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Pharmacokinetic Study of Carboplatin Given on a 5-Day Intravenous Schedule

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We investigated whether carboplatin pharmacokinetics is altered when the drug is delivered daily over 5 days, compared to a single-day infusion. Carboplatin was infused in 11 patients with lung cancer, who were randomly assigned to 2 groups. In the first group, the agent was administered on a conventional single-day schedule in the first course and then on a 5-day schedule in the second course. In the second group, the order was reversed (crossover design). The dose was calculated using Calvert's formula with 24 h creatinine clearance (Ccr, ml/min) as a substitute for glomerular filtration rate (GFR): carboplatin (mg) = AUC × (Ccr + 25), where AUC denotes the area under the concentration versus time curve (mg ml^{-1} min). No difference of carboplatin clearance between the single-day and 5-day schedule was observed (94.8 ± 19.9 *versus* 96.1 ± 29.9 ml/min, $P = 0.818$, paired t test). The formula systematically overestimated the carboplatin clearance; the ratio of estimated clearance/observed clearance ranged from 1.01 to 1.58 (median 1.28; 95% confidence interval, 1.18 to 1.39). We concluded that the individual dosing strategy based on renal function can be applied with a 5-day schedule as well as a single-day schedule. Carboplatin is overdosed when Ccr is substituted for GFR in Calvert's formula.

Key words: Carboplatin — Pharmacokinetics — Creatinine clearance — Lung cancer

Carboplatin is a second-generation platinum-containing compound which is less nephrotoxic, neurotoxic and emetogenic than cisplatin. Myelosuppression is a dose-limiting toxicity and correlates with systemic exposure to the agent, expressed as the area under the concentration *versus* time curve (AUC). Because the total body clearance (dose/AUC) is linearly related to patients' renal function,[1,2] the administered dose should be modified based on patients' renal function rather than their body surface area. For the conventional single-day schedule, Calvert *et al.* developed a simple formula to calculate a dose to obtain a specific AUC using the patient's glomerular filtration rate (GFR).[3]

On the other hand, Kyriazis *et al.* demonstrated a schedule dependency of antitumor activity in an animal model.[4,5] Fractionated administration resulted in better activity against human urothelial cancer xenografts than the same dose given by single administration.[4] Therefore, clinical and pharmacokinetic studies for divided doses are desirable. However, whether Calvert's formula can be applied to a divided dosing schedule has not been investigated.

We therefore investigated the pharmacokinetics of carboplatin administered on a 5-day schedule[6,7] and compared it to that of a conventional single-day administration. The objective of this study was to disclose whether the pharmacokinetics is altered when the drug is delivered daily over 5 days.

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MATERIALS AND METHODS

Patient eligibility and evaluation Patients had to fulfill all of the following criteria: histologic or cytologic proof of lung cancer; no other serious disease, including uncontrollable pleural or pericardial effusion, heart failure, or infection; age ≤75 years; performance status ≤3 on the Eastern Cooperative Oncology Group scale; leukocyte count ≥3,500/μl; platelets ≥100,000/μl; and total bilirubin ≤1.5 mg/dl. There was no anti-neoplastic treatment during the 4 weeks before entry; 3 months were required after a cisplatin-containing regimen to avoid an effect on the measurement of creatinine clearance (Ccr).[8] Patients with non-small-cell lung cancer had inoperable cancers or postoperative relapse. Untreated patients and patients who were previously treated with chemotherapy, radiotherapy, or both, were eligible. Patients with small-cell lung cancer were eligible if they were refractory to, or could not tolerate, standard treatment. This study was approved by the ethical committee of the hospital, and informed consent in writing was obtained from all patients.

All patients were treated as inpatients, and randomly assigned to group A or B. In group A, carboplatin was administered on a conventional single-day schedule in the first course, then on a 5-day schedule in the second

course. In group B, the order was reversed (crossover design). In both schedules, the daily dose of carboplatin was diluted in 300 ml of 5% glucose solution and infused over 1 h as monotherapy. The dose was calculated using Calvert's formula with GFR being replaced by Ccr: carboplatin (mg) = AUC × (Ccr + 25), where AUC was 7 (mg ml^{-1} min) for chemo-naive and 5 (mg ml^{-1} min) for previously treated patients.[3] The mean of three measured Ccr from 24 h urine collection expressed as the absolute value (ml/min) without correction for the body surface area was used to calculate the dose. Colony-stimulating factors were administered along with antibiotics when a patient experienced fever and grade 4 leukopenia or neutropenia. Chemotherapy was repeated every 4 weeks. The total dose was identical in the first and second courses. The following course was delayed until the leukocyte and platelet count recovered to $\geq$3,000/μl and $\geq$100,000/μl, respectively.

