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ORIGINAL ARTICLE

Transient elevation of serum cystatin C concentrations during perioperative cisplatin-based chemotherapy in esophageal cancer patients

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Abstract
Purpose In the present study, the time–concentration profile of platinum (Pt) in plasma was compared to that of serum cystatin C (Cys C) in Japanese esophageal cancer patients receiving perioperative cisplatin-based chemotherapy.
Methods Five male and one female patients receiving 2 successive cycles of cisplatin-based chemotherapy combined with 5-fluorouracil, the treatment for esophageal squamous cell carcinoma, participated in this study. The pharmacokinetic parameters in each patient were calculated from the individual plasma Pt concentration–time curve after intravenous infusion of cisplatin using the one-compartment model.
Results Within a week of starting the first cycle of chemotherapy, serum Cys C concentrations increased in all patients from 122.6 to 143.0 %, subsequently returning to baseline levels in approximately 10 days. A similar increase in serum Cys C levels also occurred during the second treatment cycle. However, no increase in serum creatinine levels was observed during either treatment cycle. In addition, the concentration of plasma Pt 2 days after treatment in the first and second cycles did not correlate with those of either serum Cys C or creatinine. Finally, the half-life of Pt in plasma during the first treatment cycle was not significantly different from that in the second cycle.
Conclusions These findings suggest that concentration fluctuations in serum Cys C are unlikely to correlate with Pt elimination from the plasma and that renal function estimates based on serum Cys C concentration might be underestimated during perioperative cisplatin-based chemotherapy for esophageal cancer.

Keywords Cisplatin · Cystatin C · Esophageal cancer · Platinum · Renal function

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Introduction

Cisplatin (CDDP) is one of the most potent anticancer drugs in clinical use and shows efficacy against several common types of solid tumors. However, CDDP is frequently associated with renal tubular dysfunction. The cumulative impairment in renal function, manifested by a decrease in the glomerular filtration rate (GFR), is a dose-limiting factor in the use of this drug [1, 2]. It is therefore important to monitor renal function during and after CDDP chemotherapy to recognize early renal injury.

Cystatin C (Cys C) is a non-glycosylated cationic 13.3-kDa protein belonging to the cystatin superfamily of cysteine protease inhibitors [3–5]. Cys C is produced by all nucleated cells and is secreted into the blood at a constant rate [3–5]. It is freely filtered through the normal glomerular membrane and completely reabsorbed, then catabolized in the proximal tubular cells [3–5]. Thus, similar to creatinine (Cr), the biological fate of Cys C is a good endogenous marker of the GFR.

In fact, Cys C is used to estimate of pharmacokinetics of drugs such as vancomycin and carboplatin, which are mainly eliminated via kidneys [6, 7]. As CDDP is also mainly eliminated by the kidney [8], platinum (Pt) nephrotoxicity occurring during CDDP-based chemotherapy would both prolong the half-life of Pt in plasma and increase the serum Cys C concentration. Concerning a link between Cys C and CDDP, some investigators have reported an increase in serum Cys C concentration following CDDP-based chemotherapy in adults [9] and children [10], and serum Cys C appears to be a better marker than serum Cr for monitoring the decreases in GFR that occur during the chemotherapy [11]. In these reports, however, the relationship between the blood concentrations of Cys C and Pt remains unclear, and there is little published information regarding possible fluctuations in serum Cys C concentration following CDDP administration.

In patients with esophageal cancer, CDDP is used as neoadjuvant or postoperative adjuvant chemotherapy combined with a continuous infusion of 5-fluorouracil (5-FU) [12, 13]. In the present study, the time–blood concentration profile of Pt was compared to that of Cys C during 2 cycles of CDDP-based chemotherapy in Japanese esophageal cancer patients.

Patients, materials, and methods

Patients and treatment

The protocol for this study was approved by the Research Ethics Committee of Kobe University, Japan. Written informed consent was obtained from all patients before the start of the study.

