ANTICANCER RESEARCH *25*: 1283-1290 (2005)

Optimal Sampling and Limited Sampling Strategies for Estimation of Unbound Platinum AUC After Nedaplatin Infusion

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Abstract. *The aim of this study was to determine the optimal sampling design for empirical Bayesian forecasting for nedaplatin, and also to develop a simple formula for estimating the area under the plasma concentration-time curve (AUC) of platinum which relates to hematological toxicity after nedaplatin dosing using limited sampling points. Plasma unbound platinum concentration data were retrospectively collected from 27 courses administered to 20 Japanese adult patients. To determine the optimal sampling points, 1 - 5 data point(s) were selected with all combinations and clearance in each patient was estimated by the empirical Bayesian method. As measures for the Bayesian predictive performance, mean prediction error and root mean squared error were estimated. These indices suggested that the sampling time(s) of 4 hours in case of the one-point sampling gives better estimates for individual clearance. As for the limited sampling strategy, a simple formula to calculate AUC, AUC = 0.039 x dose + 11.6 x Cp_{4h} - 0.88, was obtained, where Cp_{4h} is the concentration at 4 hours after the end of infusin. These results should be helpful for adjusting dosage to achieve the target AUC.*

Nedaplatin, *cis*-diammineglycolatoplatinum (1, 2), is an anticancer drug that was developed to offer higher antitumor activity than carboplatin (CBDCA) (3, 4) and also to reduce nephrotoxicity, which is often a dose-limiting factor of cisplatin (CDDP) (5-7). In anticancer chemotherapy, the maximum tolerance dose (MTD) with respect to side-effects is usually used to achieve the maximum effect (8-10), and therefore serious adverse effects often occur, especially in patients exposed to a high platinum concentration. To minimize the frequency of adverse effects, the optimal dosage regimen should be individualized by taking the pharmacokinetic variability into consideration. For this purpose, we have shown that the area under the plasma concentration-time curve (AUC) of unbound platinum after nedaplatin administration is related to hematological toxicity, especially thrombocytopenia, and a target AUC can be set based on tolerable nadir and pre-dose values of platelet (11). In order to achieve the target AUC at the first (or more) dosing of nedaplatin, we have already developed a simple formula to estimate individual clearance (CL) of unbound platinum corresponding to the patient's renal function after nedaplatin administration (12), which is similar to the Calvert's formula (13). We have also determined the population pharmacokinetic parameter estimates (14), which are especially useful for dosage individualization based on the empirical Bayesian method.

In order to optimize the dosage regimen at the second (and more) dose, it is ideal to measure the plasma platinum concentrations after the first dose and use them to predict individual pharmacokinetics based on the empirical Bayesian method. The predictive performance by the Bayesian method depends on the sampling time of the drug concentration data (15-18). Although the amount of available data for the inference is usually very small to minimize the patient's burden, the individual pharmacokinetic parameters should be estimated as accurately as possible. Thus, the optimal sampling strategy for Bayesian inference in the case of nedaplatin therapy was examined in this study.

In addition, the limited sampling strategy for nedaplatin was also examined to obtain a simple formula for predicting the individual AUC of platinum using a small number of data points and information on the patient's background. The empirical Bayesian method is popular but requires sophisticated computer programs such as NONMEM and OPT (19, 20), which can make it complicated to perform in routine drug therapy.

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Key Words: Pharmacokinetics, pharmacodynamics, nedaplatin, AUC, optimal sampling, limited sampling, platelet.

Patients and Methods

Patients and data collection. A total of 183 courses administered to 141 Japanese adult cancer patients as a part of the post-marketing surveillance of nedaplatin in multiple centers in Japan were retrospectively collected and were used for the population pharmacokinetic analysis described in our previous report (14).

