Evaluation of the Observed Cisplatin Nephrotoxicity in Adult Cancer Inpatients: A Historical Cohort Study by Using Clinical Data Warehouse

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Objectives: To evaluate the observed cisplatin (CDDP) nephrotoxicity in adult cancer inpatients by using Clinical Data Warehouse (CDW). Methods: A historical cohort study was conducted in Osaka University Hospital. Adult cancer inpatients (2000/1/1–2004/12/31) whose sCr level on admission < 1.2 mg/dl were divided into three groups based on the exposure of CDDP, non-exposure of CDDP but with (Non-CDDP group) or without (Control group) other anticancer agents. Patients whose sCr ≥ 1.2 mg/dl at least once during hospitalization were considered as those having the occurrence of the nephrotoxicity and their sCr < 1.2 mg/dl on discharge as having recovered from the nephrotoxicity. After matching patients' characteristics through stratification and randomization, the rates of nephrotoxicity and the rates of recovery among the three groups were compared. Logistic regression was performed to investigate the CDDP doses — nephrotoxicity associations. Results: The rate of observed nephrotoxicity was 28.0% (127/454) in the CDDP group, 19.6% (89/454) in the Non-CDDP group and 19.4% (88/454) in the Control group, respectively (p = 0.002). The risk ratio (RR) was 1.43 (95%CI: 1.13–1.81), 1.44 (95%CI: 1.14–1.83) and 1.01 (95%CI: 0.78–1.41) between CDDP *vs*. Non-CDDP, CDDP *vs*. the control and Non-CDDP *vs*. the Control group. The recovery rate was 69.3% (88/127), 61.8% (55/89) and 69.3% (61/88) in the three groups, respectively (p = 0.903). The observed CDDP nephrotoxicity was dose associated (p = 0.037) but not total accumulated doses associated (p = 0.144). Conclusions: CDDP is a risk factor to the observed nephrotoxicity in our adult cancer inpatients. The observed nephrotoxicity was CDDP dose related and is considered to be reversible.

Key words —— cisplatin, nephrotoxicity, historical cohort study, Clinical Data Warehouse

INTRODUCTION

Cisplatin (CDDP) is an effective anticancer agent for the treatment of solid tumors. However, nephrotoxic side effects including acute and chronic renal insufficiency are major concerns by clinicians in their routine practices. Early reports indicated that nephrotoxicity might occur in as many as 50 to 75% of patients receiving this drug, and is dose-limiting.[1)] The mechanisms, modifying factors, and management issues of cisplatin nephrotoxicity have been well investigated in animal data.[2)] Studies in humans suggested that routine fluid infusion therapy had markedly reduced the incidence of acute renal failure.[3)] The addition of mannitol plus hydration[4)] and various agents such as magnesium[5)] and prochlorperazine[6)] have also been reported to reduce nephrotoxicity. Several factors may be playing a role in the development of cisplatin nephrotoxicity. Stewart D. J., *et al*. reported that nephrotoxicity in patients treated with cisplatin may be correlated with autopsy kidney platinum concentrations,[7)] while Skinner R., *et al*. demonstrated that cisplatin dose rate is a risk factor for nephrotoxicity in children.[8)] No clinical research has yet been reported on the estimation of the frequency of cisplatin nephrotoxicity in hospitalized adult cancer patients.

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Table 1. Patient Characteristics

	CDDP (n = 521)	Non-CDDP (n = 1993)	Control (n = 6157)	$p^{a)}$
Gender				< 0.0001
Male	389	666	3653	
Famale	132	1327	2504	
Age (years)	59.58 ± 12.27 (58.52–60.63)	55.71 ± 13.16 (55.13–56.29)	60.69 ± 13.25 (60.41–60.97)	< 0.0001
sCr (mg/dl) on admission	0.74 ± 0.17 (0.73–0.75)	0.67 ± 0.18 (0.66–0.68)	0.73 ± 0.18 (0.73–0.74)	< 0.0001
LOS (days)	88.54 ± 58.72 (83.48–93.59)	68.90 ± 65.10 (66.04–71.76)	29.96 ± 27.23 (29.27–30.64)	< 0.0001

Numbers in parentheses stand for 95% CI. *a*) One-way ANOVA test.

In the present report, we have conducted a historical cohort study to evaluate the observed cisplatin nephrotoxicity in adult cancer inpatients treated at a national university hospital in Japan.