Five male and one female patients receiving neoadjuvant or adjuvant CDDP-based chemotherapy for esophageal squamous cell carcinoma diagnosed at Kobe University Hospital participated in this study. Table 1 lists the clinical characteristics of the patients in this study. Diagnosis of esophageal carcinoma was based on clinical, endoscopic, radiological, and histopathological findings. All clinical data were collected from the patient medical records at the time of enrollment, and no patient had a history of previous chemotherapy. The perioperative CDDP-based chemotherapy consisted of a 2-hour drip infusion of 80 mg m^{-2} CDDP on day 1 and a 5-day protracted venous infusion of 800 mg m^{-2} day^{-1} 5-FU on days 1–5. All 6 patients received 2 successive cycles of the chemotherapy. We defined the first cycle as the interval from the beginning of the first cycle until the beginning of the second one, and the second cycle was defined as the beginning of the second cycle until the date of surgery (for patients #1 to #5) or until changing to a tri-weekly docetaxel regimen as a second-line chemotherapy (for patient #6). The duration of the first and second cycles was 28–42 days and 21–64 days, respectively. Baseline measurements were taken at the start of CDDP administration for each cycle (Fig. 1).

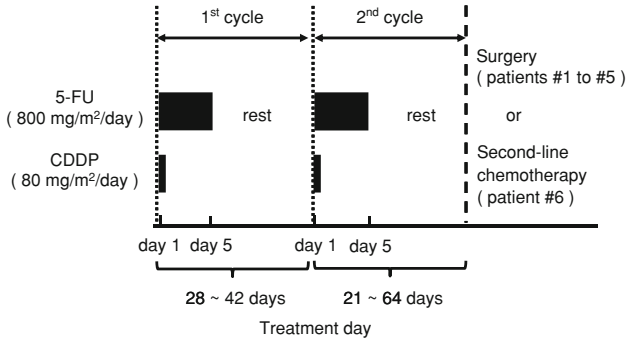

Fig. 1 Treatment schedule of CDDP-based chemotherapy. *5-FU* 5-fluorouracil, *CDDP* cisplatin

Table 1 Clinical characteristics of patients

Patient	Age (years)	Gender	Surgical history
#1	50	Female	No
#2	55	Male	No
#3	72	Male	No
#4	70	Male	No
#5	76	Male	No
#6	59	Male	Yes

Dose reductions in the second cycle were made for 2 patients (#1 and #5) based on treatment-related adverse events recorded during the first cycle. The patients received appropriate hydration and antiemetic premedication consisting of granisetron (1 mg on day 1), dexamethasone (6.6 mg on day 1 and 3.3 mg on days 2 and 3), and aprepitant (125 mg on day 1 and 80 mg on days 2 and 3). One patient (#1) received palonosetron (0.75 mg on day 1 of the first and second treatment cycles) instead of granisetron.

Blood samples

Peripheral venous blood (5 mL) was drawn at 11–16 points from each patient into duplicate tubes either containing or not containing ethylenediaminetetraacetic acid

(EDTA). The first blood sample of each cycle was taken 2 days after the start of the CDDP infusion. Subsequently, blood samplings were performed on days 4 and 7, and thereafter at 2- to 23-day intervals. In patient #6, blood samples were collected on days 6 and 8 of the first cycle, instead of days 4 and 7. Blood samples containing EDTA were centrifuged (5 min at 3,000 rpm) to provide a plasma sample for the determination of plasma Pt concentration, and samples without EDTA were used for routine laboratory tests and to determine the serum Cys C concentration. Plasma and serum samples were stored at −40 °C prior to testing.

Determination of serum Cys C concentration

Serum Cys C concentrations were determined by latex immunonephelometry using a Dimension Vista 500 analyzer (Siemens Healthcare Diagnostics Inc., USA). The results were routinely validated to confirm that acceptable accuracy was obtained.