Informed consent and ethics approvals were obtained at each institution. To evaluate the optimal sampling strategy, it is necessary to use a sufficient number of plasma concentration data from a patient, so the data from courses with 5 sampling points were picked and used as a analysis data set. As a result, plasma unbound platinum concentration data of 27 courses from 20 patients were collected. In these courses, the plasma concentration data were obtained at the end of infusion, at 1, 2, 4 and either 6 or 8 h post-infusion (total 5 points), and no samples were taken during infusion. Although some data were taken from different courses in the same patients, we treated the data as if they were taken from different patients because; i) nedaplatin was administered with about one-month interval and no pharmacokinetic accumulation was considered, and ii) it has already been shown that multiple dosing of nedaplatin does not affect patients' clearance (12, 14). As the validation data set for the limited sampling strategy formula, the rest of the collected data were used. However, as shown below, our results suggested that the plasma platinum concentration data at 4 h after dosing (Cp_{4h}) was the significant covariate to estimate AUC, and thus the data from 33 courses given to 26 patients, in which Cp_{4h} was available, were used as a validation data set.

Demographic data including gender, age, body weight (BWT), serum creatinine level (Scr) and creatinine clearance (CLcr) were also recorded. The Scr and CLcr were determined at each institution and not only the observed CLcr, but also the calculated CLcr according to the Cockcroft-Gault formula, were used (21). The patients' characteristics and dose for the test data set and for the validation data set were compared by *t*-test at 0.05 of significant level.

The dose and the infusion duration of the test data varied among the patients with ranges of 51-180 mg and 1-3 h, respectively. All the plasma platinum concentrations prior to nedaplatin infusion were under the determination limit (<0.2 μg/mL). Although both 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 the unbound platinum that is related to the cytotoxic effects (22, 23).

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 at Shionogi Biomedical Laboratories (Osaka, Japan) (24). The lower determination limit for this method is 0.2 μg/mL. Demographic data and measured values in clinical laboratory tests were obtained from each hospital.

Optimal sampling strategy. AUC was not evaluated directly by the Bayesian estimation, but CL, which is one of the pharmacokinetic parameters, was evaluated taking into consideration that patients received different doses of nedaplatin. Since AUC should be normalized by dose for inter-patient comparison, AUC was obtained as a ratio of the dose and CL. The observed values for individual CL (CL_{obs}) were estimated using the AUC calculated by the trapezoidal rule and extrapolated to infinity. The predicted CL (CL_{pred}), obtained using the empirical Bayesian method with a variety of combinations for the data points, were compared with CL_{obs} as follows. In order to determine the optimal number of sampling points and sampling times, all possible combinations of data points using 1 - 5 point(s) from observed concentration data for each patient were selected, and individual CL_{pred} were estimated. The population pharmacokinetic parameters that we have already reported (14) were incorporated in the empirical Bayesian method, and the NONMEM program (Ver.5) (19) was used with the *POSTHOC* option for the Bayesian computation. In order to evaluate the predictive performance for CL to find the optimal sampling points, the mean prediction error (ME) as a measure of bias and root mean squared error (RMSE) as a measure of precision were compared among the combinations (25). Relationships between CL_{obs} and CL_{pred} with preferable sampling points were plotted.

Limited sampling strategy. A simple formula for estimating individual AUC was constructed by multiple linear regression analysis based on observed plasma concentrations and the patient's characteristics. The following data were tested by the multiple linear regression analysis as independent variables: plasma concentrations at each sampling time, age, BWT, dose, duration of infusion, rate of infusion, Scr, observed CLcr, calculated CLcr and reciprocal of Scr. However, plasma concentration data at 6 and 8 h after the end of infusion were not used because they were not available for some patients. The significant covariates were selected by a stepwise regression method based on the *F*-value at 5% of the significance level. To validate the final model ("Limited Sampling Formula"), the AUC values predicted by the final model were compared with the AUC values calculated by the trapezoidal rule for each patient. Furthermore, the ME and RMSE by the final formula (Limited Sampling Strategy, LSS) were compared with those indices by the following different methods: i) predicted AUC using the population mean (PPK) for CL including CLcr as a covariate (14), ii) the Bayesian estimate using all data points for each individual (BLS(ALL)), iii) the Bayesian estimate using a limited sampling point (as described below using only Cp_{4h}, BLS(4h)), iv) the AUC estimate by ordinary least-squared (OLS) method using all data points, and v) a simple formula using only CLcr (12) (CLCR). We used the estimates of AUC by empirical Bayesian method for the validation data set, because the Bayesian method is a population way for parameter estimation in therapeutic drug monitoring.