Pharmacokinetic study Blood samples were collected in a tube coated with a coagulation accelerant (Insepack, Sekisui Medical Co., Ltd., Osaka), at 0, 0.25, 0.5, 1, 2, 4, and 8 h following the end of infusion via a peripheral venous catheter. In the 5-day schedule, blood was taken on days 1 and 5, and an additional sampling was performed just before the infusion on day 5. The serum was immediately separated by centrifugation, and ultrafiltered serum was obtained using a Millipore Ultrafree-C3 filter unit (UFC3LGC00, Japan Millipore Ltd., Tokyo). The ultrafiltrates were stored at -20°C until analysis.

The ultrafiltered platinum level was measured by flameless atomic absorption spectrometry. The lower limit of detection was 25 ng/ml. The intra- and inter-assay coefficient of variation was 2.6% (at 1,600 ng/ml) and 4.1% (at 1,400 ng/ml), respectively. The carboplatin level was calculated based on the molar ratio of platinum: carboplatin, and expressed in micrograms per milliliter.[1, 9]

Carboplatin AUC was calculated by the trapezoidal method with extrapolation to infinity using PCNONLIN (version 4.0, Scientific Consulting Inc., Apex, NC). An AUC of the 5-day schedule was obtained as five times the average of AUC on days 1 and 5. Total carboplatin clearance was calculated by use of the following formula: clearance = dose/AUC. The elimination half-life ($T_{1/2}$) was reported as the harmonic mean $\pm$ jackknife standard deviation (SD).[10] The distribution volume (V_d) was calculated as follows: V_d = clearance/β, where β is the elimination rate constant.

Statistical analysis Carry-over and period effects were evaluated using a standard procedure.[11] When we define y_{first} and y_{second} as the values obtained in the first and the second courses, respectively, we have

$$\text{Group A: } sA;\ dA = yA_{first} \pm yA_{second}$$
$$\text{Group B: } sB;\ dB = yB_{first} \pm yB_{second}$$

Differences between $\bar{s}A$ (mean of sA in group A) *versus* $\bar{s}B$ and $\bar{d}A$ *versus* $-\bar{d}B$ were tested for carry-over and period effects, respectively. We considered them to be not significant if the two-tailed P values were more than 0.20 in the t test. Comparisons of pharmacokinetic parameters were performed by paired t test and evaluated in terms of the correlation coefficient (r). A difference was considered statistically significant if the two-tailed P value was less than 0.05. The accuracy of Calvert's formula was evaluated in terms of the mean prediction error and its standard error (MPE $\pm$ SE) and root-mean-squared prediction error (RMSE) calculated as shown below.[12]

$$\text{MPE} = \frac{1}{n} \times \sum \left(\frac{\text{predicted} - \text{observed}}{\text{observed}} \times 100 \right) (\%)$$

$$\text{RMSE} = \left\{ \frac{1}{n} \times \sum \left(\frac{\text{predicted} - \text{observed}}{\text{observed}} \times 100 \right)^2 \right\}^{\frac{1}{2}} (\%)$$

Table I. Characteristics of Patients

Group[a)]		Total	A	B
Gender	F/M	2/9	2/3	0/6
Age (years)	median	60 (47–70)	56 (47–64)	62.5 (52–70)
Prior therapy	chemotherapy	7	4	3
	chemo-naive	4	1	3
Serum creatinine (mg/dl)	mean $\pm$ SD	0.68 $\pm$ 0.14	0.68 $\pm$ 0.19	0.68 $\pm$ 0.10
	range	0.5–1.0	0.5–1.0	0.5–0.8
Ccr (ml/min)	mean $\pm$ SD	94.6 $\pm$ 19.3	96.6 $\pm$ 15.4	93.0 $\pm$ 23.5
	range	64–125	81–121	64–125
Weight (kg)	median (range)	54 (41–85)	56.5 (52–69)	52 (41–85)
Body surface area (m^2)	median (range)	1.54 (1.37–1.89)	1.53 (1.43–1.70)	1.55 (1.37–1.89)
Carboplatin dosage (mg)	range	405–1162	529–1022	405–1162

SD, standard deviation; Ccr, creatinine clearance.
a) In group A, carboplatin was administered on a single-day schedule in the first course then on a 5-day schedule in the second course. In group B, the order was reversed.