Determination of plasma Pt concentration

Pt concentrations in plasma were measured as described previously [14]. Briefly, each sample (0.1 mL) was reduced to ash by repeated treatment with nitric acid (for poisonous metal determination, Wako), hydrogen peroxide (for atomic absorption spectrochemical analysis, Wako), and perchloric acid (for poisonous metal determination, Wako) under heat at 200 °C. Sample ash was dissolved in 5 mL of 7 % nitric acid and then analyzed by inductively coupled plasma-mass spectrometry (ICP-MS) using a Shimadzu ICPM-8500 (Shimadzu, Kyoto, Japan). We determined the levels of platinum content (m/z 195) in 3 replicates per sample. Contamination from tubes and other sources was avoided for Pt. The concentration of Pt in each sample was calculated using linear regression of a Pt standard curve prepared using a Pt standard solution. The Pt standard curve exhibited linear regression in the range of 1–500 ng mL^{-1} ($r = 0.999$).

Data analysis

The pharmacokinetic parameters for each patient were calculated from individual plasma Pt concentration–time curves after intravenous infusion of CDDP by a one-compartment model using a nonlinear least squares program (MULTI) [15]. Each least-square fit involved a total of 5–9 sample concentrations per patient in each cycle. Weighting was set at the reciprocal of each Pt concentration, and the pharmacokinetic parameters determined included the elimination rate constant (K_{el}) and half-life ($t_{1/2}$) in the first and second treatment cycles.

Statistical analysis

Data are expressed as means ± standard deviation (SD). The differences in individual serum Cys C concentrations between baseline and treatment days after the start of the chemotherapy for each cycle were tested using the non-parametric Friedman test and Steel–Dwass multiple comparison test. Comparisons between the pharmacokinetic parameters of Pt in the first and second treatment cycles were performed using a paired t test. Correlations were tested with the Pearson correlation test. P values of <0.05 (2-tailed) were considered to be significant.

Results

To determine the effect of the CDDP-based chemotherapy on the renal function in patients, serum concentrations of Cys C and Cr in the first and second cycles were compared. The baseline serum concentrations of Cys C and Cr in the 6 patients were 0.77 ± 0.12 mg L^{-1} and 0.84 ± 0.19 mg dL^{-1}, respectively (Table 2). As shown in Fig. 2, the serum Cys C concentrations varied between 87.0 and 235.6 % of the baseline values for each patient during the first cycle and between 58.9 and 183.3 % during the second cycle. There was a significant difference in the average baseline serum Cys C concentrations in the first and second cycles of the chemotherapy treatment regime (Table 2). It is noteworthy that after the start of the first cycle, the serum Cys C concentration increased within a week, in the range of 122.6 % (patient #1) to 143.0 % (patient #6) of their respective baseline levels, which was equivalent to a change in the estimated GFR from 121.0 to 97.9 mL min^{-1} 1.73 m^{-2} and from 94.8 to 64.9 mL min^{-1} 1.73 m^{-2}, respectively (calculated on the basis of the serum Cys C concentration using Hoek's formula [16]). The values subsequently returned to the baseline levels by around 10 days for all patients. This pattern of Cys C expression was also observed during the second cycle. During the first week after the start of the chemotherapy, the overall Friedman test demonstrated a significant difference in serum Cys C concentrations between baseline and 2–7 treatment days. The Steel–Dwass post-test showed significant differences in those between baseline and 2, 4, and 7 treatment days for the first cycle ($N = 5$; patient #6 was excluded from the analysis). For the second cycle ($N = 6$), there were also significant differences between baseline and 2 and 4 treatment days, but not between baseline and 7 treatment days. Average serum Cr concentration in all 6 patients was 0.95 ± 0.15 mg dL^{-1} and 1.15 ± 0.25 mg dL^{-1} during the first and second cycles, respectively. Serum Cr concentrations varied between 98.0 and 274.5 % of the baseline values during the first cycle, and this variation was greater than in the