Results

Optimal sampling strategy. Table I shows the summary of the patients' characteristics for the test data set for the optimal sampling strategy and the limited sampling strategy, and for the validation data set for a limited sampling strategy used in this study. Results of the statistical test for difference between the test and the validation data sets are given in Table I. Figure 1 shows the time course profiles of the unbound platinum concentration after the end of infusion for the test data. Table II and Figure 2 show ME and RMSE values in the optimal sampling strategy for all combinations of sampling points. The 95% confidence intervals (C.I.) for ME and RMSE are also presented in Table II. For the one-point sampling strategy, the values for ME and RMSE were smallest in the case sampled at 6 and 4 h, respectively. For the two-point sampling strategy, ME was smaller when the data at 6 h was combined with the

Table I. *Summary of patient characteristics for the test and the validation data sets.*

	Test Data		Validation Data	
Number of courses	27		33	
Dose (mg)	113±32	[51-180]	89.8±40.3	[20-160]*
Infusion rate (mg/h)	82±32	[30-160]	78.6±31.3	[20-160]
Infusion duration (h)	1.52±0.58	[1-3]	1.15±0.36	[1-2]*
Age (year)	57.0±8.3	[36-68]	51.8±9.1	[29-66]*
Weight (kg)	54.6±10.4	[39.5-81]	52.5±9.6	[37.5-76]
Scr (mg/dL)	0.81±0.22	[0.5-1.2]	0.67±0.15	[0.5-1.1]*
CLcr (mL/min)	69.7±23.5	[37-122]	84.4±28.9	[19-162]*
Calculated Lcr (mL/min)	71.9±21.9	[39-111]	85.8±26.2	[52-153]*

Mean ± S.D.
Values in parenthesis are the [Minimum – Maximum].
CLcr: Observed CLcr value
Calculated CLcr: CLcr calculated by Cockcroft-Gault formula
*: Significant difference between test and validation data at 5% level by *t*-test

data at 1 or 2 h, and RMSE was smaller when the data at 4 h was combined with the data at 0 or 1 h. For the three-point sampling strategy, ME at 1, 2 and 6 h combination and RMSE at 0, 4 and 6 h combination were smallest. The values of ME and RMSE seemed almost the same when more than three points were used for the empirical Bayesian method, except when the points at 0, 1 and 2 h were used. Figure 3 shows the relationship between CL_{obs} and CL_{pred} for the combinations of data points in the cases that ME and RMSE showed the smaller values. In these cases, the correlation for these combinations was as good as when all data points were used (ALL), suggesting that these combinations for the limited sampling strategy are practically useful for predicting platinum CL. Among these combinations, we would recommend, on consideration of the prediction accuracy and the patient's burden, that the first choice of sampling time is 4 h after the end of infusion and an additional sampling is either 0 or 1 h. The sampling time at 6 h after infusion could be another choice, however, we recommend the use of 4 h data because of the reduced possibility that the plasma platinum concentration comes below the determination limit at 4 h, as shown below. To confirm the possibility that the plasma concentration comes lower than the determination limit, confidence intervals with respect to the inter-individual variability for the population mean plasma platinum concentration at 4 and 6 h were predicted. As typical examples, we considered the cases when nedaplatin was administered at doses of 100 mg, 140 mg, or 170 mg to patients whose CLcr was 80 or 100 mL/min. Typical (population mean) plasma concentrations and the 95% confidence intervals at 4 and 6 h after the end of infusion were calculated using the population parameters for nedaplatin (14) based on the law of propagation of variances with first-order approximation. As shown in Table III, the lower limits at 4 h were greater than the determination limit (0.2 μg/mL) in most of the cases. However, the lower limits at 6 h were all under the detection limit. These predictions suggest that the data sampling at 4 h is better than 6 h to obtain the measurable plasma concentration.

