Evaluation of Calvert's Formula for Dosage Adjustment of Carboplatin in Japanese Patients with Hormone Refractory Prostate Cancer

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For hormone refractory prostate carcinoma, a combination therapy of paclitaxel and carboplatin is used to expect life extension. We investigated the pharmacokinetics of carboplatin in Japanese prostate cancer patients ($n=10$, 55–72 years), and evaluated the usefulness of Calvert's formula in the individualized dosing adjustment. They were intravenously administered carboplatin (area under the free plasma concentration *versus* time curve (AUC)=5 mg·min/ml), following the intravenous administration of paclitaxel (175 mg/m²). The dosage of carboplatin for each patient was determined with Calvert's formula using individual creatinine clearance values. Plasma concentration of total platinum was measured sequentially and the pharmacokinetic parameters of carboplatin were determined in each patient. Plasma concentration of total carboplatin after intravenous infusion well fitted the two-compartment model. Carboplatin clearance was 62.0 ± 12.7 ml/min (mean $\pm$ S.D.), and linearly related to the individual creatinine clearance ($r^2=0.64$, $p<0.01$). The actual AUC for total carboplatin was 8.20 ± 1.11 mg·min/ml, and its inter-individual variability was decreased to 65% of that in carboplatin clearance, indicating the effectiveness of Calvert's formula for dosage adjustment of carboplatin. Leucopenia of grade 4 according to the National Cancer Institute's Common Toxicity Criteria was found in one patient, but no patient demonstrated thrombocytopenia. In conclusion, determining carboplatin dosage based on Calvert's formula decreased the inter-individual variability in the actual AUC compared with that in the carboplatin clearance, and a target AUC of 5 mg·min/ml of carboplatin was comparatively safe for Japanese patients with prostate cancer.

Key words carboplatin; pharmacokinetics; Calvert's formula; prostate cancer; paclitaxel; toxicodynamics

Carboplatin, an analogue of cisplatin, was introduced in 1981 and has proven effective against various malignancies. Carboplatin has less nonhematological toxicity such as renal failure than its parent compound cisplatin,¹⁾ and thrombocytopenia is a dose-limiting factor of this drug.²⁾ Since the 1990's, carboplatin in combination with paclitaxel has been used in the treatment of several solid tumors such as ovarian, breast and lung cancers.^{3–5)} At present, no chemotherapy is considered effective enough for prostate cancer, although regimens of mitoxantrone or taxanes was recently reported to be effective.⁶⁾ Especially, the combination therapy of carboplatin and paclitaxel has been regarded as valid for hormone refractory prostate carcinoma.^{7,8)} Therefore, we used a regimen of paclitaxel and carboplatin every four weeks as performed in the treatment of other solid tumors, to prolong the life of patients with hormone refractory prostate cancer.

Dosages of carboplatin are frequently determined based on Calvert's formula: dose (mg)=target $AUC \times (GFR+25)$, where AUC is the area under the concentration *versus* time curve (mg·min/ml) for free carboplatin, and GFR is the glomerular filtration rate (ml/min).⁹⁾ Since carboplatin is eliminated depending on glomerular filtration,¹⁰⁾ Calvert *et al.*⁹⁾ designed this simple formula to predict the AUC based on the glomerular filtration rate. The efficacy and toxicity of carboplatin were more closely related to AUC than dosage,²⁾ and to control the actual AUC of carboplatin into the target range is considered to be important. Although Calvert *et al.*⁹⁾ primarily measured the glomerular filtration rate using the [⁵¹Cr]-EDTA method, creatinine clearance is generally used instead because of the inconvenience of measuring the glomerular filtration rate directly. Moreover, it is known that

creatinine clearance is higher than the glomerular filtration rate, since creatinine is not only filtered by glomeruli but secreted by renal tubules.^{11,12)} Therefore, using creatinine clearance in place of the glomerular filtration rate may result in an overdose of carboplatin, and several studies have been done to examine the accuracy for prediction of carboplatin clearance, or to re-arrange the Calvert's formula for various types of tumors.^{13–16)} However, only a limited amount of information on the pharmacokinetics of carboplatin as well as efficacy of Calvert's formula is available in Japanese cancer patients.^{17–19)}

In this study, we attempted the pharmacokinetic analysis of carboplatin, and evaluated the usefulness of Calvert's formula in prostate cancer patients treated with a combination therapy of paclitaxel and carboplatin. The relationships between the pharmacokinetics of carboplatin and clinical laboratory tests as well as toxicity were also evaluated.

