Cancer Chemother Pharmacol (2007) 59:575–580
DOI 10.1007/s00280-006-0298-2

ORIGINAL ARTICLE

Pharmacokinetics of low-dose nedaplatin and validation of AUC prediction in patients with non-small-cell lung carcinoma

Takenori Niioka · Tsukasa Uno · Norio Yasui-Furukori · Takenori Takahata · Mikiko Shimizu · Kazunobu Sugawara · Tomonori Tateishi

Received: 31 March 2006 / Accepted: 19 July 2006 / Published online: 16 August 2006

Abstract
Purpose The aim of this study was to determine the pharmacokinetics of low-dose nedaplatin combined with paclitaxel and radiation therapy in patients having non-small-cell lung carcinoma and establish the optimal dosage regimen for low-dose nedaplatin. We also evaluated predictive accuracy of reported formulas to estimate the area under the plasma concentration–time curve (AUC) of low-dose nedaplatin.
Patients and methods A total of 19 patients were administered a constant intravenous infusion of 20 mg/m^2 body surface area (BSA) nedaplatin for an hour, and blood samples were collected at 1, 2, 3, 4, 6, 8, and 19 hf after the administration. Plasma concentrations of unbound platinum were measured, and the actual value of platinum AUC (actual AUC) was calculated based on these data. The predicted value of platinum AUC (predicted AUC) was determined by three predictive methods reported in previous studies, consisting of Bayesian method, limited sampling strategies with plasma concentration at a single time point, and simple formula method (SFM) without measured plasma concentration. Three error indices, mean prediction error (ME, measure of bias), mean absolute error (MAE, measure of accuracy), and root mean squared prediction error (RMSE, measure of precision), were obtained from the difference between the actual and the predicted AUC, to compare the accuracy between the three predictive methods.
Results The AUC showed more than threefold inter-patient variation, and there was a favorable correlation between nedaplatin clearance and creatinine clearance (Ccr) ($r = 0.832$, $P < 0.01$). In three error indices, MAE and RMSE showed significant difference between the three AUC predictive methods, and the method of SFM had the most favorable results, in which %ME, %MAE, and %RMSE were 5.5, 10.7, and 15.4, respectively.
Conclusions The dosage regimen of low-dose nedaplatin should be established based on Ccr rather than on BSA. Since prediction accuracy of SFM, which did not require measured plasma concentration, was most favorable among the three methods evaluated in this study, SFM could be the most practical method to predict AUC of low-dose nedaplatin in a clinical situation judging from its high accuracy in predicting AUC without measured plasma concentration.

Keywords Nedaplatin · Low-dose · Pharmacokinetics · AUC · Predictability · Therapeutic drug monitoring

T. Niioka (✉) · T. Uno · K. Sugawara
Department of Pharmacy, Hirosaki University Hospital, Hirosaki 036-8563, Japan
e-mail: tniio-hki@umin.ac.jp

N. Yasui-Furukori · T. Takahata · M. Shimizu · T. Tateishi · T. Uno
Department of Clinical Pharmacology, Hirosaki University School of Medicine, Hirosaki, Japan

N. Yasui-Furukori
Department of Neuropsychiatry, Hirosaki University School of Medicine, Hirosaki, Japan

T. Takahata
First Department of Internal Medicine, Hirosaki University School of Medicine, Hirosaki, Japan

Introduction

Nedaplatin (*cis*-diammineglycolatoplatinum), a platinum-containing compound with antineoplastic effect, was synthesized to reduce nephrotoxicity which is known to be associated with cisplatin (CDDP), and has been reported to have higher antitumor activity than carboplatin (CBDCA) [13, 20]. In phase II clinical studies, high activities have been demonstrated against non-small-cell lung carcinoma (NSCLC) [6, 15] and therapeutic dose of nedaplatin in each course is recommended to be from 80 to 100 mg/m^2 body surface area (BSA). Since combined therapy of a platinum agent-based chemotherapy and radiotherapy showed a decrease in the relative risk of mortality rate in unresectable NSCLC [19], we carried out the clinical trial to demonstrate the therapeutic effect of low-dose nedaplatin (20 mg/m^2 BSA), paclitaxel and concurrent thoracic radiation therapy in NSCLC patients of stage III, resulting in favorable outcomes [7].

