. The units of each PLT and AUC are 10,000 counts/µL and µg·h/mL, respectively. θ<sub>1</sub> is the slope for the relationship and the intercept of the regression can be fixed at zero under the assumption that PLT<sub>nadir</sub> without nedaplatin should be equal to PLT<sub>pre</sub>. The data is divided into two groups, one being that after nedaplatin monotherapy and the other being that after combination therapy, in order to examine the influence of the other cancer drugs on the AUC-toxicity relationship.

To confirm the occasional difference in the relationships among these groups, the results of regression analysis using only the data for the first dosing of nedaplatin were compared with those for more dosing based on the F-value at a 5% significance level. When there was no occasional difference, the data were combined and θ<sub>1</sub> was estimated using the pooled data.

To clarify the influence of the concomitant drugs, the results of the regression for the data after monotherapy were compared with those after combination therapy based on the F-value at 5% significance level. When there was no difference between the cases of monotherapy and combination therapy, the data of both groups were also pooled. In order to evaluate the effect of some concomitant drugs on the relationship, the data for each concomitant drug used in more than three treatment courses were separated and analyzed using Eq.(2).

$$\frac{(PLT_{nadir} - PLT_{pre})}{PLT_{pre}} \times 100 (\%) = \theta_1 \times \left( 1 + \sum_{j=1}^k \theta_{j+1} \times CA_j \right) \times AUC \quad (2)$$

In Eq.(2), the factor (1 + θ<sub>j+1</sub> × CA) was considered where CA<sub>j</sub> is a categorical value that takes 1 for the case of combination therapy with a drug j, and takes 0 for other cases. θ<sub>j+1</sub> represents additional parameters for the effect of combination therapy with drug j. The statistical significance of the parameter (θ<sub>j+1</sub>) was tested by stepwise method based on the difference of AIC (Akaike's Information Criterion) (32, 33).

In order to evaluate the dependence of WBC, linear regression analysis was applied using the same model as those for PLT given by Eq.(1') and Eq.(2'), where the unit of WBC is counts/µL.

$$\frac{(WBC_{nadir} - WBC_{pre})}{WBC_{pre}} \times 100 (\%) = \theta_1 \times AUC \quad (1')$$

$$\frac{(WBC_{nadir} - WBC_{pre})}{WBC_{pre}} \times 100 (\%) = \theta_1 \times \left( 1 + \sum_{j=1}^k \theta_{j+1} \times CA_j \right) \times AUC \quad (2')$$

The predictive performance of the final regression models was evaluated using the mean prediction error (ME) and the root

Table I. Summary of data sets and patient characteristics.

Total number of courses*	108	
in males	53	
in females	55	
Number of plasma samples	474	
samples/patient	4.4±1.1	[2-8]
Infusion time (min)	119.9±48.0	[60-300]
Dose (mg/human)	124.9±26.3	[40-180]
Dose (mg/m <sup>2</sup> )	83.8±12.4	[40-110]
Age (years old)	59.2±10.6	[32-81]
Body weight (kg)	54.1±10.3	[36.9-83]
Demographic data before administration		
Scr (mg/dL)	0.76±0.20	[0.40-1.22]
Observed CLcr (mL/min : n=101)	81.7±24.8	[34.0-165.6]
Calculated CLcr (mL/min)	79.3±29.3	[34.2-178.8]
WBC (counts/ $\mu$ L)	6085±3550	[2000-28100]
PLT (counts x 10 <sup>4</sup> / $\mu$ L)	26.2±9.9	[10.4-58.1]
Demographic data after administration		
Scr (mg/dL : n=99)	0.83±0.30	[0.4-2.65]
Observed CLcr (mL/min : n=59)	70.6±21.7	[31.0-122.4]
Calculated CLcr (mL/min : n=99)	75.0±30.0	[19.5-187]
WBC (counts/ $\mu$ L)	2658±1452	[190-8700]
PLT (counts x 10 <sup>4</sup> / $\mu$ L)	12.3±6.90	[0.6-34.2]

\* Total number of patients, 74 (male: 41, female: 33)  
Mean±S.D.

Values in parenthesis: [Minimum – Maximum]

square mean error (RMSE) as the indices of bias and precision, respectively (34). Furthermore, the final regression models were validated by the leave-one-out cross-validation procedure (35). The values of ME and RMSE in the leave-one-out method were compared with those for the final regression models, respectively.