MATERIALS AND METHODS

Materials —— All of the data were obtained from Clinical Data Warehouse (CDW) in Osaka University Hospital and processed *via* Microsoft Access 2003.

Patient Population —— Osaka University Hospital is a 1024-bed tertiary national university hospital in Japan. An average of 3000 adult cancer patients are admitted annually. For this analysis, we investigated the 9724 adult cancer inpatients (age > 18 years old) admitted for at least 3 consecutive days and with length of stay (LOS) less than 365 days between 2000 and 2004.

Eligibility and Study Design —— Of the 9724 patients, 1053 were excluded since their sCr concentrations were ≥ 1.2 mg/dl, which was considered as the preexisting renal dysfunction presented. The remaining 8671 patients whose sCr were < 1.2 mg/dl were divided into three groups based on the exposure of CDDP, non-exposure of CDDP but with (Non-CDDP group) or without (Control group) other anticancer agents.

Nephrotoxicity Evaluation —— Patients whose sCr ≥ 1.2 mg/dl at least once during hospitalization were defined as having the occurrence of the nephrotoxicity and their sCr < 1.2 mg/dl on discharge as having the recovery from the nephrotoxicity.

Adjusted and Matched Study Subjects Through Stratification and Randomization —— In order to form the relatively similar three groups, we categorized the patients based on gender, age, sCr levels on admission and LOS. Then we compared the number of patients in each category among the three groups, and randomly selected patients from groups with a larger number to equalize the number of patients among them.

Statistical Analyses —— All statistical analyses were performed using StatView 1998 Japanese Version for Windows. One-way analysis of variance (ANOVA), Chi-squared test along with risk ratio were applied where appropriate. Logistic regression was performed to evaluate associations between the dichotomized outcomes (*e.g.*, observed nephrotoxicity) and the CDDP doses. *p*-Values were considered as 2-tailed.

RESULTS AND DISCUSSION

Patient Population before and after Adjustments of the Study Subjects

Totals of 521 patients in the CDDP group, 1993 patients in the Non-CDDP group and 6157 patients in the Control group were identified in this study. Their characteristics are listed in Table 1. The significant differences were found on gender, age, sCr level on admission and LOS among the three groups. Through the processes of stratification and randomly selecting patients to equalize their number among the three groups in Table 2, 454 patients in each group were identified. The diversities of characteristics among them were eliminated to some extent (Table 3). The lack of other alternative exposures has been argued as a common problem with historical cohort studies.[9] In this study, as we have massive clinical data pooled in the CDW, we were able to solve this problem by forming the Non-CDDP group as an alternative exposure for enhancing the analyses.

Table 2. Stratification and Adjustment of the Study Subjects among the Three Groups