In previous studies, the relationship between the area under curve (AUC) of platinum and its antitumor efficacy or toxicity has been demonstrated, and a formula is proposed to calculate the dose of carboplatin [1, 2, 14]. In nedaplatin, the population pharmacokinetics parameters have been evaluated in the recommended dose, and formulas to predict its optimal dosage have been proposed based on these data [11]. In combination of chemotherapy with multiple anticancer agents and radiotherapy, the adverse effects of chemotherapy can be severe, and a dependable formula for determining optimal dosage is needed to minimize the risk of toxic effects, even in a smaller dose. However, there has been no information reported about whether the pharmacokinetic parameters of low-dose nedaplatin are similar to those of the recommended dose and a dependable formula is still available for predicting optimal dosage to low-dose of nedaplatin.

In this study, we therefore evaluated the pharmacokinetics of low-dose nedaplatin (20 mg/m^2) based on the plasma concentration data of phase I/II studies by Hasegawa et al. in which safe and effective treatment results were obtained. In addition, accuracy of three existing predictive methods of area under the plasma concentration–time curve (AUC) for nedaplatin was validated.

Methods

Patients and eligibility criteria

A total of 19 consecutive chemotherapy-naive NSCLC patients were enrolled in this study. Patients with histologically or cytologically documented locally advanced NSCLC were enrolled. Other eligibility criteria included the following: (1) age younger than 75 years; (2) Eastern Cooperative Oncology Group (ECOG) performance status of less than 2; (3) measurable or assessable tumor; (4) adequate bone marrow function (granulocytes > 2,000/ml, hemoglobin level > 10 g/dl and platelet count > 100,000/ml), renal function [creatinine clearance (Ccr) by 24 h urine collection > 60 ml/min] and pulmonary function (arterial oxygen partial pressure PaO_2 > 65 Torr); (5) adequate cardiac function as determined by electrocardiogram and echocardiogram; (6) absence of central nervous system metastases, polyneuropathy or active infection; (7) life expectancy of more than 8 weeks; (8) absence of previous chemotherapy or thoracic RT; and (9) no serious medical or psychiatric illness that would preclude informed consent. All patients gave written informed consent before enrollment. This protocol was approved by the Ethical Committee for Research at Hirosaki University.

Treatment, data collection, and assay methods

Nedaplatin (Shionogi Pharmaceutical Co., Osaka, Japan) was administered at a fixed dose of 20 mg/m^2, and paclitaxel (Bristol-Myers K.K., Tokyo, Japan) was administered at a starting dose of 30 mg/m^2 with an incremental increase of 5 mg/m^2 until dose-limiting toxicity occurred in more than one-third of the patients. The chemotherapy was performed once a week for 6 weeks, starting on the first day of local radiation therapy. The radiation therapy was given at a single daily dose of 2 Gy for 5 days per week. Paclitaxel and nedaplatin were sequentially administered as 1-h intravenous infusion each. All patients received pretreatment medications to prevent hypersensitivity reactions; dexamethasone (20 mg, i.v.), diphenhydramine (50 mg, orally), and ranitidine (50 mg, i.v.) were administered 30 min before chemotherapy.

Plasma samples for pharmacokinetic evaluation of nedaplatin were collected from 19 patients in their first course of therapy. Blood samples were obtained through an indwelling catheter placed in the antecubital vein of each subject before and 1, 2, 3, 4, 6, 8, and 19 h after the administration of nedaplatin. Plasma was separated immediately after blood collection, and its unbound fraction was obtained by the ultrafiltration method. The samples were kept at –20°C until analysis. Unbound fraction of plasma platinum concentration was measured by a validated atomic absorption spectrometry assay method [8], and the limit of quantification for this method was 0.2 μg/ml.