## Results

Table I shows the summary of the data set and the patients' characteristics. For 27 out of the 74 patients, the second or later dosing with nedaplatin was given after an interval of about a month. The number of courses where the plasma concentrations were measured after the first course was 70, and that in the second or later courses was 38. The numbers of courses using monotherapy and combination therapy were 26 and 82, respectively. The details for concomitant anticancer drugs were as follows: cyclophosphamide, 8 courses; combinations including ifosfamide, 30; 5-FU, 13; combination of methorexane, vinblastin and adreamycin, 1; gemcitabine, 2; vinorelbine, 21; and vindesine, 8.

Figure 1 shows histograms of the change of post-dose values from the pre-dose values for Scr (a), CLcr (b), PLT (c) and WBC (d). The mean Standard Deviation (S.D.) values of change in Scr and CLcr in the case of

monotherapy were 0.16 (0.36) mg/dL and -4.7 (22.7) mL/min, respectively, and the results of the paired *t*-test suggested no significant changes in both Scr and CLcr. In the case of combination therapy, significant changes in both Scr and CLcr were found, but the mean values of the changes in Scr (0.03 (0.11) mg/dL) and CLcr (-8.88 (19.3) mg/dL) were close to zero, and therefore we concluded that these differences are clinically less important. Considering these results and some reports suggesting little nephrotoxicity of nedaplatin (2, 3, 13), no further assessments for Scr and CLcr were performed.

The results of the paired *t*-test suggested that PLT and WBC significantly decreased in both cases of monotherapy and combination therapy. The mean (S.D.) values of change in PLT in the cases of monotherapy and combination therapy were -13.7 (8.6) x 10,000 counts/ $\mu$ L and -13.9 (9.7) x10,000 counts/ $\mu$ L, respectively. The mean (S.D.) values of change in WBC were -1640 (1210) counts/ $\mu$ L and -3990 (3560) counts/ $\mu$ L, respectively.

The number of courses in each toxic grade (Grade 0 - Grade 4) is summarized in Table II with the mean (S.D.) AUC values and mean (S.D.) values for the pre-dose count and nadir in the corresponding treatment courses in each grade for PLT (Table II(a)) and WBC (Table II(b)). None of the courses showed Grade 4 for both PLT and WBC in the case of monotherapy, only one course showed Grade 4 for PLT, and nine courses showed Grade 4 for WBC in the case of combination therapy. In Table II, there was no clear relationship between the toxicity grade and AUC, probably because the pre-dose values for PLT and WBC varied between the patients. Therefore, in the current regression analysis, the relative changes in PLT and WBC were used as dependent variables as explained in the Patients and Methods section, and a linear regression analysis was performed.

The results of regression analysis and F-test for PLT are as follows. In Step 1, no significant differences were found for both cases of monotherapy ( $F=0.003$ ,  $p=0.957$ ) and combination therapy ( $F=1.55$ ,  $p=0.216$ ) between the regression results for the data after the first dosing (monotherapy:  $n=14$ , combination:  $n=56$ ) and at further dosing (monotherapy:  $n=12$ , combination:  $n=26$ ). This confirmed that there was no occasional difference for the change in PLT and the data were pooled. In Step 2, as no significant difference was found between the regression results of the pooled monotherapy data ( $n=26$ ) and the pooled combination therapy data ( $n=82$ ) ( $F=1.45$ ,  $p=0.231$ ), all the data were pooled. In Step 3, to evaluate the influence of specific concomitant drugs, Eq.(2) was applied to the pooled data sets. The difference in AIC values for the concomitant drug such as cyclophosphamide, ifosfamide, 5-FU, vinorelbine and vindesine were 1.77, 2.00, 1.59, 1.81 and -0.63, respectively, suggesting no significant concomitant effect on the regression result.