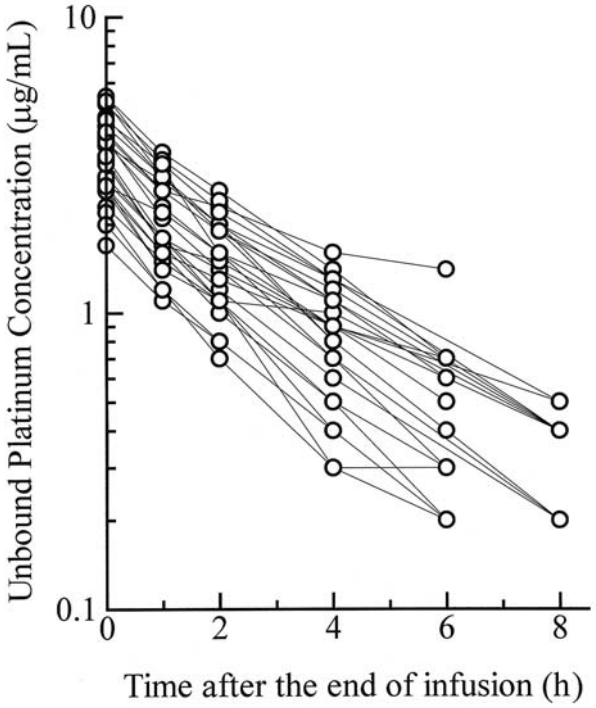

Figure 1. *Time course profiles of plasma unbound platinum concentration after nedaplatin infusion.*

Table III. *Predicted plasma concentration at 4 and 6 hours after the end of infusion using population pharmacokinetic parameters of nedaplatin.*

Patient condition	Dose (mg)	Predicted Value (μg/mL)					
			95% C.I. at 4 h			95% C.I. at 6 h	
		Mean	Lower	Upper	Mean	Lower	Upper
CLcr: 80mL/min	100	0.62	0.26	1.48	0.32	0.09*	1.11
BWT: 55 kg	140	0.86	0.36	2.08	0.45	0.13*	1.55
	170	1.05	0.44	2.52	0.54	0.16*	1.89
CLcr: 100mL/min	100	0.49	0.18*	1.33	0.23	0.06*	0.96
BWT: 55 kg	140	0.69	0.25	1.86	0.33	0.08*	1.34
	170	0.83	0.31	2.26	0.40	0.10*	1.63

95% C.I.: 95% confidence interval
*: The value was lower than the detection limit (0.2 μg/mL).

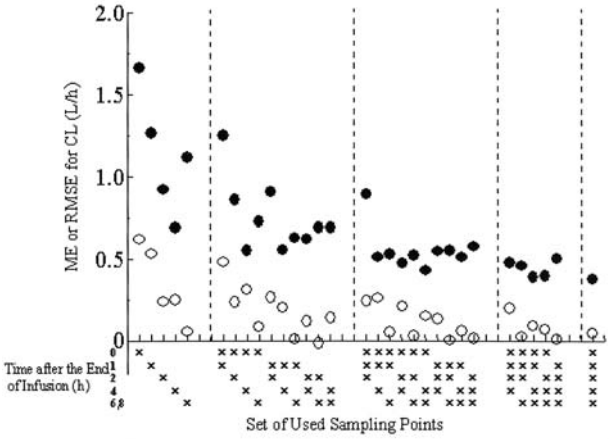

Figure 2. *ME (open circles) and RMSE (closed circles) for CL estimation. The symbols under the x-axis indicate the combinations of sampling times.*

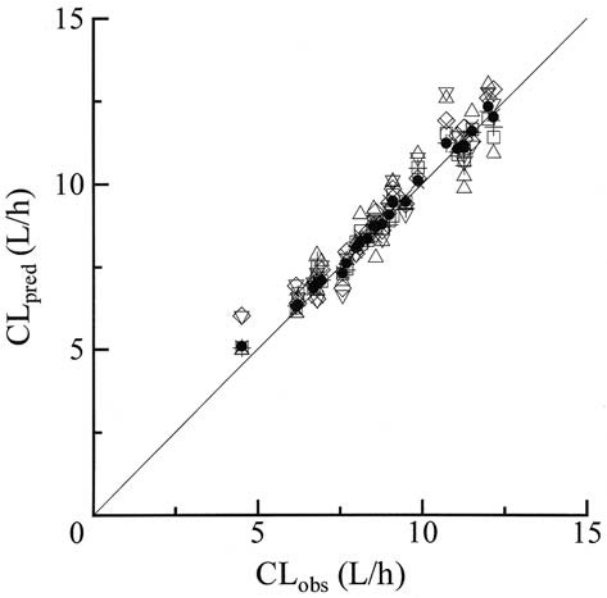

Figure 3. *Relationship between CL_{obs} and CL_{pred} by the empirical Bayesian method using typical combinations of sampling points. The identity line is inserted. The symbols indicate using all data (closed circles), 1, 2 and 6 h (crosses), 0, 4, 6 h (diagonal crosses), 1 and 6 h (rectangles), 0 and 4 h (diamonds), 6 h (triangles) and 4 h (reversed triangles).*