Data analysis

The pharmacokinetic parameters were calculated by a two-compartment model in the pharmacokinetic analysis package, WinNonlin Version 2.1 (Pharsight, Mountain View, CA, USA). The Ccr was determined a few days before starting the treatment by two methods: observed Ccr by 24 h urine collection and calculated Ccr by Cockcroft–Gault formula [3]. Although the observed and the calculated levels of Ccr were well correlated ($r = 0.800$, $P \leq 0.01$), two patients showed lower value than the eligibility criteria. The predicted AUC were calculated by the following three methods: (1) the Bayesian method (BM) with Ishibashi's population pharmacokinetic parameters based on a two-compartment model [11] and C4, where C4 was the plasma concentration 4 h after administration, (2) the limited sampling strategies (LSS) using Ishibashi's formula (AUC = 0.039 × dose + 11.6 × C4 – 0.88) [9] with C4, and (3) the simple formula method (SFM) using Ishibashi's formula (CL = 0.0836 × Ccr + 3.45, AUC = dose/CL) [12]. Correlation between pharmacokinetics parameters of nedaplatin and the background data of patients (age, body height, body weight, BSA, and Ccr) was tested using regression analysis. The predictive performance of BM, LSS, and SFM was determined by the method of Sheiner and Beal [18]. Three error indices, the mean prediction error (ME), the mean absolute error (MAE), and the root mean squared prediction error (RMSE), were calculated with the following expressions to evaluate predictive accuracy (bias) and precision:

$$\mathrm{ME} = \frac{1}{N}\sum_{i=1}^{N}(\mathrm{Pred} - \mathrm{Obs}), \tag{1}$$

$$\mathrm{MAE} = \frac{1}{N}\sum_{i=1}^{N}|\mathrm{Pred} - \mathrm{Obs}|, \tag{2}$$

$$\mathrm{RMSE} = \left[\frac{1}{N}\sum_{i=1}^{N}(\mathrm{Pred} - \mathrm{Obs})^2\right]^{1/2}. \tag{3}$$

The relative values for these indices were also examined using the following expressions, respectively:

$$\mathrm{ME}(\%) = \frac{1}{N}\sum_{i=1}^{N}\frac{\mathrm{Pred} - \mathrm{Obs}}{\mathrm{Pred}} \times 100, \tag{4}$$

$$\mathrm{MAE}(\%) = \frac{1}{N}\sum_{i=1}^{N}\frac{|\mathrm{Pred} - \mathrm{Obs}|}{\mathrm{Pred}} \times 100, \tag{5}$$

$$\mathrm{RMSE}(\%) = \left\{\frac{1}{N}\sum_{i=1}^{N}\left[\frac{(\mathrm{Pred} - \mathrm{Obs})}{\mathrm{Pred}}\right]^2\right\}^{1/2} \times 100. \tag{6}$$

In expressions (1)–(6), Pred was the predicted value of AUC (predicted AUC), Obs was the observed value of AUC (actual AUC), and N was the number of patients. One-way ANOVA was used for comparisons among the predictive performances of BM, LSS, and SFM, while they were analyzed for statistical differences using Scheffe's correction. Statistical analysis was performed using a statistical program, SPSS 12.0J for Windows (SPSS Japan Inc., Tokyo). A P value of 0.05 or less was regarded to be statistically significant.

Results

Table 1 summarizes the demographic characteristics of the patients. The stage of disease was IIIA in four patients and IIIB in 15 patients. Eleven patients had squamous cell carcinoma, seven adenocarcinoma and one large cell carcinoma.

Table 2 shows the pharmacokinetics parameters of nedaplatin. Relatively large inter-patient variation was observed in each parameter, and more than threefold variation was found in the AUC. Table 3 shows the correlation between each pharmacokinetic parameter of nedaplatin and patients' background data. Although nedaplatin CL showed a correlation with most background data including BSA ($r = 0.489$, $P < 0.05$), which was used to determine the administration dose, the most significant correlation was between nedaplatin CL and the calculated Ccr ($r = 0.832$, $P < 0.01$). In addition, there was a favorable correlation between nedaplatin AUC and the calculated Ccr ($r = -0.757$, $P < 0.01$). Figure 1 shows the correlation between observed AUC and predicted AUC calculated by BM, LSS, and SFM, and predictive performance of each predictive method is summarized in Table 4. Whereas ME (measure of bias) showed no significant difference,