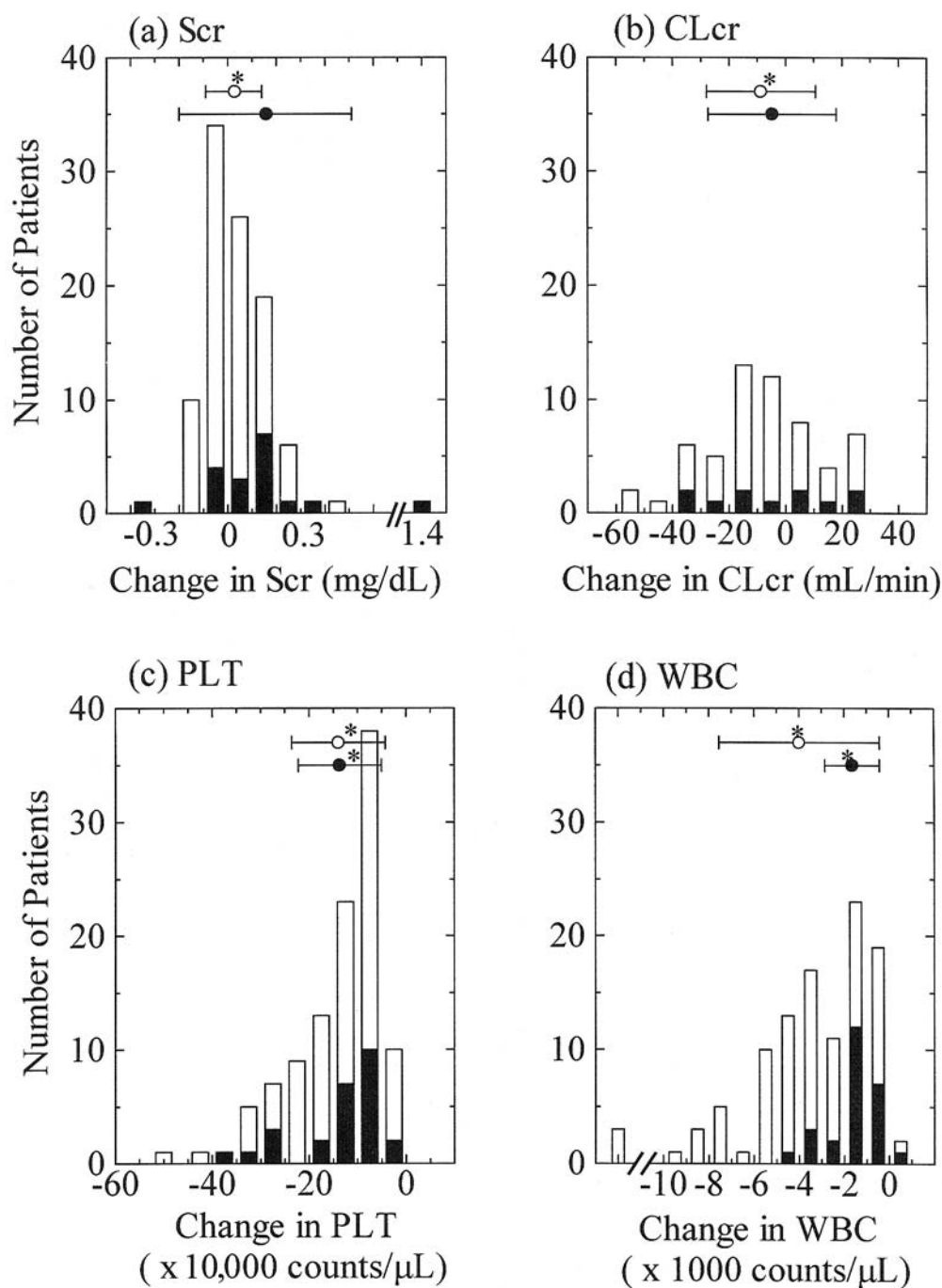


Figure 1. Histograms of change in Scr (a), CLcr (b), PLT (c) and WBC (d) after nedaplatin administration, and plots of mean and S.D. Closed bars: monotherapy data, open bars: combination therapy data, closed circles: mean (and S.D.) in monotherapy, open circles: mean (and S.D.) in combination therapy, \*: significant difference at 5% levels by paired t-test.

For PLT, the final model is given by Eq.(3), where the 95% confidence interval for slope (Lower, Upper) was (-4.04, -3.47). The multiple correlation coefficient was 0.929.

$$\frac{(PLT_{nadir} - PLT_{pre})}{PLT_{pre}} \times 100 (\%) = -3.76 \times AUC \quad (3)$$

Figure 2 shows the relationship between AUC and the relative decrease ratio of PLT. The predicted line by Eq.(3) and the lines of  $\pm 1$  RMSE as the index of precision are shown in Figure 2. The values of ME and RMSE and their 95% confidence intervals (Lower, Upper) (%) were 2.55 (-1.32, 6.42) and 20.59 (17.23, 23.47), respectively. The



Table II. Number of courses at each toxic grade for PLT and WBC with values of AUC, pre-dose and nadir values for PLT (a) and WBC (b).

