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ORIGINAL ARTICLE

Evaluation of a formula for individual dosage of nedaplatin based on renal function

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Abstract
Purpose Nedaplatin (NDP), a platinum derivative, has been developed to reduce nephrotoxicity and gastrointestinal toxicity of cisplatin. The pharmacokinetic profile of NDP is similar to that of carboplatin (CBDCA). The optimal dosing for CBDCA is determined by the area under the curve (AUC) using Calvert's formula. However, the administration dose of nedaplatin (NDP) is determined based on the body surface area in clinical treatment. Ishibashi et al. reported a formula for predicting NDP clearance based on renal function like Calvert's formula for CBDCA. We conducted the present study to evaluate the Ishibashi's formula.
Methods A total of 22 patients with cervical or ovarian cancer, who underwent chemotherapy consisting of NDP and irinotecan (CPT-11), were examined in this study. Blood samples were collected at 0, 1, 2, 4, and 6 h after the end of infusion of NDP (48–80 mg/m^2), and free platinum concentrations were measured. Observed AUCs were compared with predicted AUCs, which were calculated by the Ishibashi's formula. In addition, the relative reduction in platelets (PLTs) was assessed as a parameter of adverse effects.
Results The observed AUC of NDP ranged from 4 to 14 ($\mu g\,h^{-1}\,ml^{-1}$) with large variation. The predicted AUC based on renal function was correlated with the observed AUC. There was a relationship between observed AUC and the decrease in PLTs.
Conclusions Ishibashi's formula would be predictable and useful for estimating the individual dose of NDP.

Keywords Nedaplatin · AUC · Formula · Renal function

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Introduction

Nedaplatin (cis-diammineglycolatoplatinum, NDP), a platinum derivative, has been developed to reduce nephrotoxicity and gastrointestinal toxicity of cisplatin (CDDP) [1]. NDP has higher antitumor activity than carboplatin (CBDCA) [2, 3]. In the literature, high activities against head and neck cancer, non-small-cell lung carcinoma, esophageal cancer, testicular tumor, and cervical cancer have been demonstrated [4–9]. In addition, a high response rate has also been reported for the combination of irinotecan (CPT-11) and platinum for ovarian and cervical cancer [10–12]. Matsumura et al. reported 80.4% response rate for this combination in neoadjuvant chemotherapy for cervical cancer [13].

It is known that the area under the curve (AUC) of platinum correlates with its antitumor efficacy and toxicity [14, 15]. In practice, the optimal dosing of CBDCA has been determined by the AUC using Calvert's formula. The plasma concentration profile of unbound platinum after NDP infusion is similar to that of total platinum, and the protein binding of NDP has been shown to be lower than that of CDDP [16]. Although the pharmacokinetic profile of NDP is similar to that of CBDCA, the administration dose of NDP is determined by the body surface area (BSA), not the AUC [17]. Ishibashi et al. reported a formula for predicting NDP clearance based on pharmacokinetics that

NDP is eliminated mainly via kidney [18]. To reduce adverse effects, the optimal dosage should be individualized by considering the variability of the renal function of each patient. We conducted the present study to evaluate Ishibashi's formula, comparing predicted AUC with observed AUC. Furthermore, as a parameter of adverse effects, the predictability of thrombocytopenia was examined in this study.

Methods

A total of 22 patients, who underwent chemotherapy consisting of NDP and CPT-11 at the Jichi Medical College and Tottori University Hospital, were enrolled in this study. The eligibility criteria included the following: age older than 19 and younger than 80 years, Eastern Cooperative Oncology Group (ECOG) performance status of less than 2, adequate bone marrow function (granulocytes $\geq$ 2,000/mm^3, platelet (PLT) count $\geq$ 100,000/mm^3, hemoglobin level $\geq$ 9.0 g/dl), adequate liver function (aspartate transaminase [AST] $\leq$ 100 IU/l, alanine transaminase [ALT] $\leq$ 100 IU/l, t-bilirubin $\leq$ 1.5 mg/dl), renal function (serum creatinine $\leq$ 1.2 mg/dl, creatinine clearance (Ccr) by Cockcroft-Gault formula $\geq$ 50 ml/min), and cardiac function (normal electrocardiogram [ECG] or minor change without treatment).

All patients gave written informed consent before enrollment. This protocol was approved by the Institutional Review Board for Research at both Tottori University and Jichi Medical College.