PATIENTS AND METHODS

Patients and Chemotherapy Regimen Ten patients with hormone refractory prostate carcinoma were enrolled in this study. All were inpatients at the Department of Urology, Kyoto University Hospital, and had received chemotherapy with paclitaxel and carboplatin for the first time. This study was performed in accordance with the Declaration of Helsinki and its amendments, and approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee. Written informed consent was obtained from each patient.

Patients received 175 mg/m² of paclitaxel (Taxol[®]) as a 3-h

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intravenous infusion, followed by carboplatin (Paraplatin®) as a 2.5-h intravenous infusion. The dose of carboplatin was calculated using Calvert's formula with a target free *AUC* of 5 mg·min/ml: carboplatin dose (mg)=5×(GFR (ml/min)+25).⁹⁾ The glomerular filtration rate was replaced by the 24-h creatinine clearance measured on the day prior to the study. Serum and urine creatinine levels were measured by enzymatic method using specific test kit (L-type wako creatinineF®, Wako Pure Chemical Ind., Ltd., Osaka, Japan). In three patients, a modified dose of carboplatin was administered by physicians' decision; an increase of 35 or 45 mg for two patients and a decrease of 85 mg for one patient. All patients were premedicated with an intravenous administration of dexamethasone, one of histamine type 2 receptor antagonists (famotidine or ranitidine hydrochloride), and chlorpheniramine maleate before the paclitaxel infusion. One of serotonin type 3 receptor antagonists (ramosetron hydrochloride or granisetron hydrochloride) was administered before the carboplatin. Concomitant therapies were not restricted in this study. Patients received chemotherapy every four weeks, and pharmacokinetic analysis was performed at the first administration. The characteristics of the patients are summarized in Table 1.

Pharmacokinetic and Toxicodynamic Analyses Blood samples were collected at 0.5, 1.5, 5.5 and 23.5 h after the start of carboplatin administration. Plasma was separated by centrifugation, and stored at -20 °C in a polypropylene tube until the time of analysis. The concentration of total platinum in plasma was measured using inductively coupled plasma-mass spectrometry (ICP-MS) by the Shin Nippon Biomedical Laboratories, Ltd. Pharmacokinetics and Bioanalysis Center (Kainan, Japan). Individual pharmacokinetic parameters were estimated by the Bayesian post hoc method with the nonlinear mixed effect modeling program NONMEM version V using the POSTHOC option.²⁰⁾ The actual *AUC* for total carboplatin was computed as follows: *AUC* (mg·min/ml)=Dose (mg)/CLcarb (ml/min), where CLcarb is the estimated carboplatin clearance. Hematological toxicities were classified using the National Cancer Institute Common Toxicity Criteria (Version 3, 2004).

Statistical Analysis Data were expressed as the mean±standard deviation (S.D.). The correlations between the carboplatin clearance and patient characteristics including clinical laboratory tests, and relationships between total carboplatin *AUC* and hematological toxicities were analyzed using simple linear regression. The difference of carboplatin clearance and hematological toxicities between patients with or without irradiation was calculated using Student's *t*-test. The decrease in blood cell counts after chemotherapy was evaluated with the paired *t*-test. When a *p*-value was less than 0.05, the difference was considered significant. Statistical analysis was performed with the program StatView 5.0 (Abacus Concepts, Berkeley, CA, U.S.A.).

RESULTS

We attempted a pharmacokinetic analysis of the total carboplatin plasma concentration in ten patients with prostate cancer. The median age of the patients was 67, and no patient had reduced liver function (Table 1). The median creatinine clearance was 72.5 ml/min, and values ranged widely from