Table 1 Patient characteristics

Total no. of patients	19	
Sex		
Male	17	
Female	2	
Age (years)	62.1 ± 10.5	38–74
Body height (m)	1.64 ± 0.07	1.48–1.81
Body weight (kg)	57.2 ± 10.1	41–75
Body surface area (m^2)	1.62 ± 0.16	1.37–1.88
Creatinine clearance (ml/min)		
Observed	89.7 ± 30.9	45.0–173.3
Calculated	92.5 ± 36.4	44.9–176.5

Values are means ± SD with ranges

Table 2 Pharmacokinetic parameters of nedaplatin

	Means ± SD	Ranges
CL (l/h)	13.9 ± 6.1	8.4–30.4
Vc (l)	19.1 ± 8.0	9.2–37.6
K_{12} (1/h)	1.58 ± 1.74	0.06–4.63
K_{21} (1/h)	1.53 ± 1.11	0.26–3.84
AUC (μg/ml h)	2.59 ± 0.7	1.14–3.64
$t_{1/2}$ß (h)	2.1 ± 0.7	1.0–4.5
C_{max} (μg/ml)	1.01 ± 0.21	0.60–1.42

$n = 19$

significant difference was found in MAE (measure of accuracy) and RMSE (measure of precision) between the three methods, BM, LSS, and SFM. LSS showed higher MAE and RMSE than the other two methods, and SFM showed the most favorable values in all parameters regarding the difference between predicted AUC and actual AUC [expressions (4)–(6)].

Discussion

We evaluated the pharmacokinetics of low-dose nedaplatin (20 mg/m^2), and the pharmacokinetic parameters were almost similar to those of previous studies in which the recommended dose (80–100 mg/m^2) was administered [11, 12]. Although the dose of nedaplatin was decided based on BSA in the present study, the AUC showed more than threefold inter-patient variation. Large inter-patient variation of plasma concentration has been criticized when the dosage regimen of platinum derivatives such as CDDP and CBDCA was established based on BSA [4, 5, 17]. In nedaplatin, reduction in leukocytes and platelets, which is its major adverse event, was reported to correlate with the AUC [10, 16], and large inter-patient variation would lead to severe hematological toxicity in some patients. Since the calculated Ccr showed more favorable correlation with nedaplatin CL than BSA did, the dosage regimen should be established based on calculated Ccr rather than BSA to determine the optimal dose, even with low-dose nedaplatin administration.

Table 3 Correlation between pharmacokinetic parameters of nedaplatin and patient characteristics

	CL	Vc	AUC	$t_{1/2}$ß	C_{max}
Dose	0.489*	0.429	–0.313	0.151	–0.238
Age	–0.560*	–0.127	0.591**	0.334	0.224
Body height	0.370	0.261	–0.293	0.061	–0.218
Body weight	0.494*	0.456*	–0.292	0.191	–0.237
Body surface area	0.489*	0.429	–0.313	0.151	–0.238
Creatinine clearance					
Observed	0.488*	–0.050	–0.481*	–0.494*	–0.152
Calculated	0.832**	0.357	–0.757**	–0.208	–0.482*

Values are correlation coefficient

* $P < 0.05$; ** $P < 0.01$

In addition, the CL in low-dose nedaplatin was within the range reported previously [12], suggesting that formulas proposed in higher dose [12] would be applicable even when low-dose nedaplatin was administered. We also evaluated the predictive performance of each predictive method proposed previously [9, 11, 12] with the data of our present study. Predictive accuracy for nedaplatin AUC of LSS was inferior to that of BM or SFM. In the difference between predicted AUC and actual AUC, SFM showed the most favorable values in all parameters of %ME (5.5), %MAE (10.7), and %RMSE (15.4), though no significant difference was noted between BM and SFM. Since the predictive accuracy of BM without measured plasma concentration was inferior to that with concentration [9], SFM is considered to be the most practical method in a clinical situation judging from its high accuracy in predicting AUC without measured plasma concentration. In predicting platinum AUC, the measure of GFR may affect the results of accuracy. Since the original formula for determining carboplatin AUC was validated by 51Cr EDTA clearance [2], measured or calculated Ccr was considered to result in biased estimates of its AUC. However, in our present study, the predictive performance using calculated Ccr was better than observed Ccr (%ME = 9.5, %MAE = 23.4, and %RMSE = 29.9) and then the correlation between CL or AUC of nedaplatin and calculated Ccr was also better than observed Ccr.