Limited sampling strategy. Multiple linear regression analysis was applied to determine a limited sampling strategy using the test data. The concentration data at 4 h after the end of infusion (Cp_{4h}) was first selected from all candidates as an independent variable as it showed the highest correlation, as presented in Table IV. The dose was next selected based on the stepwise rule, but no more candidates were selected as significant variables. Finally, the result of multiple linear regression analysis suggested that platinum AUC can be well predicted using the dose and only the Cp_{4h}. The final formula for the limited sampling strategy is given by Eq. (1):

$$AUC = 0.039 \times dose + 11.6 \times Cp_{4h} - 0.88 \quad (1)$$

The units of AUC, dose and Cp_{4h} are μg·h/mL, mg and μg/mL, respectively.

Figure 4 shows the relationships between the AUC calculated by the trapezoidal rule with the AUCs by using Eq.(1) and also by other methods. The values of ME and RMSE for each method are listed in Table V with their 95% confidence intervals. The predictive performance of Eq.(1) (LSS, see Methods section for abbreviations) is no less than those by the Bayesian methods (BLS (ALL), BLS (4 h)) and OLS method. In OLS, there were large positive biases in two patients because the plasma concentrations at 4 and 6 h were almost the same and markedly longer elimination half-lives were estimated in these patients.

Table II. *ME and RMSE for estimation of CL.*

Number of used points	Time* of used points	ME	(95%C.I.)	RMSE	(95%C.I.)
1	0	0.622	(0.029, 1.216)	1.665	(0.944, 2.157)
	1	0.534	(0.092, 0.977)	1.268	(0.738, 1.635)
	2	0.240	(-0.103, 0.584)	0.925	(0.582, 1.171)
	4	0.250	(0.002, 0.499)	0.694	(0.392, 0.899)
	6	0.058	(-0.363, 0.480)	1.120	(0.159, 1.575)
2	0, 1	0.482	(0.038, 0.927)	1.252	(0.711, 1.622)
	0, 2	0.238	(-0.081, 0.556)	0.862	(0.546, 1.091)
	0, 4	0.315	(0.141, 0.490)	0.553	(0.350, 0.699)
	0, 6	0.086	(-0.187, 0.360)	0.731	(-, 1.072)
	1, 2	0.266	(-0.068, 0.600)	0.909	(0.516, 1.177)
	1, 4	0.202	(0.002, 0.402)	0.558	(0.335, 0.715)
	1, 6	0.012	(-0.226, 0.250)	0.631	(-, 0.939)
	2, 4	0.120	(-0.116, 0.355)	0.624	(0.408, 0.783)
	2, 6	-0.013	(-0.275, 0.248)	0.693	(-, 0.987)
	4, 6	0.142	(-0.114, 0.398)	0.694	(0.418, 0.888)
3	0, 1, 2	0.246	(-0.085, 0.577)	0.896	(0.509, 1.160)
	0, 1, 4	0.262	(0.092, 0.431)	0.512	(0.277, 0.670)
	0, 1, 6	0.053	(-0.147, 0.253)	0.533	(-, 0.818)
	0, 2, 4	0.209	(0.044, 0.374)	0.477	(0.262, 0.622)
	0, 2, 6	0.032	(-0.165, 0.228)	0.523	(-, 0.789)
	0, 4, 6	0.153	(0.001, 0.305)	0.431	(0.254, 0.555)
	1, 2, 4	0.136	(-0.069, 0.341)	0.551	(0.338, 0.701)
	1, 2, 6	0.005	(-0.203, 0.214)	0.554	(-, 0.809)
	1, 4, 6	0.059	(0.113, 0.252)	0.514	(0.124, 0.716)
	2, 4, 6	0.017	(-0.201, 0.235)	0.579	(0.237, 0.784)
4	0, 1, 2, 4	0.201	(0.034, 0.368)	0.478	(0.243, 0.630)
	0, 1, 2, 6	0.028	(-0.145, 0.202)	0.461	(-, 0.711)
	0, 1, 4, 6	0.092	(-0.051, 0.236)	0.391	(-, 0.560)
	0, 2, 4, 6	0.069	(-0.079, 0.217)	0.398	(-, 0.572)
	1, 2, 4, 6	0.013	(-0.178, 0.203)	0.505	(-, 0.731)
5	0, 1, 2, 4, 6	0.051	(-0.091, 0.194)	0.381	(-, 0.576)

