Regular Article

Risk Factors Associated with Cisplatin-Induced Nephrotoxicity in Patients with Advanced Lung Cancer

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Received June 13, 2016; accepted September 27, 2016

Cisplatin (CDDP) combination chemotherapy is widely administered to patients with advanced lung cancer. The dose depends on multiple factors, including whether the tumor is non-small-cell lung cancer (NSCLC) or small-cell lung cancer (SCLC). Although efficacy is limited by cisplatin-induced nephrotoxicity (CIN), little is known about the risk factors for this complication. The aim of this study was to identify the risk factors for CIN in patients with advanced lung cancer, both NSCLC and SCLC. We retrospectively reviewed clinical data for 148 patients who underwent initial chemotherapy including CDDP ≥ 50 mg/m² per patient per day for the first course at Kyushu Medical Center between October 2010 and September 2013. All data were collected from the electronic medical record system. Nephrotoxicity was defined as an increase in serum creatinine concentration of at least grade 2 during the first course of CDDP chemotherapy, as described by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. CIN was observed in nine patients. Univariate analysis revealed that cardiac disease and lower baseline serum albumin (Alb) values conferred a higher risk of nephrotoxicity ($p < 0.05$). The cut-off value of Alb was 3.8 g/dL, calculated by receiver operating characteristics (ROC) curves. Multivariable logistic regression analysis revealed that cardiac disease (odds ratio=11.7; $p=0.002$) and hypoalbuminemia (odds ratio=6.99 $p=0.025$) significantly correlated with nephrotoxicity. In conclusion, cardiac disease and low baseline Alb values are possible risk factors for CIN.

Key words lung cancer; serum albumin; cardiac disease; cisplatin; risk factor; nephrotoxicity

Lung cancer is a leading cause of cancer death in Japan and other developed countries.¹⁾ Platinum-based cytotoxic doublet chemotherapy is the main treatment for advanced lung cancer. Cisplatin (CDDP), an inorganic platinum chemotherapeutic drug, is widely administered either alone or in combination with other agents for the clinical treatment of various solid tumors, including lung, gastric, esophageal, bladder, and head and neck cancers.²⁾ CDDP-based combination chemotherapy regimens have been used for first-line treatment of advanced lung cancer.³⁾ However, CDDP chemotherapy is often limited by its cumulative nephrotoxicity,^{4,5)} which is dose-dependent.^{6,7)} Standard procedures to reduce this risk include aggressive hydration with saline and simultaneous administration of diuretics such as furosemide and mannitol.⁸⁾ Despite these approaches, cisplatin-induced nephrotoxicity (CIN) still occurs.^{9–11)} The ability to identify patients at risk for nephrotoxicity would improve the efficacy and safety of CDDP. Although the risk factors for CIN have been extensively investigated and many factors have been reported,^{12–15)} CIN prevention methods are not 100% successful. Therefore, assessment of renal function in patients treated with CDDP in the early course of treatment is necessary to prevent permanent damage to the kidneys.

The aims of this study were to investigate risk factors in patients undergoing early cycles of chemotherapy for ad-

vanced lung cancer and to prevent permanent and continuous damage to the kidneys.

PATIENTS AND METHODS

Patients and Study Setting Patients were eligible for the study if they were diagnosed with advanced or recurrent lung cancer (non-small cell or small-cell) and scheduled to receive CDDP at a dose of ≥ 50 mg/m² per patient per day at Kyushu Medical Center between October 2010 and September 2013. Patients who had a history of prior treatment with CDDP or whose renal function could not be evaluated, such as those with multiple organ failure, were excluded because of their unstable clinical status.

Data Collection and Assessment All data were collected from the hospital electronic medical record system (EGMAIN-GX version 5[®], Fujitsu, Tokyo, Japan). We collected information regarding patient gender, age, body mass index (BMI), histology, prior chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status (PS), clinical stage, complications, antineoplastic agents received, concurrent radiation, single dose per body-surface area of CDDP, hydration volume, use of analgesics, history of contrast studies, and baseline laboratory data. Patients with a history of angina, myocardial infarction, atrial fibrillation, arrhythm-

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mia, or valvular disease were defined as patients with cardiac disease in this study.