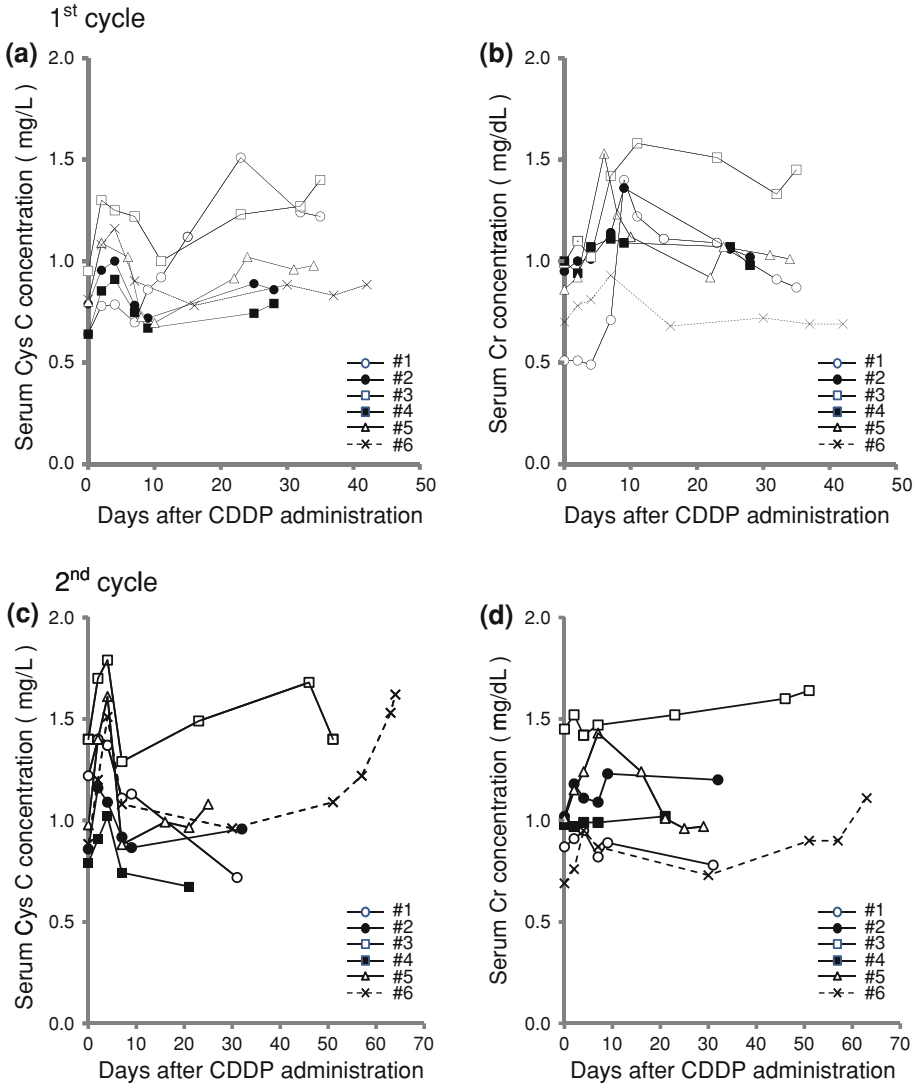

Fig. 2 Time–concentration profiles of Cys C and Cr in serum during the first (**a**, **b**) and second (**c**, **d**) cycles of the CDDP-based chemotherapy in 6 patients with esophageal cancer. The patients received neoadjuvant (*solid line*) or adjuvant (*dotted line*) chemotherapy

second cycle (ranging from 89.7 to 160.9 %; see Fig. 2). In contrast, a transient elevation was not observed in the serum Cr concentrations of all patients.