Table II (a) PLT.

Monotherapy Grade	n	AUC $\mu\text{g}\cdot\text{h}/\text{mL}$		PLT ( $\times 10,000$ counts/ $\mu\text{L}$ )		Nadir	
		Mean (S.D.)	(S.D.)	Mean (S.D.)	(S.D.)	Mean (S.D.)	(S.D.)
Grade 0	15	14.2	(4.8)	25.3	(8.3)	13.4	(2.6)
Grade 1	5	16.0	(3.2)	27.5	(11.1)	7.9	(0.4)
Grade 2	2	12.8	-	12.8	-	6.5	-
Grade 3	4	18.9	(5.2)	20.1	(5.8)	3.8	(0.9)
Grade 4	0	-	-	-	-	-	-
Concomitant Therapy							
Grade 0	52	10.9	(4.1)	28.5	(9.9)	17.3	(5.8)
Grade 1	9	13.8	(3.5)	24.3	(6.1)	8.5	(0.6)
Grade 2	7	13.2	(3.7)	23.2	(4.9)	6.4	(0.7)
Grade 3	13	14.6	(4.4)	22.9	(13.5)	3.5	(1.4)
Grade 4	1	28.5	-	45.2	-	0.6	-

Table II (a) WBC.

Monotherapy Grade	n	AUC $\mu\text{g}\cdot\text{h}/\text{mL}$		WBC (counts/ $\mu\text{L}$ )		Nadir	
		Mean (S.D.)	(S.D.)	Mean (S.D.)	(S.D.)	Mean (S.D.)	(S.D.)
Grade 0	5	14.8	(6.1)	6538	(1953)	5236	(606)
Grade 1	9	14.8	(4.5)	5189	(985)	3583	(265)
Grade 2	6	16.3	(4.7)	4700	(1180)	2587	(312)
Grade 3	6	14.7	(4.8)	3305	(661)	1805	(206)
Grade 4	0	-	-	-	-	-	-
Concomitant Therapy							
Grade 0	11	10.8	(4.1)	11075	(7358)	5316	(1370)
Grade 1	12	9.9	(3.4)	6649	(2591)	3434	(330)
Grade 2	22	12.2	(5.0)	5597	(2640)	2355	(267)
Grade 3	28	13.2	(5.0)	5639	(2631)	1602	(219)
Grade 4	9	14.0	(3.5)	5234	(927)	661	(295)

values of ME and RMSE and their 95% confidence interval for the prediction based on the leave-one-out method were 2.53 (-1.38, 6.45) and 20.83 (17.39, 23.77), respectively. As similar values for ME and RMSR by the leave-one-out method were obtained to those by the final model, this confirmed the final model to be robust and useful for predictive purposes.

The results of regression analysis and F-test for WBC are as follows. In Step 1, no significant differences were found for both cases of monotherapy ( $F=0.12$ ,  $p=0.733$ ) and combination therapy ( $F=2.09$ ,  $p=0.152$ ) between the regression results for the data after first dosing (monotherapy:  $n=14$ , combination:  $n=56$ ) and at further dosing (monotherapy:  $n=12$ , combination:  $n=26$ ). This

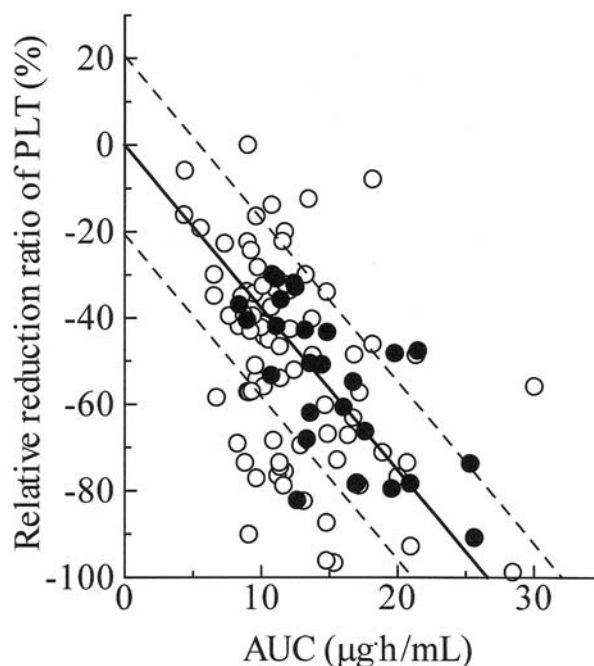


Figure 2. Relationships between the relative reduction ratio of PLT and AUC of unbound platinum. Closed circles: monotherapy data, open circles: combination therapy data, solid line: regression line given by Eq.(3) and dashed line: regression line  $\pm$  RMSE (20.59).