The dose of NDP (Shionogi Pharmaceutical Co., Osaka, Japan) was determined using the BSA (mg/m^2) calculated with formula of Dubois [(Weight$^{0.425}$ $\times$ Height$^{0.725}$) $\times$ 0.007184]. The dosage was 60 mg/m^2 for ovarian cancer and 80 mg/m^2 for cervical cancer. Three recurrent patients, who had needed reduction in dosage at the primary chemotherapy, were given the agent at 48 mg/m^2 as the 80% dosage of 60 mg/m^2.

CPT-11 (Irinotecan HCL; Yakult Honsha Co., Ltd. Tokyo, Japan) was administered at a fixed dose of 60 mg/m^2. Blood samples were collected at 0, 1, 2, 4, and 6 h after the end of intravenous administration of NDP with 1-h infusion duration, and free platinum and total platinum concentrations were measured. Demographic data, including age, body weight, serum creatinine level, and Ccr, were also recorded for each patient.

The plasma unbound fraction was separated by using an ultrafiltration method [19]. The concentrations of total and free platinum in the plasma were measured by a validated atomic absorption spectrometry assay method at the NAC laboratories (Tokyo, Japan). The lower determination limit for this method is 0.2 μg/mL. Measured values in clinical laboratory tests were obtained from each hospital.

To evaluate the predictability of the AUC by using Ishibashi's formula, the predicted AUC was compared with the observed AUC that was calculated by the trapezoidal method. The relationship between the predicted and observed free platinum clearance (CL) was also evaluated because the AUC was calculated according to the CL.

Ishibashi reported a simple formula (Eq. 1) based on a population pharmacokinetic model [20]. Since they proved that only Ccr was found to be a significant covariate of CL, CL was calculated according to this formula on the basis of the individual Ccr.

$$\mathrm{CL} = 0.0738 \times \mathrm{Ccr} + 4.47 \tag{1}$$

Predicted AUC: The predicted AUC was calculated using Eq. 2 on the basis of pharmacokinetics; the individual CL was predicted by Ishibashi's formula on the basis of the individual Ccr.

$$\mathrm{AUC} = \mathrm{dose}/\mathrm{CL} \tag{2}$$

Observed AUC: The observed AUC was calculated and extrapolated to infinity using Eq. 3.

$$\mathrm{AUC} + \mathrm{AUC}_{\mathrm{last}} + (\mathrm{Ct}/\lambda z), \tag{3}$$

where $\mathrm{AUC}_{\mathrm{last}}$ is AUC from 0 to the time point of the last measurable plasma concentration and calculated by the trapezoidal method on the basis of the individual plasma unbound platinum concentrations. Ct is the last measurable plasma concentration, and λz is the magnitude of the slope of the linear regression of the log-transformed concentration versus time during the terminal phase.

Evaluation: The predictability of the CL and AUC was evaluated by two indices, the mean prediction error (ME) as a measure of bias (Eq. 4) and the root mean squared error (RMSE) as a measure of precision (Eq. 5) [21].

$$\mathrm{ME} = 1/N \cdot \Sigma(\mathrm{Pred} - \mathrm{Obs}) \tag{4}$$

$$\mathrm{RMSE} = \sqrt{1/N} \cdot \Sigma(\mathrm{Pred} - \mathrm{Obs})^2 \tag{5}$$

$$\mathrm{ME}(\%) = 1/N \cdot \Sigma(\mathrm{Pred} - \mathrm{Obs})/\mathrm{Pred} \times 100 \tag{6}$$

$$\mathrm{RMSE}(\%) = \sqrt{1/N} \cdot \Sigma\{(\mathrm{Pred} - \mathrm{Obs})/\mathrm{Pred}\}^2 \times 100 \tag{7}$$

In Eqs. 4–7, 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.

NDP dosing, especially the decrease in PLT count, relates to AUC. The relationship between the decrease in PLT count and AUC is shown in Eq. 8.

$$(\mathrm{PLT}_{\mathrm{nadir}} - \mathrm{PLT}_{\mathrm{pre}})/\mathrm{PLT}_{\mathrm{pre}} \times 100(\%) = -3.76 \times \mathrm{AUC}, \tag{8}$$

where PLT_{nadir} is the nadir of the PLT count after NDP administration and PLT_{pre} is the PLT count before NDP administration.