The laboratory data were from samples drawn on the day before chemotherapy. For evaluation of nephrotoxicity, the increase in serum creatinine (SCr) concentration was calculated as the maximum value within two weeks after CDDP administration minus the baseline value. For most patients, SCr was measured at least once every two weeks. The laboratory data included the levels of serum albumin (Alb), aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase, sodium, potassium, as well as SCr, creatinine clearance (CCr), hemoglobin, platelet count, and white blood cell count with differential. SCr was determined by an enzymatic method. CCr for males was calculated using the Cockcroft–Gault (CG) equation¹⁶⁾:

$$\text{CCr (mL/min)}^{\text{male}} = \frac{([140 - \text{age}] \times \text{body weight [kg]} / 72) \times \text{SCr (mg/dL)}}{1}$$

CCr for women was then calculated using the following equation:

$$\text{CCr (mL/min)}^{\text{female}} = \text{CCr (mL/min)}^{\text{male}} \times 0.85$$

Definition of Nephrotoxicity In accordance with a previous study,¹⁷⁾ we adopted an increase in SCr as a measure of nephrotoxicity. The rationale for considering screening for early-stage nephrotoxicity includes detection of mild renal dysfunction due to aging. We excluded patients with renal dysfunction $\geq$ grade 1 before the first cycle of chemotherapy. Nephrotoxicity was defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0), after one chemotherapy cycle.¹⁸⁾ Because grade 1 nephrotoxicity is mild and often temporary, and chemotherapy is discontinued with grade 2 or higher nephrotoxicity in most cases, identification of risk factors for $\geq$ grade 2 is clinically important. Therefore, when the post-CDDP level of SCr was ≥ 2 grades higher than that before CDDP administration, the patient was placed in the nephrotoxicity group. The remaining patients were assigned to the non-nephrotoxicity group.

Statistical Analysis Differences in continuous data were compared using the Mann–Whitney *U*-test and differences in categorical data were compared using Fisher's exact test. Multiple logistic regression analysis of data from hematology and biochemical evaluations was used to analyze factors associated with nephrotoxicity. To identify factors associated with CIN, univariate analysis was performed using age, BMI, ECOG PS, clinical stage, hypertension, diabetes, cardiac disease (defined as the presence of angina, myocardial infarction, atrial fibrillation, arrhythmia, or valvular disease), concurrent radiation, CDDP dose, hydration volume (total amount of solution administered to prevent CIN), Alb (normal range in our hospital is 3.8–5.3 g/dL), sodium, potassium (3.5–4.8 mEq/L), and CCr (male: 90–120 mL/min, female: 80–110 mL/min) as independent variables. Differences between each factor were tested for statistical significance ($p < 0.15$) using Fisher's exact test. Variables with a $p < 0.15$ in the initial analysis were included, and only those variables with a $p < 0.05$ remained in the final model in the multivariate logistic regression analysis. The magnitude of the association was expressed as an odds ratio (OR) and 95% confidence interval (95% CI). The sensitivity, specificity, and cut-off values for factors obtained

by univariate analysis were estimated by calculating the area under the receiver-operator characteristics (ROC) curve. The area under the curve (*AUC*) was calculated to determine the inherent ability of the test to discriminate between nephrotoxicity and non-nephrotoxicity. All statistical analyses were performed with commercial software (EZR[®], Saitama Medical Center, Jichi Medical University, <http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html>), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R commander (version 1.8–4)¹⁹⁾ designed to add statistical functions frequently used in biostatistics. A $p < 0.05$ was considered statistically significant.

Ethics This study was approved by the ethics committee of the National Hospital Organization Kyushu Medical Center. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the guidelines of the International Conference on Harmonization Good Clinical Practice.^{20,21)}

RESULTS

Patient Characteristics A total of 148 patients who had undergone therapy with CDDP were included in the study. Baseline characteristics and biochemical parameters of these 148 patients are summarized in Tables 1 and 2. CIN was observed in nine (6.1%) patients, with six (4.1%) and three (2.0%) cases of grade 2 and 3, respectively. All patients who developed CIN were male. The median (IQR: interquartile range) of CDDP dosage and CCr was 74.5 mg/m² (68.2–75.0 mg/m²) and 86.8 mL/min (75.1–102.6 mL/min), respectively. Compared with patients without CIN, the proportion of patients who had cardiac disease was significantly higher in patients with CIN (44.4% vs. 7.2%, $p = 0.005$). In addition, median baseline Alb values were significantly different between the nephrotoxicity and non-nephrotoxicity groups (3.4 g/dL vs. 3.9 g/dL, respectively, $p = 0.007$).