Figure 3 shows the time–concentration profiles of plasma Pt for all 6 patients. Plasma Pt concentrations were measured in a total of 18–30 samples for each patient. Plasma Pt concentrations at day 2 following the start of treatment (C_{2d}) were 965 ± 82 ng mL^{-1} and $1{,}335 \pm 394$ ng mL^{-1} in the first and second cycles, respectively. The C_{2d}/dose value (obtained by subtracting the baseline level from C_{2d} and adjusting for the CDDP dose) was greater in the second cycle than that in the first cycle, although the difference was not significant (9.4 ± 2.8 ng mL^{-1} mg^{-1} and 7.5 ± 1.2 ng mL^{-1} mg^{-1}, respectively). However, these values did not correlate with the corresponding day 2 serum Cys C and Cr concentrations. Although there is a tendency for an inverse correlation between the C_{2d}/dose value and serum albumin concentration in the first and second cycles ($r = -0.802$ and -0.676, respectively) and a positive correlation between the C_{2d}/Dose value and the duration of the first cycle ($r = 0.792$), these studies were not sufficiently powerful to reach statistical significance ($P = 0.055$, 0.141, and 0.060, respectively). After day 2, the plasma Pt concentrations decreased rapidly, although 4 patients appeared to exhibit secondary or tertiary peaks during the first and/or second cycles. Table 2 lists the pharmacokinetic parameters of Pt obtained from all 6 patients. K_{el} and $t_{1/2}$ in the first cycle were 0.0534 ± 0.0121 h^{-1} and 321.7 ± 55.1 h, respectively, and these values did not differ significantly from those in the second cycle (0.0456 ± 0.0136 h^{-1} and 397.0 ± 136.1 h).

Discussion

Although serum Cr level is the most widely used marker for measuring renal function, Cys C has recently attracted a great deal of attention following reports that Cys C serum

Table 2 Baseline laboratory tests, dose of CDDP, and plasma pharmacokinetic parameters of Pt

Patient	Baseline serum Cys C concentration[a] (mg L^{-1})		Baseline serum Cr concentration[a] (mg dL^{-1})		Baseline serum albumin concentration[a] (g dL^{-1})		Cycle duration (days)	
	1st cycle	2nd cycle	1st cycle	2nd cycle	1st cycle	2nd cycle	1st cycle	2nd cycle
#1	0.64	1.22	0.51	0.87	3.2	4.0	35	31
#2	0.79	0.86	0.95	1.02	3.7	3.3	28	36
#3	0.95	1.40	0.99	1.45	3.8	3.9	35	51
#4	0.64	0.79	1.00	0.98	3.7	4.1	28	21
#5	0.80	0.98	0.86	1.01	2.9	2.8	34	29
#6	0.81	0.88	0.70	0.69	3.0	2.7	42	64
Mean	0.77	1.02	0.84	1.00	3.4	3.5	33.7	38.7
SD	0.12	0.24	0.19	0.25	0.4	0.6	5.2	15.9
P value[d]		*0.035*[e]		0.094		0.671		0.361

Patient	CDDP dose (mg)		C_{2d}/dose[b] (ng mL^{-1} mg $CDDP^{-1}$)		K_{el} (h^{-1})		$t_{1/2}$ (h)	
	1st cycle	2nd cycle	1st cycle	2nd cycle	1st cycle	2nd cycle	1st cycle	2nd cycle
#1	116	100[c]	7.3	9.4	0.0475	0.0475	350.6	350.5
#2	138	136	7.7	9.9	0.0489	0.0519	340.0	320.8
#3	161	160	5.6	9.4	0.0470	0.0444	353.6	374.5
#4	140	137	7.1	4.9	0.0530	0.0259	313.7	643.2
#5	114	90[c]	8.6	8.9	0.0777	0.0663	214.0	250.8
#6	114	112	8.9	13.6	0.0464	0.0376	358.2	442.4
Mean	130.5	122.5	7.5	9.4	0.0534	0.0456	321.7	397.0
SD	19.1	26.3	1.2	2.8	0.0121	0.0136	55.1	136.1
P value[d]		0.098		0.134		0.139		0.213

[a] The baseline data were obtained on the first day of CDDP administration for each cycle

[b] The value was obtained by subtracting the baseline level from C_{2d} adjusted by CDDP dose

[c] Dose reductions in the second cycle were made in 2 patients (patients #1 and #5)

[d] The paired *t* test was used to compare mean values in the first and second cycles