confirmed that there was no difference for the change in WBC and the data were pooled. In Step 2, as a significant difference was found between the regression results of the pooled monotherapy data ( $n=26$ ) and the pooled combination therapy data ( $n=82$ ) ( $F=21.9$ ,  $p=0.000$ ), the data were not pooled. Table III shows the summary of the test to find possible effects by the concomitant drugs by Eq.(2') for WBC using the data for combination therapy. Based on the AIC, Eq.(4) was obtained, the coefficients for vinorelbine and vindesine being 0.80 and 0.78, respectively.

$$\frac{(\text{WBC}_{\text{nadir}} - \text{WBC}_{\text{pre}})}{\text{WBC}_{\text{pre}}} \times 100 (\%) = -3.32 \times (1 + 0.80 \times \text{VNB}) \times (1 + 0.78 \times \text{VP}) \times \text{AUC} \quad (4)$$

where VNB and VP are categorical parameters that take 1 for the case of concomitant administration of vinorelbine and vindesine, and 0 otherwise. As there were no courses in which vinorelbine and vindesine were administered simultaneously, the interaction (correlation) between these coefficients was not considered. If these drugs are simultaneously used with nedaplatin, Eq.(4) should be applied carefully because we do not know the effect of simultaneous dosing of these drugs on the change in WBC. The 95% confidence intervals for the slope (-3.32), factors for vinorelbine (0.80) and vindesine (0.78) (Lower, Upper) were (-3.85, -2.79), (0.38, 1.23) and (0.27, 1.30), respectively. The multiple correlation coefficient

Table III. Test for influence of concomitant drugs on WBC.

Trial No.	Data	Tested concomitant drug	Δ AIC <sup>1)</sup>	Significance <sup>2)</sup> Compared <sup>3)</sup>
1	In concomitant therapy (n=82, AIC=923.7)			
2		cyclophosphamide	-7.78	p<0.05
3		ifosphamide	-0.26	NS
4		5-FU	-0.63	NS
5		vinorelbine	-11.7	p<0.05
6		vindesine	-4.05	p<0.05
7		cyclophosphamide and vinorelbine	-4.47	p<0.05
8		vinorelbine and vindesine	-9.51	p<0.05
9		cyclophosphamide and vindesine	-2.24	NS
10		cyclophosphamide, vinorelbine and vindesine	-2.13	NS

<sup>1)</sup>Difference of AIC

<sup>2)</sup>NS means "not significantly different".

<sup>3)</sup>Trial No. compared AIC

was 0.881. The final model for WBC in the case of monotherapy is given by Eq.(5), and the 95% confidence interval for the coefficient was (-2.56, -1.63). The multiple correlation coefficient was 0.905.

$$\frac{(WBC_{nadir} - WBC_{pre})}{WBC_{pre}} \times 100(\%) = -2.09 \times AUC \quad (5)$$

Figure 3 shows the relationship between AUC and the relative decrease ratio of WBC. The predicted lines based on Eq.(5) and Eq.(4) in which both VNB and VP are equal to 0, and the lines of ± 1 RMSE are shown in Figure 3(a) and 3(b), respectively. In Figure 3(b), the predicted lines in the case of concomitant administration of vinorelbine and vindesine are also indicated by dotted line(s). Because the factors for the slope of AUC were similar for these drugs (0.78 and 0.80), the lines almost overlapped each other. The values for ME and RMSE and their 95% confidence intervals (Lower, Upper) (%) were 4.53 (-1.07, 10.13) and 26.12 (22.63, 29.19), respectively, for Eq.(4); and 1.11 (-5.85, 8.07) and 17.79 (9.68, 23.22), respectively, for Eq.(5). The values for ME and RMSE and their 95% confidence intervals for the prediction based on the leave-one-out method were 5.69 (-0.94, 12.32) and 29.21 (24.24, 33.46), respectively, for the case of combination therapy, and 1.01 (-6.21, 8.24) and 18.45 (10.25, 23.99), respectively, for the case of monotherapy. Similar values were obtained by the leave-one-out method as those from the final model, thus confirming the robustness of the final model.