CCr before and after Administration of CDDP Table 3 shows CCr before and after administration of CDDP. The mean CCr of the non-nephrotoxic group of patients was 86.9 mL/min before administration and 73.4 mL/min after administration ($p = 0.446$). Values in the nephrotoxic group of patients were 84.3 and 22.8 mL/min, respectively ($p < 0.001$).

Univariate Analysis Univariate analysis revealed that cardiac disease (OR: 10.3, 95% CI: 2.39–44.6, $p = 0.005$), baseline Alb values (OR: 6.2, 95% CI: 1.25–31.1; $p = 0.03$) and K value (OR: 4.85, 95% CI: 1.08–21.7, $p = 0.06$) were significantly associated with CIN (Table 4).

Multivariate Analysis We carried out a multivariate logistic regression analysis using the factors of cardiac disease and Alb values which remained by univariate analysis. The results of the multivariate logistic regression analysis are shown in Table 5. Multivariate logistic regression analysis suggested that patients who had cardiac disease (OR: 11.70, 95% CI: 2.14–57.2, $p = 0.002$) and Alb values (OR: 6.99, 95% CI: 1.28–38.2, $p = 0.025$) had a higher risk of CIN.

ROC Analysis To estimate the predictive value of Alb level for CIN, the ROC curve and *AUC* obtained by univariate analysis of Alb was calculated. The cut-off value of Alb calculated by the ROC curve was 3.8 g/dL (Fig. 1). The *AUC* was 0.77, which was evaluated as having moderate accuracy for

Table 1. Patient Characteristics

Parameter		Nephrotoxicity		<i>p</i> Value
		– <i>n</i> =139	+ <i>n</i> =9	
Gender	Male/Female	94/45	9/0	0.058 ^{a)}
Age (years)	Median (IQR)	64 (59.5–69)	61 (60–71)	0.751 ^{b)}
BMI (kg/m ²)	Median (IQR)	22.2 (20.2–24.2)	20.6 (18.0–25.1)	0.591 ^{b)}
Histology	Small cell	33 (23.7%)	2 (22.2%)	1.000 ^{a)}
	Non-small cell	96 (69.1%)	5 (55.6%)	0.466 ^{a)}
	Others	10 (7.2%)	2 (22.2%)	0.158 ^{a)}
ECOG PS	0	93 (66.9%)	5 (55.6%)	0.487 ^{a)}
	1, 2	46 (33.1%)	4 (44.4%)	
Clinical stage	III	42 (30.2%)	3 (33.3%)	1.000 ^{a)}
	IV, Recurrence	97 (69.8%)	6 (66.7%)	
Prior chemotherapy	0	121 (87.1%)	9 (100%)	0.601 ^{a)}
	≥1	18 (12.9%)	0 (0%)	
Comorbidities	Hypertension	50 (36.0%)	5 (55.6%)	0.293 ^{a)}
	Diabetes	16 (11.5%)	2 (22.2%)	0.300 ^{a)}
	Hyperlipidemia	27 (19.4%)	0 (0%)	0.366 ^{a)}
	Cardiac disease	10 (7.2%)	4 (44.4%)	0.005 ^{a)}
Co-administered drugs	Pemetexed±Bevacizumab	78 (56.1%)	4 (44.4%)	0.513 ^{a)}
	Docetaxel	11 (7.9%)	1 (11.1%)	0.543 ^{a)}
	Vinorelbine	13 (9.4%)	1 (11.1%)	1.000 ^{a)}
	Irinotecan	20 (14.4%)	1 (11.1%)	1.000 ^{a)}
	Etoposide	14 (10.0%)	1 (11.1%)	1.000 ^{a)}
	Gemcitabine	2 (1.4%)	1 (11.1%)	0.173 ^{a)}
	Tegafur·gimstatat·otastat	1 (0.7%)	0 (0%)	1.000 ^{a)}
Concurrent radiation	+	26 (18.7%)	2 (22.2%)	0.679 ^{a)}
	–	113 (81.3%)	7 (77.8%)	
Cisplatin dose (mg/m ²)	Median (IQR)	74.5 (68.2–75.0)	75 (73.2–79.1)	0.290 ^{b)}
Hydration volume (mL)	Median (IQR)	5000 (5000–6000)	5000 (5000–5000)	0.273 ^{b)}
Use of analgesics (including NSAIDs)		40 (28.8%)	3 (33.3%)	0.720 ^{a)}
History of contrast studies		139 (100%)	9 (100%)	—

a) Fisher's exact test. b) Mann–Whitney *U*-test. IQR; interquartile range, BMI; body mass index, ECOG; Eastern Cooperative Oncology Group, PS; performance status; Hydration volume; total amount of solution administered during cisplatin infusion, NSAIDs; Non-steroidal anti-inflammatory drugs. *Significance level was set at *p*<0.05.