[e] $P < 0.05$ compared with the value in the first cycle

levels could be a more sensitive marker for moderate renal dysfunction than serum Cr levels. We also consider serum Cys C to be superior to serum Cr, as its levels are less dependent on age, sex, race, and muscle mass [3–5]. In the present study, a transient elevation in serum Cys C concentration was observed in all 6 patients during both the first and second cycles of CDDP-based chemotherapy (Fig. 2). Since CDDP can induce nephrotoxicity, which is usually the dose-limiting toxicity, acute renal injury after completion of CDDP treatment may contribute to the transient elevation of serum Cys C concentration. In contrast, serum Cr concentrations did not to change in a similar way (Fig. 2). Keevil et al. [17] conducted a variability analysis of serum Cys C and Cr levels in healthy subjects, reporting an intra-individual variation of 13.3 and 4.9 %, respectively. However, their results do not explain the transient change of serum Cys C concentrations observed in our present study. Our study indicates that using serum Cys C concentration as a marker to estimate GFR would result in an underestimation of normal renal function by 19.1 % or more.

CDDP is mainly eliminated via the kidneys and acute renal injury induced by CDDP treatment could result in delayed elimination from the body. The half-life of plasma Pt in patient #4 was twofold longer in the second cycle compared to the first, without significant changes in the serum concentrations of Cys C and Cr. In contrast, the serum concentrations of Cys C and Cr reached 250 % or more of baseline for patient #1, although the Pt half-lives in plasma in the first and second cycles were comparable. The findings are intriguing, although there are some limitations. The concentration measurement of Pt not CDDP did not allow us to evaluate individual pharmacokinetics of CDDP and its metabolites. Since the blood sampling schedule after the first week of the chemotherapy was different among patients, it is unclear whether the transient serum Cys C elevation influenced the pharmacokinetics of CDDP