RESULTS

Eleven patients entered the study between November 1994 and January 1996 (Table I). Four patients had received prior chemotherapy with cisplatin. There was no treatment-related death, but one patient in group B committed suicide on day 21 in the second course. Although pharmacodynamic comparisons were not the intent of the study, toxicities of the two schedules are summarized in Table II.

Pharmacokinetic analysis The carry-over and period effects were not significant for AUC or clearance (AUC: $P=0.779$, $P=0.624$; clearance: $P=0.474$, $P=0.888$, respectively). Therefore, we considered that all patients could be analyzed as one group.[11]

The comparison between the single-day and 5-day divided schedules revealed no differences in the parameters ($P=0.645$ for AUC, $P=0.818$ for clearance, Table III), and showed a good correlation ($r=0.729$ for AUC and 0.781 for clearance, Fig. 1). When the parameters on days 1 and 5 in the 5-day schedule were compared, no difference was observed ($P=0.083$ for AUC and $P=0.313$ for clearance, Table III). The relative level of platinum just before the infusion on day 5 at the maximum concentration was 0.4±0.7% (mean±SD) with a median of 0%, suggesting that there was no evidence of accumulation of this agent.

In the analysis of the single-day regimen, the clearance estimated by Calvert's formula using 24 h Ccr was systematically higher than the observed clearance (119.6±19.3 *versus* 94.8±19.9, mean±SD, $P<0.001$ by paired t test, Fig. 2). There was no impact of prior cisplatin

Table II. Toxicities ($n=11$)

		Single-day schedule	5-day schedule
Leukocytes (μl^{-1})	median	3,400[b]	3,200
	range	1,400–5,600[b]	1,500–4,500
Neutrophils (μl^{-1})	median	2,000[b]	1,200
	range	600–4,100[b]	200–3,200
Platelets (μl^{-1})	median	73,000[b]	43,000
	range	15,000–278,000[b]	13,000–225,000
Nausea	grade 3–4[a]	0	0
	grade 1–2	7	5

a) World Health Organization grade.
b) One patient died on day 21 in the second course (single-day schedule). Therefore, the hematologic toxicities of this patient were excluded.

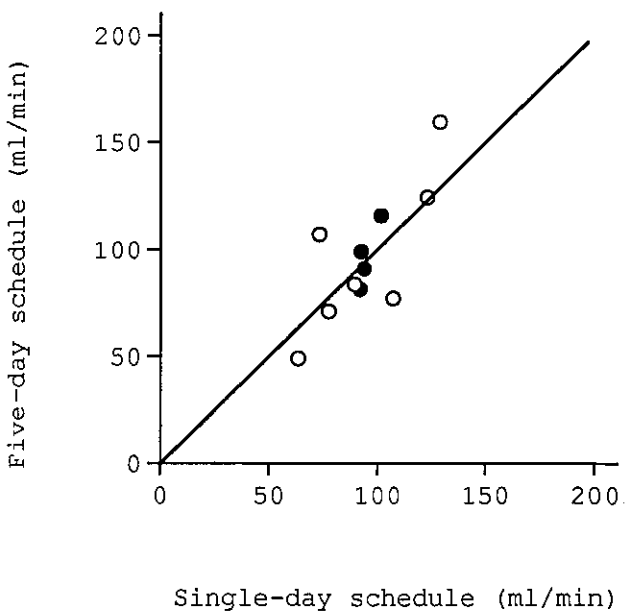

Fig. 1. Relationship of carboplatin clearance between single-day and 5-day schedules ($r=0.781$ and $P=0.818$). Closed circles represent the patients who had had prior chemotherapy with cisplatin. The line denotes the line of identity.