Table 2. Patient Baseline Biochemical Parameters

Parameter	Nephrotoxicity		<i>p</i> Value
	–	+	
Alb (g/dL)	3.9 (3.5–4.2)	3.4 (3.2–3.7)	0.007*
AST (IU/L)	22 (18–28)	22 (22–32)	0.193
ALT (IU/L)	21 (15–28)	25 (13–32)	0.773
γ-GTP (IU/L)	33 (20–53)	29 (21–75)	0.610
Na (mEq/L)	139 (138–140)	138 (137–141)	0.737
K (mEq/L)	4.2 (4.0–4.5)	4.2 (4.1–4.3)	0.667
CCr (mL/min)*	86.9 (75.5–102.7)	84.3 (73.1–92.4)	0.446
WBC (×10 ³ /μL)	6.9 (5.7–8.1)	8.1 (5.1–9.8)	0.697
Hb (g/dL)	12.9 (12.1–13.9)	12.7 (12.4–13.0)	0.340
PLT (×10 ³ /μL)	280 (232–345)	300 (240–465)	0.537
Neut (×10 ³ /μL)	4.27 (3.58–5.58)	5.56 (2.71–6.90)	0.785
Ly (×10 ² /μL)	1.45 (1.12–1.92)	1.58 (0.73–1.63)	0.404
Mono (×10 ² /μL)	4.40 (3.52–5.38)	4.65 (3.52–6.67)	0.739

All quantities are expressed as median (IQR). *Calculated by the Cockcroft–Gault equation, Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; CCr, creatinine clearance rat. *Significance level was set at *p*<0.05.

detecting some events. Using this cut-off value, the sensitivity and specificity of Alb level to detect the risk for CIN were 56.8 and 88.9%, respectively.

Table 3. Creatinine Clearance (CCr) before and after Administration of CDDP

Parameter	Before administration	After administration	<i>p</i> Value
	Median (IQR)	Median (IQR)	
Non nephrotoxicity patients	86.9 (75.5–102.8)	73.4 (60.2–86.0)	0.446
Nephrotoxicity patients	84.3 (73.9–92.4)	22.8 (14.1–32.9)	0.001*

All quantities are expressed as median (IQR), CCr for males was calculated using the Cockcroft–Gault equation.¹⁴⁾ Differences in continuous data were compared using the Mann–Whitney *U*-test. *Significance level was set at *p*<0.05.

DISCUSSION

Although CDDP dosing regimens for individual patients have been established using recommended parameters²²⁾ such as dose per body surface area and the results of hematologic and biochemical examinations,²³⁾ the main factors linked to renal failure in lung cancer patients treated with CDDP remain unclear. The main risk factors for CIN such as older age, female gender, smoking, hypoalbuminemia, diabetes mellitus, and cardiovascular disease have been extensively studied.^{10,17,24)} However, these risk factors are not considered when making clinical decisions about treatment continua-

Table 4. Univariate Analysis for Cisplatin-Induced Nephrotoxicity

Factors	Odds ratio	95% CI	p Value
Age (years)	0.43	0.10–1.77	0.430
BMI (kg/m ²)	1.23	0.32–4.78	1.000
ECOG PS, ≥ 1	1.62	0.41–0.31	0.488
Clinical stage, III	0.87	0.21–3.63	0.870
Hypertension	2.23	0.57–8.67	0.293
Diabetes	2.20	0.42–11.50	0.300
Cardiac disease	10.32	2.39–44.61	0.005*
Concurrent radiation	1.24	0.24–6.33	0.679
Cisplatin dose (mg/m ²)	1.92	0.46–7.97	0.497
Hydration volume (mL)	0.30	0.03–2.87	0.318
Alb (g/dL)	6.23	1.25–31.14	0.028*
Na (mEq/L)	1.54	0.37–6.51	0.691
K (mEq/L)	4.85	1.08–21.70	0.059*
CCr (mL/min)	1.43	0.34–5.96	0.737

CI, confidence interval; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; Alb, albumin; CCr, creatinine clearance rate; Hydration volume, total amount of solution administered during cisplatin infusion
*Significantly different, $p < 0.05$. p -values were calculated from the Fisher's exact test for categorical.