Gender	Age	sCr	LOS	CDDP				Non-CDDP			
				No. of patients Original	%	No. of patients adjusted	%	No. of patients Original	%	No. of patients adjusted	%
0	0	I	A	6	1.15	6	1.32	8	0.40	6	1.32
0	0	I	B	12	2.30	12	2.64	31	1.56	12	2.64
0	0	I	C	24	4.61	11	2.42	29	1.46	11	2.42
0	0	I	D	6	1.15	3	0.66	13	0.65	3	0.66
0	0	II	A	17	3.26	17	3.74	60	3.01	17	3.74
0	0	II	B	67	12.86	67	14.76	129	6.47	67	14.76
0	0	II	C	56	10.75	36	7.93	76	3.81	36	7.93
0	0	II	D	11	2.11	2	0.44	35	1.76	2	0.44
0	0	III	A	2	0.38	2	0.44	13	0.65	2	0.44
0	0	III	B	13	2.50	13	2.86	25	1.25	13	2.86
0	0	III	C	11	2.11	10	2.20	23	1.15	10	2.20
0	0	III	D	2	0.38	2	0.44	9	0.45	2	0.44
0	1	I	A	3	0.58	3	0.66	6	0.30	3	0.66
0	1	I	B	9	1.73	9	1.98	13	0.65	9	1.98
0	1	I	C	4	0.77	4	0.88	7	0.35	4	0.88
0	1	I	D	0	0.00	0	0.00	1	0.05	0	0.00
0	1	II	A	20	3.84	20	4.41	23	1.15	20	4.41
0	1	II	B	58	11.13	58	12.78	76	3.81	58	12.78
0	1	II	C	40	7.68	29	6.39	29	1.46	29	6.39
0	1	II	D	6	1.15	4	0.88	4	0.20	4	0.88
0	1	III	A	7	1.34	7	1.54	14	0.70	7	1.54
0	1	III	B	11	2.11	11	2.42	30	1.51	11	2.42
0	1	III	C	4	0.77	4	0.88	12	0.60	4	0.88
0	1	III	D	0	0.00	0	0.00	0	0.00	0	0.00
1	0	I	A	11	2.11	11	2.42	346	17.36	11	2.42
1	0	I	B	29	5.57	29	6.39	227	11.39	29	6.39
1	0	I	C	23	4.41	23	5.07	113	5.67	23	5.07
1	0	I	D	8	1.54	1	0.22	48	2.41	1	0.22
1	0	II	A	8	1.54	8	1.76	134	6.72	8	1.76
1	0	II	B	9	1.73	9	1.98	112	5.62	9	1.98
1	0	II	C	4	0.77	4	0.88	43	2.16	4	0.88
1	0	II	D	3	0.58	2	0.44	24	1.20	2	0.44
1	0	III	A	1	0.19	1	0.22	4	0.20	1	0.22
1	0	III	B	0	0.00	0	0.00	5	0.25	0	0.00
1	0	III	C	0	0.00	0	0.00	1	0.05	0	0.00
1	0	III	D	0	0.00	0	0.00	3	0.15	0	0.00
1	1	I	A	2	0.38	2	0.44	59	2.96	2	0.44
1	1	I	B	11	2.11	11	2.42	62	3.11	11	2.42
1	1	I	C	10	1.92	10	2.20	24	1.20	10	2.20
1	1	I	D	0	0.00	0	0.00	6	0.30	0	0.00
1	1	II	A	1	0.19	1	0.22	41	2.06	1	0.22
1	1	II	B	9	1.73	9	1.98	35	1.76	9	1.98
1	1	II	C	2	0.38	2	0.44	15	0.75	2	0.44
1	1	II	D	0	0.00	0	0.00	5	0.25	0	0.00
1	1	III	A	0	0.00	0	0.00	6	0.30	0	0.00
1	1	III	B	1	0.19	1	0.22	6	0.30	1	0.22
1	1	III	C	0	0.00	0	0.00	8	0.40	0	0.00
1	1	III	D	0	0.00	0	0.00	0	0.00	0	0.00

Note; Gender: 0: Male; 1: Female. Age (years): 0: ≤ 65; 1: > 65. sCr (mg/dl) on admission: I: 0.3–0.6; II: 0.6–0.9; III: 0.9–1.2. LOS (days): A: ≤ 30; B: 30–90; C: 90–180; D: 180–365.

Table 2. Continued

Gender	Age	sCr	LOS	Control			
				No. of patients Original	%	No. of patients adjusted	%
0	0	I	A	170	2.76	6	1.32
0	0	I	B	115	1.87	12	2.64
0	0	I	C	11	0.18	11	2.42
0	0	I	D	3	0.05	3	0.66
0	0	II	A	789	12.81	17	3.74
0	0	II	B	351	5.70	67	14.76
0	0	II	C	36	0.58	36	7.93
0	0	II	D	2	0.03	2	0.44
0	0	III	A	216	3.51	2	0.44
0	0	III	B	85	1.38	13	2.86
0	0	III	C	10	0.16	10	2.20
0	0	III	D	4	0.06	2	0.44
0	1	I	A	156	2.53	3	0.66
0	1	I	B	81	1.32	9	1.98
0	1	I	C	7	0.11	4	0.88
0	1	I	D	0	0.00	0	0.00
0	1	II	A	758	12.31	20	4.41
0	1	II	B	330	5.36	58	12.78
0	1	II	C	40	0.65	29	6.39
0	1	II	D	4	0.06	4	0.88
0	1	III	A	319	5.18	7	1.54
0	1	III	B	147	2.39	11	2.42
0	1	III	C	17	0.28	4	0.88
0	1	III	D	2	0.03	0	0.00
1	0	I	A	683	11.09	11	2.42
1	0	I	B	283	4.60	29	6.39
1	0	I	C	32	0.52	23	5.07
1	0	I	D	1	0.02	1	0.22
1	0	II	A	283	4.60	8	1.76
1	0	II	B	123	2.00	9	1.98
1	0	II	C	19	0.31	4	0.88
1	0	II	D	2	0.03	2	0.44
1	0	III	A	22	0.36	1	0.22
1	0	III	B	14	0.23	0	0.00
1	0	III	C	1	0.02	0	0.00
1	0	III	D	0	0.00	0	0.00
1	1	I	A	362	5.88	2	0.44
1	1	I	B	194	3.15	11	2.42
1	1	I	C	20	0.32	10	2.20
1	1	I	D	1	0.02	0	0.00
1	1	II	A	245	3.98	1	0.22
1	1	II	B	141	2.29	9	1.98
1	1	II	C	9	0.15	2	0.44
1	1	II	D	1	0.02	0	0.00
1	1	III	A	40	0.65	0	0.00
1	1	III	B	26	0.42	1	0.22
1	1	III	C	1	0.02	0	0.00
1	1	III	D	1	0.02	0	0.00