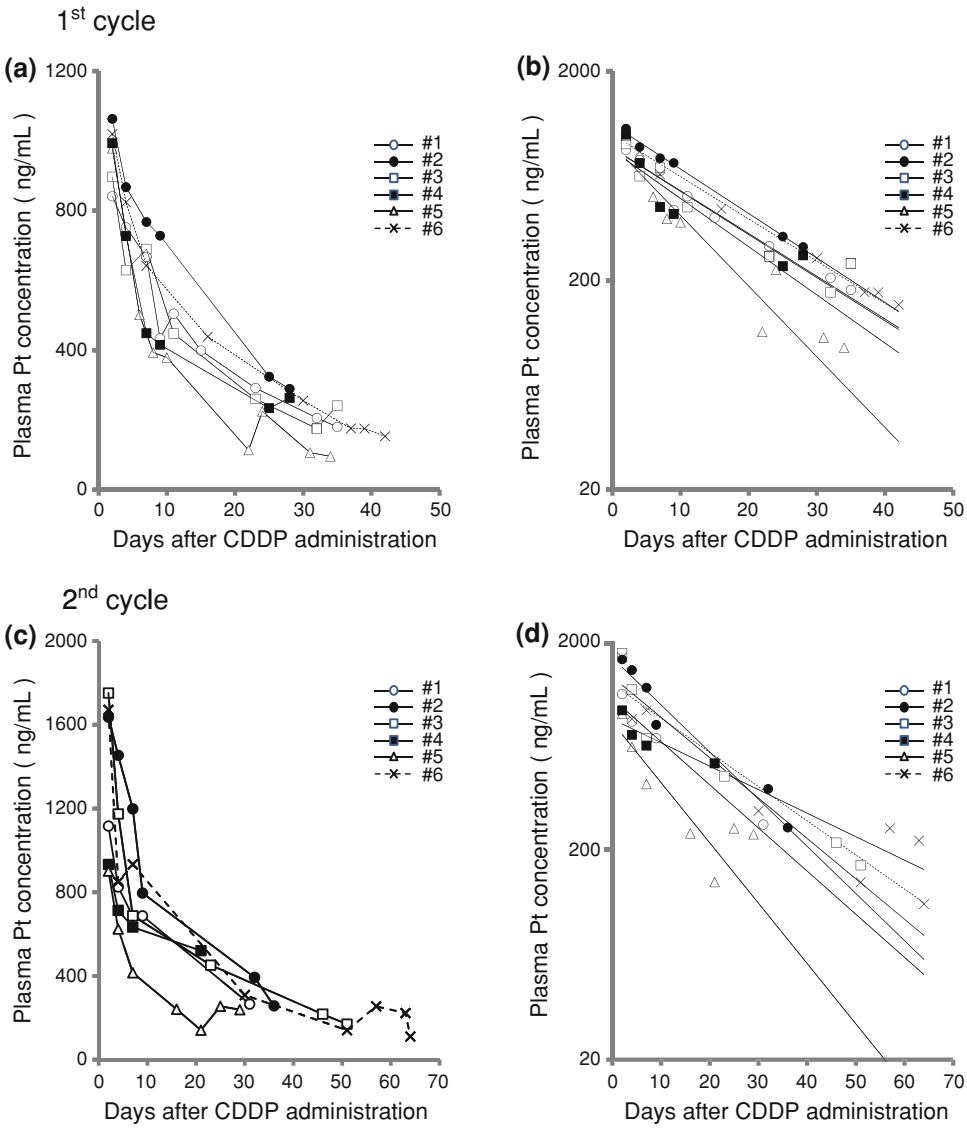

Fig. 3 Time–plasma Pt concentration profiles during the first (**a**, **b**) and second (**c**, **d**) cycles of CDDP-based chemotherapy in 6 patients with esophageal cancer. The patients received neoadjuvant (*solid line*) or adjuvant (*dotted line*) chemotherapy. *Left* (**a**, **c**) and *right* (**b**, **d**) panels indicate the observed and simulated pharmacokinetic profiles, respectively (see text for more details)

between the early and terminal treatment periods. As renal tubular secretion is involved in the renal excretion of Pt, the extent to which renal tubular function contributes to renal excretion of Pt remains obscure. Therefore, more studies are required to appropriately address these issues.

Interestingly, when CDDP-based chemotherapy is carried out, antiemetic drugs, such as a 5-HT_3 serotonin receptor antagonist, dexamethasone or aprepitant, are administered to prevent treatment-associated nausea and vomiting [18]. It was reported that Cys C expression and secretion from HeLa cells into tissue culture medium increased 3 days after treatment with dexamethasone (>10^{-7} mol/L) [19]. Based on the results of the previous clinical studies, dexamethasone could reach more than 10^{-7} mol/L on day 1 in the high dose (125/80 mg) aprepitant therapy group [20, 21]. Although the dexamethasone dosages required to maintain this concentration remain unclear, the results of these studies seem to parallel the transient elevation of serum Cys C concentration that we observed in our clinical study. Meanwhile, there is little information about the effect of other antiemetic and anticancer drugs on the concentration fluctuation of serum Cys C. Fehrenbacher and co-investigators reported that cytosolic cysteine cathepsin activity increased in NIH3T3-derived cells treated with 50 μmol L^{-1} CDDP [22], whereas treatment with cisplatin (100 μmol L^{-1}) did not induce cathepsin S mRNA expression in MCF7 cells [23]. Exposure of 5-FU (10 μmol L^{-1}) resulted in cleavage of cathepsin B within 72 h in human colon carcinoma cell lines [24], although our previous study showed that the plasma concentration of 5-FU was maintained at 0.5–1.5 μmol L^{-1} in esophageal cancer patients receiving CDDP/5-FU-based chemoradiotherapy [25]. Since Cys C targets cathepsins, the lysosomal leakage of cathepsins triggered by CDDP and/or 5-FU under certain conditions may be accompanied by an increase in the intracellular Cys C level and its subsequent extracellular secretion [26, 27]. We consider that synergistic effects of dexamethasone

and CDDP/5-FU might enhance changes in the serum Cys C concentration in the present study, although further analyses are required to clarify the mechanism underlying the regulation of Cys C expression and aid the interpretation of serum Cys C levels in clinical assays.

In summary, we observed a transient elevation in serum Cys C concentration during approximately 10 days after the start of CDDP-based chemotherapy in esophageal cancer patients, which was not accompanied by changes in either serum Cr concentration. These findings suggested that renal function estimates based on serum Cys C levels might be underestimated during this early treatment period.

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

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