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

Abstract Purpose: To predict the optimal dosage for nedaplatin (cis-diamminediglycolatoplatinum), 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): \( \text{CL} = 0.0836 \times \text{CLcr} + 3.45 \). 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

Introduction

Nedaplatin (cis-diamminediglycolatoplatinum) 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/m² 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.

\[
CL = \frac{Dose}{AUC} \quad (1)
\]

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.

\[
CLcr = \frac{(140 - Age) \cdot BWT}{72 \cdot Scr} \cdot 0.85^{Gender} \quad (2)
\]

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.

\[
ME = \frac{1}{N} \sum (Pred - Obs) \quad (3)
\]

\[
RMSE = \sqrt{\frac{1}{N} \sum (Pred - Obs)^2} \quad (4)
\]

\[
ME(\%) = \frac{1}{N} \sum \left( \frac{Pred - Obs}{Pred} \right) \times 100 \quad (5)
\]

\[
RMSE(\%) = \sqrt{\frac{1}{N} \sum \left( \frac{Pred - Obs}{Pred} \right)^2} \times 100 \quad (6)
\]

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 |