Table 1. Patient Data Used in the Analysis of Carboplatin

Number of patients	10
Age (years)	67 (55–72) ^{a)}
Body weight (kg)	64.3 (59–78) ^{a)}
Body surface area (m ²)	1.71 (1.60–1.90) ^{a)}
Biochemical parameters	
Creatinine clearance (ml/min)	72.5 (41–114) ^{a)}
Blood urea nitrogen (mg/dl)	14.5 (9–37) ^{a)}
Aspartate aminotransferase (IU/l)	19.5 (11–27) ^{a)}
Alanine aminotransferase (IU/l)	16 (8–24) ^{a)}
γ-Glutamyl transpeptidase (IU/l)	23 (9–170) ^{a)}
Carboplatin dose (mg)	500 (330–640) ^{a)}
Carboplatin infusion time (h)	2.5 (2–4) ^{a)}
Paclitaxel dose (mg)	298 (280–330) ^{a)}
Paclitaxel infusion time (h)	3.26 (2.83–4.4) ^{a)}
Number of patients receiving concomitant therapy	
LH-RH analogue	8
Estramustine sodium phosphate	10
Flutamide	1
Cyclophosphamide	2
Tegafur-Uracil	1
Radiation	6 ^{b)}

a) Median (range) of 10 patients. b) Irradiation within a week before and after chemotherapy.

Fig. 1. Individual Carboplatin Plasma Concentration–Time Profiles in Ten Patients with Prostate Cancer

Open circles show the total carboplatin plasma concentrations measured by the ICP-MS method. Each line shows a simulation curve fitted to the two-compartment model for an individual patient.

41 to 114 ml/min. Based on Calvert's formula, the carboplatin dosage of each patient differed between 330 and 640 mg for free *AUC* of 5 mg·min/ml. Six patients received radiation within a week before and after the chemotherapy.

Figure 1 shows the plasma concentration–time profiles in all patients. Plasma concentrations of total carboplatin after the intravenous infusion well fitted the two-compartment model. Objective functions (–2 log likelihood) fitted to the one- and two-compartment model were 127.9 and 92.0, respectively. Pharmacokinetic parameters of total carboplatin based on the two-compartment model are shown in Table 2. The coefficient of variation (CV%) in carboplatin clearance between patients was 20.5%, while that in the actual *AUC* was 13.6%. Creatinine clearance and blood urea nitrogen showed a significant correlation with carboplatin clearance (Fig. 2). Age, body weight, body surface area, and biochemical parameters of liver function (aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase) did not correlate with carboplatin clearance. There was no difference in carboplatin clearance between patients with or without irradiation within a week before and after chemotherapy (*p*=0.32).

Results of hematological tests conducted before and after the chemotherapy are shown in Table 3. The numbers of leucocytes, neutrophils and platelets in all patients were significantly decreased after the chemotherapy. Severe leucopenia and neutropenia with grade 4 was found in the same patient, but no patients showed thrombocytopenia. No significant relationship was found between the actual *AUC* and nadir of leucocyte, neutrophil or platelet counts (leucocyte, $r^2=0.016$, $p=0.73$; neutrophil, $r^2=0.024$, $p=0.67$; platelet, $r^2=0.13$, $p=0.31$). Irradiation did not significantly influence any hematological toxicities (leucocyte, $p=0.84$; neutrophil,

$p=0.55$; platelet, $p=0.28$).

DISCUSSION

In this study, we measured the concentrations of total platinum in plasma, and used them to evaluate pharmacokinetic parameters. Generally, pharmacokinetic analyses of carboplatin focus on the free form, since protein-bound carboplatin has no cytotoxic activity.^{21,22} Indeed, numerous carboplatin pharmacokinetic parameters have been reported based on the free form, that is, the ultrafiltrated plasma carboplatin concentration.^{9,13–16} However, since majority of carboplatin acts as the free form immediately after the administration,¹⁰ we considered that results of the pharmacokinetic analysis for total carboplatin in this study showed a similar tendency to that for the free form.

Since the clearance based on free form of plasma carboplatin is closely correlated with the glomerular filtration rate,¹⁰ Calvert *et al.*⁹) established a simple formula for the determination of carboplatin dosage to attain a target *AUC* based on the glomerular filtration rate. This formula is widely used in the treatment of several type of carcinoma.^{23–27} Although it is generally considered that creatinine clearance does not accurately reflect the glomerular filtration rate,^{11,12} creatinine clearance is frequently used instead because of the inconvenience of measuring the glomerular filtration rate directly. Actually, some reported an arrangement of Calvert's formula using creatinine clearance.^{13,14} In this study, carboplatin clearance was linearly related to creatinine clearance ($r^2=0.64$, $p<0.01$, Fig. 2A) and blood urea nitrogen which also reflects renal function ($r^2=0.56$, $p<0.05$, Fig. 2B). The inter-individual variability of the actual *AUC* which was already adjusted by the Calvert's formula was smaller than that of carboplatin clearance (Table 2), indicating the effectiveness of Calvert's formula for the adjustment of carboplatin dosage. In addition, we considered that using creatinine clearance instead of the glomerular filtration rate was adequate when calculating the carboplatin dosage at least when target free *AUC* was set at 5 mg·min/ml.