The nadir of the PLT count retrospectively predicted by using the predicted AUC based on Eq. 8 was compared with the observed nadir of the PLT count after NDP administration.

Results

The age of the study participants ranged from 35 to 71 years (average 53.9). Their height, body weight, and BSA ranged from 135 to 166 cm (153), from 40.0 to 62.0 kg (50.7), from 1.29 to 1.61 m^2 (1.46), respectively. The averages of serum creatinine and creatinine clearance were 0.64 mg/dl (0.48–1.17) and 86.4 ml/min (51–126). There were 15 cervical carcinomas and 7 ovarian carcinomas. Fourteen patients with cervical cancer previously received concurrent chemoradiotherapy (CCRT). The doses of NDP were 48 mg/m^2 in three patients, 60 mg/m^2 in 8 patients, and 80 mg/m^2 in 11 patients. The actual dosage of NDP distributed from 73.4 to 125.6 mg.

The range of the observed AUC of NDP was wide (4–14 $\mu g\ h^{-1}\ ml^{-1}$). There was no relationship between the observed AUC and dose based on the BSA (Fig. 1). The AUC showed a more than threefold inter-patient variation. On the other hand, there was a favorable correlation between observed AUC and dose normalized by Ccr (Fig. 2). The predicted AUC was correlated with the observed AUC (Fig. 3). The ME and RMSE were 0.92 (8.0%) and 2.72 (27.8%).

There was a relationship between the observed AUC and the relative reduction ratio of PLTs (Fig. 4). The dose of NDP based on BSA did not relate to the relative reduction ratio of PLTs. Five patients showed unexpectedly grade 4 thrombocytopenia, and the predicted PLT did not follow the regression line. These 5 patients received CCRT.

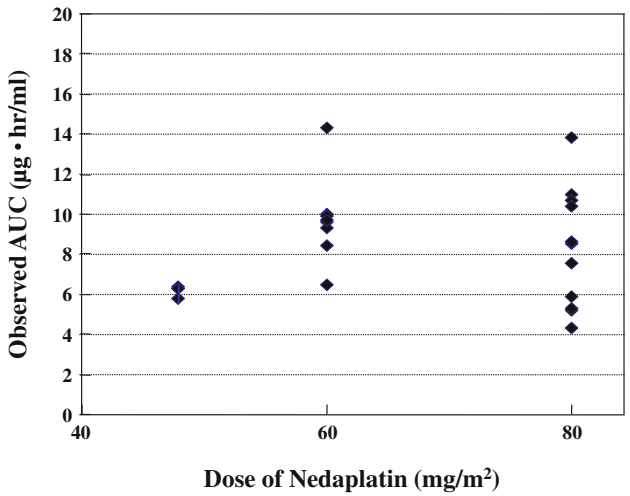

Fig. 1 Observed AUC and dose of nedaplatin (mg/m^2)