Table 5. Multivariate Analysis for CDDP Nephrotoxicity

Factor	Odds ratio	95% CI	p Value
Alb	6.99	1.28–38.2	0.025*
Cardiac disease	11.70	2.14–57.2	0.002*

95% CI, 95% confidence interval; Alb, albumin. *Significance level was set at $p < 0.05$.

tion, because they are non-numerical objective phenomena and cannot be used for treatment planning. Only conventional criteria such as body surface area (BSA) or CCr level are used for administration plans.²⁵⁾ In this study, heart disorders and hypoalbuminemia were risk factors for CIN, similar to recent findings.²⁴⁾ Thus we clarified the threshold of the Alb value quantitatively. Multivariate logistic regression analysis suggested that cardiac disease and baseline Alb were significant risk factors. In this study, we suggested that low Alb value is a risk factor of renal dysfunction, and several previous reports support these results.^{12,26)} Although sensitivity was definitely not high (56.8%) when using Alb values, a high Alb value is less likely to be a risk of renal dysfunction. Thus, close monitoring of changes in Alb value during CDDP treatment may prevent the development of CIN in these patients.

CIN remains a clinical problem in 28–42% of patients.²⁷⁾ Most cases are transient and reversible, but irreversible CIN sometimes occurs and can limit treatment. Generally, in patients with cardiac disease, a reduction in renal perfusion caused by decreased cardiac output may affect the clearance of drugs eliminated by renal clearance, such as CDDP, ABK (arbakacin) and TEIC (teicoplanin). Ishida *et al.*²⁸⁾ reported that the clearance of ABK, an antibiotic that is eliminated by renal clearance, was significantly decreased in patients with cardiac disease compared with those without cardiac disease. Renal excretion of TEIC and vancomycin is also decreased in patients with heart disorders.^{29,30)} Thus, decreased renal perfusion associated with cardiac disease may influence the clearance of CDDP. A decrease in renal blood flow due to heart disorders reduces renal clearance, inducing renal dysfunction. Although the patients with cardiac disease developed renal

Fig. 1. Receiver Operating Characteristic (ROC) Analysis

The sensitivity, specificity, and cut-off values using ROC curves between Alb level (independent variable, x) and the probability of renal failure development (dependent variable, y).

dysfunction (Table 1, $p = 0.005$), baseline CCr did not differ between patients with and without cardiac disease (Table 2, $p = 0.446$). In this study, the number of patients with cardiac disease was extremely small. Most of the subjects were elderly, with the reduction in muscle mass that accompanies aging, and 25 patients had BMI ≤ 18.5 . The muscle mass greatly affects serum creatinine, resulting in glomerular filtration rate (GFR) being overestimated, because the CCr level calculated by the CG equation depends on SCr. Therefore, we think that mild renal insufficiency in patients with low muscle mass might be missed, because GFR is overestimated, CIN is considered to primarily affect the proximal tubule cells.³¹⁾ On this basis, prevention is based on the use of hydration combined with diuretics to reduce CDDP contact time with the proximal tubule. Mathe *et al.*³²⁾ also reported that CIN was aggravated by comorbidity with cardiac disease in lung cancer patients.

The second independent risk factor we identified for CIN was low baseline Alb values. CIN is considered to be caused by lower levels of plasma proteins binding CDDP. One study reported that approximately 98% of CDDP immediately binds to plasma proteins, mainly Alb,³³⁾ while various other studies demonstrated that CIN is related to the peak plasma CDDP concentration and/or the area under the plasma CDDP concentration-time curve of unbound CDDP.^{34–36)} These findings suggest that nephrotoxicity may result from decreased protein binding due to low serum Alb.

In patients with renal dysfunction, the pharmacokinetics of CDDP vary with the degree of renal dysfunction. Adjustment of CDDP dose is made according to CCr level.²⁷⁾ We hypothesize that decreased binding of CDDP in the presence of low Alb values can lead to renal dysfunction, particularly in patients with compromised renal perfusion due to cardiac dysfunction. By analyzing the association between Alb level (independent variable, x) and the probability of renal failure

development (dependent variable, y) using ROC curves, we determined that the cut-off value for the development of renal dysfunction was an Alb value of 3.8 g/dL. As seven of the nine patients with CIN had Alb values <3.8 g/dL, our preliminary results suggest that a lower baseline Alb value is a risk factor for CIN.