To decrease hematological toxicities to a low frequency, a

Fig. 2. Relationships between Carboplatin Total Body Clearance and Creatinine Clearance or Blood Urea Nitrogen in Prostate Cancer Patients

The correlations between carboplatin clearance and creatinine clearance (A), or blood urea nitrogen (B) were analyzed using simple regression.

Table 2. Pharmacokinetic Parameters of Total Carboplatin Based on the Two-Compartment Model in Prostate Cancer Patients

	CL (ml/min)	Q (ml/min)	V ₁ (l)	V ₂ (l)	Actual <i>AUC</i> (mg·min/ml)
Mean±S.D.	62.0±12.7	41.1±1.9	15.1±4.8	32.0±4.8	8.20±1.11
CV %	20.5	4.7	31.6	15.1	13.6
Range	39.0–80.3	38.7–45.0	7.1–21.2	38.7–45.0	6.29–9.62

CL, total body clearance; Q, intercompartmental clearance; V₁, central volume of distribution; V₂, peripheral volume of distribution; *AUC*, area under the total plasma concentration versus time curve; CV, coefficient of variation.

Table 3. Hematological Toxicities in Patients with Prostate Cancer Receiving Chemotherapy with Carboplatin and Paclitaxel

Hematological test	Before ^{a)} (10 ³ /μl)	Nadir ^{a)} (10 ³ /μl)	<i>p</i> -value ^{b)}	% decrease ^{a,c)}	Time to Nadir ^{a)} (d)	Grade ^{d)}			
						1	2	3	4
Leucocytes	8.4 (2.4–12)	3.7 (0.4–7.8)	<0.01	45.9 (12.5–95.9)	8.5 (5–27)	0	2	0	1
Neutrophils	5.5 (1.4–9.5)	2.1 (0.2–6.0)	<0.01	53.8 (21.4–97.8)	12 (7–17)	3	1	0	1
Platelets	214 (150–570)	170 (107–327)	<0.01	25.0 (0–49.0)	8.5 (5–29)	0	0	0	0

a) Median (range) of 10 patients. b) Statistical significance between the value before and nadir by paired *t*-test. c) % decrease=(Before–Nadir)/Before×100. d) Classified by the National Cancer Institute Common Toxicity Criteria version 3.

free carboplatin *AUC* of 5–7 mg·min/ml was reported to be desirable.²⁾ In this study, 2 patients (20%) had leucopenia of grade 2 and one patient (10%) had leucopenia of grade 4, while no patients had thrombocytopenia (Table 3). In addition, the actual *AUC* of total carboplatin in individual patients was not correlated with the nadir of the leucocyte, neutrophil and platelet counts. Other studies which tried chemotherapy with paclitaxel (175 mg/m²) and carboplatin (free *AUC*, 5 mg·min/ml) reported that neutropenia was observed in 0–39% of patients, and thrombocytopenia in 0–1%, which is consistent with our results.^{19,28–30)} It is known that paclitaxel mainly causes leucopenia and neutropenia, but rarely causes thrombocytopenia.³¹⁾ On the other hand, carboplatin frequently causes thrombocytopenia depending on the dosage.²⁾ Accordingly, we considered that the severe leucopenia in this one patient was caused by paclitaxel, and carboplatin toxicity did not appear in this study with a target *AUC* of 5 mg·min/ml.

In conclusion, the clearance of carboplatin in individual patients was significantly related with the creatinine clearance, and calculating the dose of carboplatin based on Calvert's formula substituting creatinine clearance for the glomerular filtration rate might be appropriate for Japanese patients with prostate cancer. In addition, 175 mg/m² of paclitaxel with an *AUC* for carboplatin of 5 mg·min/ml every four weeks is comparatively safe for elderly patients.

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