**Discussion**

Nedaplatin has been reported to cause thrombocytopenia to an extent similar to that of carboplatin and more frequently than other anticancer drugs. In this paper, we clarified a significant relationship between the plasma platinum AUC

and the relative reduction ratio of PLT. WBC has also been suggested to decrease significantly in both cases of nedaplatin monotherapy and combination therapy with other anticancer drugs. In the case of combination therapy, there is greater variability in the relative reduction ratio of WBC among the courses than that observed with PLT, and thus the regression results from Eqs. (4) and (5) seem less useful than those from Eq.(3). However, even if severe leukopenia occurs after nedaplatin administration, some hemopoietic factors such as granulocyte colony-stimulating factor (G-CSF) can be used in clinical treatment to recover WBC. Therefore, it should be more important to monitor the plasma PLT level and use Eq.(3) as an index for side-effects of nedaplatin.

In the case of carboplatin, the optimal dose is usually determined based on the target AUC (14-16). In the case of nedaplatin in this study, the relative reduction ratio of PLT correlated well with AUC. Therefore, the target AUC can be estimated with Eq.(3) using the values of target nadir and the pre-dose PLT, and then the optimal dosage can be determined by taking the individual platinum clearance into consideration. However, the results should be interpreted carefully in the case of application to clinical use because the final model (Eq.(3)) includes some inaccuracy as shown by the RMSE lines in Figure 2.

In order to establish a nomogram to determine the optimal dose based on the toxicodynamic data, pharmacokinetic information for nedaplatin is necessary. We have already reported that the unbound platinum CL after nedaplatin administration is related to CLcr (13) and can be given by Eq.(6);

$$CL = 0.0738 \times CLcr + 4.47 \quad (6)$$

where units of CL and CLcr are L/h and mL/min, respectively. Based on Eqs. (3) and (6), we propose an