Previous studies have reported^{12,26)} on the relationship of CIN and Alb value. It has been suggested^{12,37)} that hypoalbuminemia reduces platinum excretion due to its effect on peritubular oncotic pressure and on the half-life of the CDDP, because the protein binding rate of the CDDP decreases and free CDDP increases, resulting in greater exposure to free CDDP. Furthermore, Mizuno *et al.* reported³⁶⁾ that lower blood pressure was significantly correlated with hypoalbuminemia, and reported hypoalbuminemia and hypotension as nephropathic risk factors. These reports support our finding that a decrease in blood pressure according to abnormalities of cardiac output and ejection fraction, and an increase in free CDDP with hypoalbuminemia are risk factors for nephrotoxicity in CDDP treatment. Especially regarding free CDDP concentration, in order to attain more effective CDDP chemotherapy with minimum nephrotoxicity, the present pharmacokinetic and pharmacodynamic studies suggest that the $C_{\max}$ or steady-state plasma level of unchanged free CDDP should be maintained between 1.5 and 2 $\mu\text{g/mL}$.³⁵⁾ Although our findings are preliminary, our ROC analysis suggests that an Alb level <3.8 g/dL may lead to the development of nephrotoxicity. The findings in this study are similar to those of previous studies,^{12–15)} therefore confirming that decreased renal perfusion and hypoalbuminemia are nephropathic risk factors associated with CDDP in lung cancer chemotherapy. However, our study was unable to elucidate criteria for dose adjustment according to cardiac disease and Alb values. Further investigation of this is necessary, as is the establishment of more effective strategies to prevent CIN for patients with these risk factors.

Several limitations of the study warrant mention. First, only a small number of patients with lung cancer with chemotherapy using CDDP were enrolled into this study. Although the small study size dictates that our results should be considered preliminary, the trends identified here support the need for a larger study. Second, several previous studies reported that intravenous supplementation with Mg (magnesium) can prevent CIN.^{26,38,39)} Because our treatment protocol did not include Mg administration, we cannot state its efficacy in patients with these risk factors. Third, we defined the patients with a history of the cardiac disease such as angina and myocardial infarction as patients with cardiac disease in this study. However, quantifiable data (*e.g.*, cardiac output and an ejection fraction) were not available. Therefore we defined heart disorders by medical history. Fourth, because our study was conducted under a retrospective design, we were unable to fully evaluate the incidence and intensity of nonhematologic toxicities. Nonhematologic toxicities, such as nausea, vomiting, and diarrhea might be correlated with an increased risk for CIN. Finally, although the use of a drug which induces renal failure may be limited by the discretion of the physician, most patients with lung cancer routinely take non-steroidal anti-inflammatory drugs (NSAIDs) and narcotic analgesics for control of pain, and may undergo CT scans using contrast media to evaluate the efficacy of the chemotherapy. Although NSAIDs pose little threat of renal insult in normal, healthy

persons at therapeutic dosages, NSAIDs administration to susceptible persons may cause decrements in renal plasma flow and glomerular filtration rate within hours.⁴⁰⁾ Sendur *et al.* suggested that radiographic procedures with intravenous contrast material should be delayed for at least 1 week in patients receiving chemotherapy with CDDP to prevent nephrotoxicity.⁴¹⁾ In the current study, all patients underwent CT scans using contrast media at an interval of about 2 weeks to 1 month after chemotherapy, which was thought to be a sufficient period to eliminate effects of the contrast media. The rates of use of analgesics were 28.8 and 33.3% in the non-nephrotoxicity and nephrotoxicity groups, respectively (Table 1). These agents were long-term analgesics taken from before chemotherapy initiation, and the dose was not changed during treatment. Therefore, comorbidities relevant to nephrotoxicity due to NSAIDs and contrast agents were not assessed in the study. Such drug-induced nephrotoxicity, including acute tubular necrosis, inflammation, and altered hemodynamics such as reduction of renal blood flow by the inhibition of prostaglandin, might be associated with an increased risk for CIN.⁴²⁾ In conclusion, our findings suggest that cardiac disease and baseline Alb values <3.8 g/dL are important risk factors for CIN in patients with advanced lung cancer. Thus, close monitoring of SCr values during CDDP treatment is recommended for patients with these risk factors.

Conflict of Interest The authors declare no conflict of interest.

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