Table III. Pharmacokinetic Parameters in Single-day Schedule and 5-day Schedule

		Single-day schedule	5-day schedule	Day 1	Day 5
AUC	(mg ml^{-1} min)	7.6±1.6	7.8±2.5	1.4±0.5	1.7±0.6
	range	5.8–10.5	5.4–13.3	0.7–2.5	0.8–2.8
Cl	(ml/min)	94.8±19.9	96.1±29.9	105.3±34.5	93.3±37.1
	range	63.3–129.0	48.9–159.3	61.7–174.1	40.5–152.3
$T_{1/2}$	(h)	2.1±0.4		2.2±0.4	2.3±0.7
	range	1.8–3.2		1.7–2.9	1.7–4.2
V_d	(liter)	17.2±2.0		20.0±5.8	19.0±5.9
	range	13.6–19.8		13.1–30.3	10.8–30.1

AUC, area under the concentration *versus* time curve (mean±SD); Cl, clearance (mean±SD); $T_{1/2}$, elimination half-life (harmonic mean±jackknife SD); V_d, distribution volume (mean±SD); SD, standard deviation.

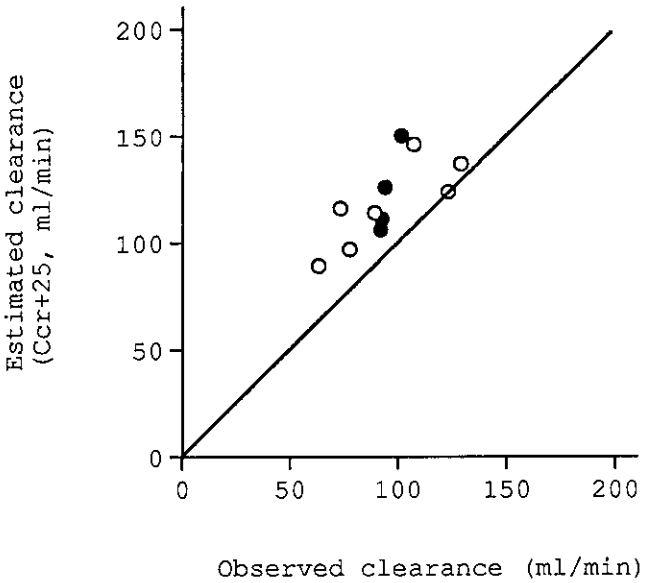

Fig. 2. Scatter plots of carboplatin clearance estimated by Calvert's formula against observed clearance. The estimated clearance in group B was adjusted using the creatinine clearance (Ccr) measured prior to the second cycle. Closed circles represent the patients who had had prior chemotherapy with cisplatin. The line denotes the line of identity.

therapy on the relationship (Fig. 2). The MPE±SE and the RMSE were 28.3±5.2% and 32.8%, respectively. The ratio of estimated clearance/observed clearance ranged from 1.01 to 1.58 (median 1.28; 95% confidence interval, 1.18 to 1.39).

DISCUSSION

We found no difference of pharmacokinetic parameters between the two schedules. This study could detect a 20% difference in the clearance with a statistical power of more than 80%.[13] Therefore, we consider that the influence of divided administration on carboplatin pharmacokinetics is clinically negligible. Other investigators have also suggested no alteration of the pharmacokinetics by daily repeated infusions of doses ranging from 300 to 1,600 mg/m^2.[6, 14, 15]

van Warmerdam *et al.* validated their limited sampling model for estimating carboplatin AUC when the agent was repeated as a 1-h infusion every day for 4 days,[14] whereas the model had been developed when the agent was infused on a single 1-h schedule.[16] The model proved to be accurate on all days, and the residual AUC from the previous course did not significantly influence the observed AUC of days 2, 3, and 4. Although their objective was not to investigate the alteration of the AUC in the different schedules, their results implied that the pharmacokinetics of the agent given on consecutive days did not differ from that of a single administration.

We applied 24 h Ccr in place of GFR in Calvert's formula because of its convenience.[3] The estimated clearances in all patients were higher than those observed, which is consistent with other reports.[17–19] Although Calvert's formula has been widely used for carboplatin dosing or pharmacologic analyses, further study is necessary to confirm the accuracy of the formula using Ccr.

This study was too small to examine the difference in toxicity or response between the two schedules. A larger study is necessary for the pharmacodynamic analysis of 5-day administration of carboplatin.

We concluded that there was no difference between the pharmacokinetic parameters for the single-day and 5-day schedules when the dose targeting AUC from 5 to 7 (mg ml^{-1} min) was administered in patients with normal renal function. Thus, individual dosing strategy targeting AUC can be applied for a 5-day schedule as well as a single-day schedule.

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