*: Time after the end of infusion
-: Not calculable

In order to validate Eq.(1), the estimated AUC by Eq.(1) was compared with the AUC estimated by the empirical Bayesian method for both the test and the validation data sets in Figure 5. In Figure 5, the results for the first dosing and the second or more dosing were plotted with different symbols in order to show that it was not affected by the occasion. The values of ME and RMSE (and 95% confidence interval) for all test data and all validation data were 0.10 (-0.32, 0.53) and 1.10 (0.69, 1.40), and -0.27 (-0.66, 0.12) and 1.16 (0.64, 1.51) μg·h/mL, respectively. The correlation coefficients for the test data and the validation data were 0.974 and 0.969, respectively. It was confirmed that the regression lines for the test and validation data were not significantly different by comparing their variation based on the *F*-value at 5% significance level. The results of validation suggest that Eq.(1) predicts well the platinum AUC from only the dose and concentration at 4 h (CP_{4h}).

Table IV. *Coefficient correlation, F- and p-values for the candidates of covariates by the linear regression.*

Covariate	*F*-value	Coefficient correlation	*p*-value
Dose	14.89*	0.611	0.001*
Rate of infusion	0.67	0.162	0.420
Duration of infusion	4.58*	0.393	0.042*
Age	0.19	0.086	0.669
BWT	0.25	0.100	0.618
Scr	2.47	0.300	0.128
CLcr	0.74	0.169	0.399
Calculated CLcr	3.53	0.352	0.072
Cp_{0h}	23.69*	0.698	0.000*
Cp_{1h}	38.24*	0.778	0.000*
Cp_{2h}	108.76*	0.902	0.000*
Cp_{4h}	202.03*	0.943	0.000*

F-value ratio of variance for the regression
p-value: for the coefficient of covariate
*: significant at the level of 5%

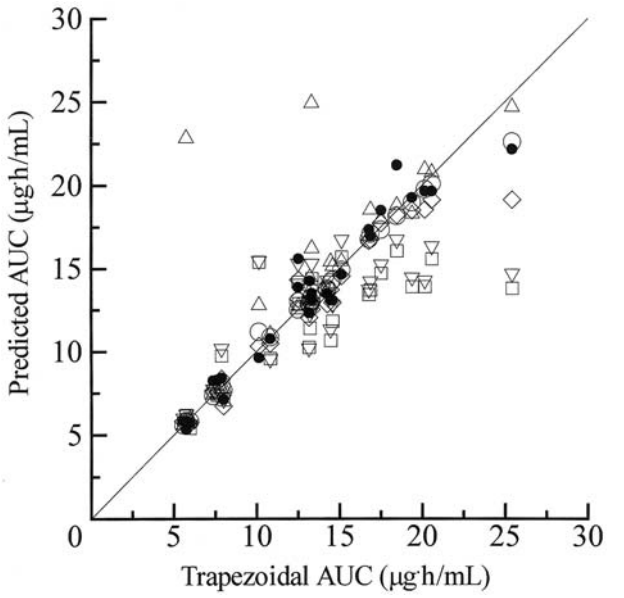

Figure 4. *Relationship between the trapezoidal AUC and the AUC estimated by other methods. The symbols indicates LSS: the limited sampling strategy (closed circles), BLS(ALL): the Bayesian estimate using all data points (open circles), BLS(4h): the Bayesian estimate using only Cp_{4h} (diamonds), PPK: the prediction using the population mean for CL including CLcr as a covariate (rectangles), OLS: the ordinary least-squared method using all data points (triangles), CLCR: a simple formula using only CLcr (reversed triangles).*