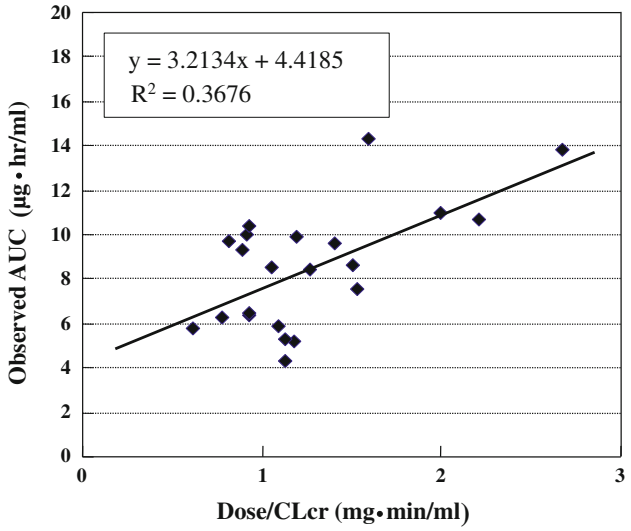

Fig. 2 Observed AUC and clearance

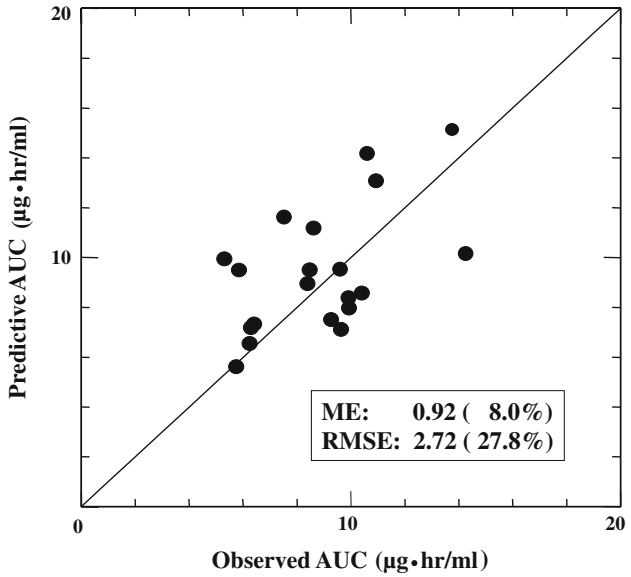

Fig. 3 Predictive and observed AUC

Discussion

The dose-limiting factor (DLT) for NDP as well as CBDCA is their hematological toxicity. The relationship between the AUC of platinum and its antitumor efficacy or toxicity has been demonstrated in previous reports. In general, the dose of CBDCA was calculated by using a targeted AUC [22]. The Calvert's formula is most frequently used for CBDCA dosing. Since the pharmacokinetic profile of NDP is similar to

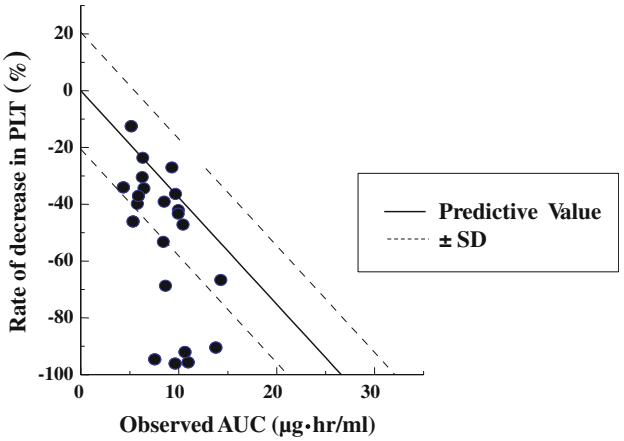

Fig. 4 Observed AUC and relative reduction rate of platelet

that of CBDCA, such a formula for NDP is necessary to use this drug more effectively. However, the dose of NDP has been determined by using the BSA, and the therapeutic dose of NDP is recommended to be between 80 and 100 mg/m^2. In the current study, we demonstrated that the AUC of NDP varies after administration of NDP based on the BSA. The range of the observed AUC of NDP was wide, and there was no relationship between the observed AUC and dose based on the BSA. Those findings suggest that dosage of NDP based on BSA involves the uncertainty of the effect as well as various risks. We found a favorable correlation between AUC and Ccr. Therefore, the renal function should be considered when NDP is administered.

Ishibashi et al. reported a formula for predicting NDP clearance on the basis of pharmacokinetics. In their study, ME and RMSE were 0.629 (−32.0%) and 3.469 (24.2%) [18]. The current study showed that ME and RMSE were 0.92 (8.0%) and 2.72 (27.8%), indicating that the bias and precision were similar to the previous data. Therefore, we could confirm good prediction accuracy of the platinum AUC with Ishibashi's formula, and Ishibashi's formula might be reliable to predict the AUC of NDP.

Ishibashi et al. also showed a linear relationship between thrombocytopenia measured by the extent of PLT decrease with the AUC of unbound platinum after NDP infusion [23]. In addition, the nadir of the PLT count was predicted by using the AUC. However, the decrease in the PLT count could not be predicted in 5 out of 22 patients. Those patients received concurrent chemoradiotherapy for cervical cancer. They had potential bone marrow suppression because they already received irradiation for whole pelvis and weekly administration of cisplatin (40 mg/m^2) concomitantly.

This study showed that Ishibashi's formula for estimating CL was useful for the treatment with NDP. Therefore, NDP might be safely administered on the basis of an adequate dose calculation using this formula. Based on the results of this study, we planned a Phase I study in which the dose of NDP was determined by AUC.

Conflict of interest None of the authors has any former or present conflict of interest related to this study.

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