Ishibashi et al. reported the reduction in platelets correlated with nedaplatin AUC, even when combined with other anticancer agents, and proposed the following formula: %decrease in platelets = –3.76 × AUC (μg/ml h) to predict the risk of thrombocytopenia, irrespective of monotherapy or combined therapy [10]. In our present study, nedaplatin AUC increased to 3.64 μg/ml h, and the percent decrease in platelets was calculated to be below 15% with their formula. However, most patients in the present study showed a decrease in platelets of over 30%, and adverse effects can be severe following combination of radiotherapy and chemotherapy with multiple anticancer agents, even after utilizing a smaller dose. Since the number of patients in the present study was not enough to evaluate the relation between nedaplatin AUC and the occurrence of adverse events or response rate, further studies will be required to evaluate the relation in the multidisciplinary management of cancer patients.

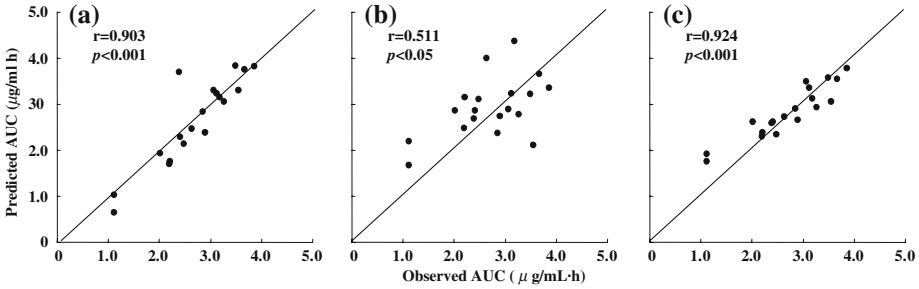

Fig. 1 Correlation between observed AUC and predicted AUC using **a** Bayesian method, **b** limited sampling strategies, and **c** simple formula method

Table 4 Summary of predictive performance for AUC

	ME (μg/l h)	MAE (μg/l h)	RMSE (μg/l h)
Bayesian method	–64.8 (–264.2, 134.5) –7.9%	285.3 (141.0, 429.5) 14.0%	407.7 (–, 594.5) 21.9%
Limited sampling strategies	221.9 (–121.8, 565.5) 9.0%	593.5* (384.2, 802.7) 21.4%	728.5* (463.4, 920.2) 27.0%
Simple formula method	112.8 (–47.4, 273.0) 5.5%	265.8 (158.7, 372.9) 10.7%	342.7 (179.4, 450.2) 15.4%

The values are means (95% confidence interval), the percentage values are relative indices given by expressions (4)–(6)

ME Mean prediction error (measure of bias), *MAE* mean absolute prediction error (measure of accuracy), *RMSE* root mean squared prediction error (measure of precision)

* $P < 0.05$ compared with the simple formula method

In conclusion, this study indicates that the dosage regimen of low-dose nedaplatin should be established based on Ccr rather than BSA. Since prediction accuracy of SFM, which did not require measured plasma concentration, was most favorable among the three methods evaluated in this study, SFM appear be the most practical method to predict AUC of low-dose nedaplatin in the clinical situation judging from its high accuracy in predicting AUC without measured plasma concentration. Naturally, further studies are required to examine prospectively by choosing doses based on Ccr and measuring nedaplatin AUC's to confirm the predictive value of the model. In addition, its predictive value has been evaluated within the range of Ccr in the current study (>60 ml/min), and the formula may not work without the range.

Acknowledgments We appreciated the great help of Professors Yoshinao Abe and Ken Okumura to carry on this study.