Table 3. Patient Characteristics after Adjustments of the Study Subjects

	CDDP (n = 454)	Non-CDDP (n = 454)	Control (n = 454)	$p^{a)}$
Gender				1.00
Male	330	330	330	
Famale	124	124	124	
Age (years)	60.38 ± 11.84	59.59 ± 13.49	62.02 ± 11.90	0.01
	(59.29–61.47)	(58.34–60.83)	(60.92–63.11)	
sCr (mg/dl) on admission	0.74 ± 0.17	0.74 ± 0.17	0.74 ± 0.18	0.75
	(0.73–0.76)	(0.73–0.76)	(0.72–0.75)	
LOS (days)	77.35 ± 48.64	76.34 ± 53.00	67.62 ± 49.03	0.01
	(72.86–81.84)	(71.46–81.23)	(63.10–72.14)	

Numbers in parentheses stand for 95% CI. *a*) One-way ANOVA test.

Table 4. Rate of the Observed Nephrotoxicity among the Three Groups

sCr Value	CDDP	Non-CDDP	Control	Total
sCr $\geq$1.2 mg/dl	127 (28.0%)	89 (19.6%)	88 (19.4%)	304 (22.3%)
sCr $<$ 1.2 mg/dl	327	365	366	1058
Total	454	454	454	1362

Table 5. Results of the Three Paired Comparisons (2 × 2 Tables)

Comparison	X^2	p
CDDP *vs.* Non-CDDP	8.772	0.0031
CDDP *vs.* Control	9.269	0.0023
Non-CDDP *vs.* Control	0.007	0.9332

Table 6. Recovery Rate of the Observed Nephrotoxicity among the Three Groups

sCr Value	CDDP	Non-CDDP	Control	Total
sCr $<$ 1.2 mg/dl	88 (69.3%)	55 (61.8%)	61 (69.3%)	204 (67.1%)
sCr $\geq$1.2 mg/dl	39	34	27	100
Total	127	89	88	304

Observed Nephrotoxicity

The rate of observed nephrotoxicity among the three groups is listed in Table 4. There was a significant difference among them (X^2 = 9.661, df = 1, p = 0.002). From the further comparisons shown in Table 5, significant differences were found between the CDDP *vs*. the Non-CDDP, and the CDDP *vs*. the Control group, but no significant difference was found between the Non-CDDP *vs*. the Control group. The risk ratio for each comparison corresponded to 1.43 (95%CI: 1.13–1.81), 1.44 (95%CI: 1.14–1.83) and 1.01 (95%CI: 0.78–1.41), respectively. Although age has been reported as a risk factor to cisplatin nephrotoxicity,[10] patients in the Control group were older than in the other groups in this study. This will not affect the assessment.

Recoveries from the Observed Nephrotoxicity

The recovery rate from the observed nephrotoxicity is listed in Table 6. No significant difference was identified among the three groups (X^2 = 0.0148, df = 1, p = 0.901).

Results of Logistic Regression

Table 7 summarizes the observed CDDP nephrotoxicity in relation to CDDP doses. We found that it was associated with CDDP dose but not associated with CDDP total accumulated doses, which is consistent with the findings shown in an other study.[8]

In conclusion, we have estimated the observed

Table 7. Logistic Regression Analysis of the Observed Nephrotoxicity in Relation to CDDP Doses

Variable	Coefficient	Standard error	z	p
Constant	−1.443	0.204	−7.071	< 0.0001
Dose	0.006	0.003	2.092	0.037
Total accumulated doses	0.001	0.001	1.462	0.144

cisplatin nephrotoxicity in our hospitalized adult cancer inpatients by using CDW. It occurred in 28.0% of patients who received this drug. The observed nephrotoxicity was associated with CDDP dose but not associated with CDDP total accumulated doses, and is considered to be reversible at the end point of therapy (discharge).

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