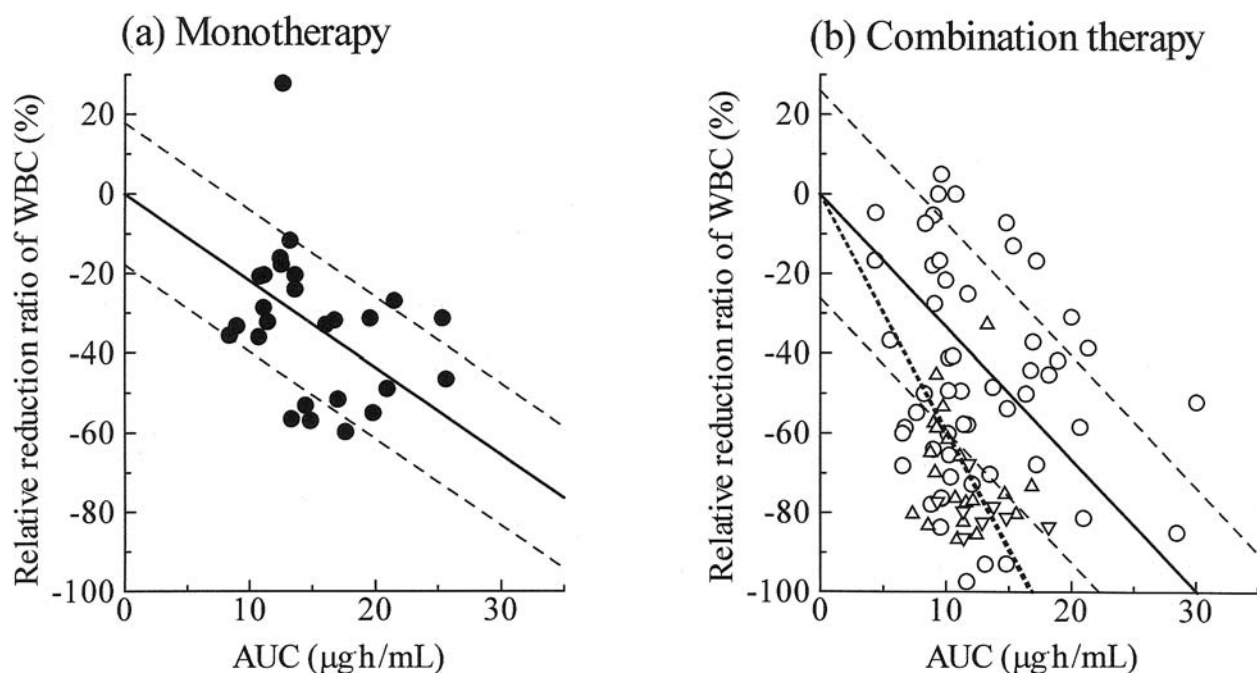


Figure 3. Relationships between the relative reduction ratio of WBC and AUC of unbound platinum in monotherapy (a) and combination therapy (b). a) Closed circles: monotherapy data, solid line: regression lines given by Eq.(5) and dotted line: regression line  $\pm$  RMSE (17.79). b): Open circles: combination therapy except the cases with vinorelbine and vindesine, open triangle: combination with vinorelbine, open reversed triangles: combination with vindesine, solid line: regression line for all combinations except vinorelbine or vindesine given by Eq.(4), dashed lines: regression line  $\pm$  RMSE (26.12), dotted lines: regression lines for vinorelbine or vindesine given by Eq.(4).

example of a nomogram that can estimate the optimal dose that gives the minimum acceptable (nadir) PLT count as shown in Figure 4.

For example, when we define the tolerable  $\text{PLT}_{\text{nadir}}$  to be 100,000 counts/ $\mu\text{L}$  in a patient whose  $\text{PLT}_{\text{pre}}$  is 250,000 counts/ $\mu\text{L}$  and creatinine clearance is 80 mL/min, we can estimate the maximum tolerable AUC to be 16  $\mu\text{g}\cdot\text{h}/\text{mL}$ . We can then estimate the optimal dose to be 160 mg/human. Of course, the results of the present study should be carefully used in clinical practice, because the recommended dose based on this study may sometimes exceed the maximum recommended dose (maximum of 100  $\text{mg}/\text{m}^2/\text{month}$ ).

In conclusion, we found a linear relationship between the thrombocytopenia measured by the extent of PLT decrease with unbound platinum AUC after nedaplatin infusion. The results enabled us to determine the maximum tolerable or target AUC, and consequently the optimal dosage regimen can be designed based on the target AUC by incorporating the individual pharmacokinetic information (individual clearance) estimated from the patient's renal function.

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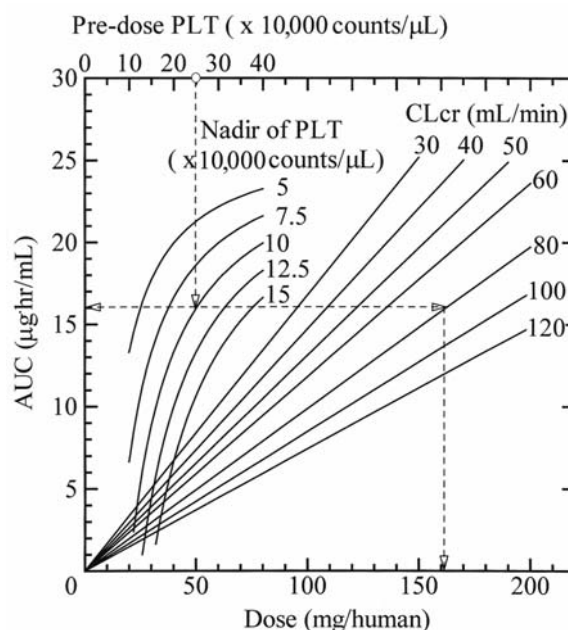


Figure 4. An example nomogram. The x-axis, y-axis and top-axis indicate dose (mg/human), AUC ( $\mu\text{g}\cdot\text{h}/\text{mL}$ ) and pre-dose value of PLT ( $\times 10,000$  counts/ $\mu\text{L}$ ), respectively. The linear lines show the relationship between dose and AUC in a patient whose CLcr value is 30, 40, 50, 60, 80, 100 and 120 ml/min, respectively. The curves show the relationship between  $\text{PLT}_{\text{pre}}$  and AUC when target  $\text{PLT}_{\text{nadir}}$  is set to 5, 7.5, 10, 12.5 and 15  $\times 10,000$  counts/ $\mu\text{L}$ , respectively.

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