References

1. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748–1756
2. Chatelut E, Canal P, Brunner V, Chevreau C, Boneu A, Roche H, Houin G, Bugat R (1995) Prediction of carboplatin clearance from standard morphological and biological patient characteristics. J Natl Cancer Inst 87:573–580
3. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
4. de Jongh FE, Verweij J, Loos WJ, de Wit R, de Jonge MJ, Planting AS, Nooter K, Stoter G, Sparreboom A (2001) Body-surface area-based dosing does not increase accuracy of predicting cisplatin exposure. J Clin Oncol 19:3733–3739
5. Felici A, Verweij J, Sparreboom A (2002) Dosing strategies for anticancer drugs: the good, the bad and body-surface area. Eur J Cancer 38:1677–1684
6. Furuse K, Fukuoka M, Kurita Y, Ariyoshi Y, Niitani H, Yoneda S, Fujii M, Hasegawa K, Nishiwaki Y, Tamura M, Kimura I, Inoue S, Oshima S, Kusume K, Sugimoto K (1992) A phase II clinical study of *cis*-diammine glycolato platinum, 254-S, for primary lung cancer (in Japanese). Jpn J Cancer Chemother 19:879–884
7. Hasegawa Y, Takanashi S, Okudera K, Aoki M, Basaki K, Kondo H, Takahata T, Yasui-Furukori N, Tateishi T, Abe Y, Okumura K (2004) Weekly paclitaxel and nedaplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer: a phase I/II study. Jpn J Clin Oncol 34:647–653
8. Ikeuchi I, Daikatsu K, Fujisaka I, Amano T (1990) Determination of platinum in biological materials by graphite furnace atomic absorption spectrometry (written in Japanese, only abstract is given in English). Iyakuhin Kenkyu 21:1082–1087
9. Ishibashi T, Fukumura K, Yano Y, Oguma T (2005) Optimal sampling and limited sampling strategies for estimation of unbound platinum AUC after nedaplatin infusion. Anticancer Res 25:1283–1289
10. Ishibashi T, Yano Y, Oguma T (2005) Determination of optimal dosage for nedaplatin based on pharmacokinetic and toxicodynamic analysis. Anticancer Res 25:1273–1281
11. Ishibashi T, Yano Y, Oguma T (2003) Population pharmacokinetics of platinum after nedaplatin administration and model validation in adult patients. Br J Clin Pharmacol 56:205–213
12. Ishibashi T, Yano Y, Oguma T (2002) A formula for predicting optimal dosage of nedaplatin based on renal function in adult cancer patients. Cancer Chemother Pharmacol 50:230–236

13. Koenuma M, Kasai H, Uchida N, Takeda Y, Shiratori O, Muraoka Y, Totani T (1995) Antitumor activity of a new platinum complex, nedaplatin (in Japanese). Clin Rep 29:3213–3222
14. Newell DR, Pearson ADJ, Balmanno K, Price L, Wyllie RA, Keir M, Calvert AH, Lewis IJ, Pinkerton CR, Stevens MCG (1993) Carboplatin pharmacokinetics in children: the development of a pediatric dosing formula. J Clin Oncol 11:2314–2323
15. Ota K (1996) Nedaplatin (in Japanese). Jpn J Cancer Chemother 23:379–387
16. Sasaki Y, Amano T, Morita M, Shinkai T, Eguchi K, Tamura T, Ohe Y, Kojima A, Saijo N (1991) Phase I study and pharmacological analysis of *cis*-diammine(glycolato)platinum (254-S; NSC 375101D) administered by 5-day continuous intravenous infusion. Cancer Res 51:1472–1477
17. Sawyer M, Ratain MJ (2001) Body surface area as a determinant of pharmacokinetics and drug dosing. Invest New Drugs 19:171–177
18. Sheiner LB, Beal SL (1981) Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 9:503–512
19. Spira A, Ettinger DS (2004) Multidisciplinary management of lung cancer. N Engl J Med 22:379–392
20. Weiss RB, Christian MC (1993) New cisplatin analogues in development. Drugs 46:360–377