Discussion

As shown in Figure 2, for the one-point sampling strategy, the predictive performance was generally better when the plasma concentration was measured at later sampling times. However, the RMSE using 6- or 8-h data was greater than that using only the 4-h data. This is because the plasma concentration at 6 h in a patient was the same as that at 4 h (0.3 μg/mL), and the Bayesian estimate using the data at 6 h showed a biased result. Because the plasma platinum concentration was reported to one decimal place, such a bias is inevitable. When this data was excluded, ME and RMSE were estimated as 0.216 and 0.802, respectively, which are similar to those values when only the 4-h data were used. For the two-point sampling strategy, the combination of taking samples both at an early time after the end of infusion (0 or 1 h) and at the terminal phase seems suitable. Thus, we recommend that the primary sampling point is at the terminal phase (4 h is the first choice), and the secondary point is at an early time after the end of infusion. As no clear differences in ME and RMSE were found in this case between using 0 h data or 1 h data, the secondary point can be either of these points.

The platinum AUC after CBDCA administration can be estimated using one or two data points of concentration (26-28). In our present study, good prediction accuracy of the platinum AUC after nedaplatin administration was obtained using the values of the dose and only the concentration data at 4 h after the end of infusion. As shown in Table V, the predictive performance of Eq. (1) is equivalent to that by the Bayesian method. This suggests that the intra-individual variation of platinum pharmacokinetics is small, and the inter-individual variation can be corrected by using the observed data point at 4 h.

Table V. *ME and RMSE for estimation of CL in test data by various methods.*

Merthod	ME	95% C.I.	RMSE	95% C.I.
LSS	-0.03	(-0.49, 0.43)	1.23	(0.68, 1.60)
BLS (ALL)	-0.22	(-0.45, 0.01)	0.64	(-, 0.99)
BLS (4h)	-0.55	(-1.08, -0.02)	1.48	(-, 2.25)
PPK	-1.59	(-2.75, -0.42)	3.48	(1.52, 4.68)
OLS	1.37	(0.06, 2.79)	4.01	(-, 6.18)
CLCR	-1.10	(-2.25, 0.05)	3.24	(1.47, 4.34)

95% C.I.: 95% confidence interval
-: Not calculable
LSS: Limited sampling strategy given by Eq. (1)
BLS: Bayesian leas-squares method
PPK: Population mean parameters
OLS: Ordinary least-squared method
CLCR: Simple formula for CL based on CLcr Values

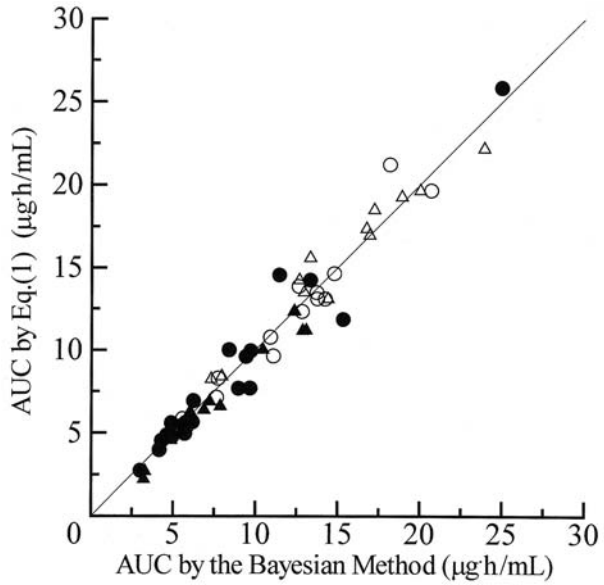

Figure 5. *Relationship between the AUC estimated by the Bayesian method using all data points and the AUC estimated by Eq.(1). Open circles and triangles indicate test data at first dosing and more dosing, respectively, and closed circles and triangles indicate validation data at first dosing and more dosing, respectively.*

Acknowledgements

This work was supported by the 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; and Department of Medicine I, Tokyo Women's Medical University, Japan.

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Received July 26, 2004
Accepted December 29, 2004