

## RESEARCH ARTICLE

# Incidence of Cisplatin-Induced Nephrotoxicity and Associated Factors among Cancer Patients in Indonesia

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## Abstract

**Background:** Cisplatin is still used as a first-line medication for solid tumors. Nephrotoxicity is a serious side effect that can decrease renal function and restrict applicable doses. This research aimed to obtain the profile of cisplatin-induced nephrotoxicity and its associated factors in adult cancer patients at Dharmais National Cancer Hospital (DNCH). **Materials and Methods:** The design was cross-sectional with data obtained from patient medical records. We retrospectively reviewed adult cancer patients treated with cisplatin  $\geq 60$  mg/m<sup>2</sup> for at least four consecutive chemotherapy cycles from August 2011 to November 2013. The nephrotoxicity criterion was renal function decline characterized by creatinine clearance  $< 60$  ml/min using the Cockcroft-Gault (CG) equation. **Results:** Eighty-eight subjects received at least four chemotherapy cycles of cisplatin. The prevalence of cisplatin nephrotoxicity was 34.1%. Symptoms could be observed after the first cycle of chemotherapy, and the degree of renal impairment was higher with increased numbers of cycles ( $r = -0.946$ ,  $r^2 = 89.5\%$ ). Factors that affected the decline of renal function were patient age ( $p = 0.008$ ,  $OR = 3.433$ ,  $95\% CI = 1.363-8.645$ ) and hypertension ( $p = 0.026$ ,  $OR = 2.931$ ,  $95\% CI = 1.120-7.670$ ). **Conclusions:** Cisplatin nephrotoxicity occurred in more than one-third of patients after the fourth cycle of chemotherapy and worsened after each cycle despite preventive strategies such as hydration. The decline of renal function induced by cisplatin  $\geq 60$  mg/m<sup>2</sup> was affected by age and hypertension.

**Keywords:** Cisplatin - Dharmais Hospital - nephrotoxicity - risk factor - hydration

*Asian Pac J Cancer Prev*, 16 (3), 1117-1122

## Introduction

Nowadays cancer is a major cause of death in developed countries and the second leading cause of death in developing countries after heart disease (ACS, 2008). GLOBOCAN reported that there were 12.7 million cancer cases and 7.6 million cancer deaths in 2008; where 56% of the cases and 64% of the deaths occurred in developing countries (Jemal et al., 2011). In addition, it was estimated that the incidence of cancer will be doubled by 2020 and nearly tripled by 2030 (Jemal et al., 2011). The number of cancer cases also increases in Indonesia. Data from Dharmais National Cancer Hospital (DNCH), a national cancer referral hospital, showed that there are an increase of about 30% in cancer cases from 1653 cases in 2003 to 2387 cases in 2007 (Sinuraya, 2012). Furthermore, this number has increased to 3083 in 2013 (DNCH Research and Development, 2013). The most common types of cancer in DNCH are nasopharyngeal cancer, lung cancer, cervical cancer and breast cancer (DNCH Research and Development, 2013).

Chemotherapy is one of the treatment options for cancer. Cisplatin (cis-diamminedichloroplatinum [II]) is a platinum-based chemotherapy drug widely used to treat solid tumors (Miller et al., 2010). For more than 30

years, cisplatin has been used as a standard component of combination chemotherapy in several cancers such as ovarian and cervical cancer, testicular cancer, head and neck cancer including nasopharyngeal, and lung cancer (Ries and Klastersky, 1986; Reed, 2008; Chu and Sartorelli, 2012; Wang et al., 2012; Erten et al., 2013). Although platinum derivatives with fewer adverse events, such as carboplatin and oxaliplatin, have been developed more recently, cisplatin still provides better survival rate in some cancers such as lung cancer (Hotta et al., 2004; Ardizzoni et al., 2007).

However, cisplatin has severe side effects such as bone marrow suppression, gastrointestinal toxicity, ototoxicity, neuropathy and nephrotoxicity. Of these, nephrotoxicity is the major side effect that may restrict the therapeutic use of cisplatin (Tiseo et al., 2007; Pabla and Dong, 2008; Mathe et al., 2011). The most severe nephrotoxicity of cisplatin is acute kidney injury, occurring in 20-30% patients treated with the drug (Miller et al., 2010). Nephrotoxicity is found in 28-36% patients who received a single dose (50 mg/m<sup>2</sup>) of cisplatin (Tezcan et al., 2013). Although nephrotoxicity is temporary and dose dependent, it can decrease glomerular filtration rate (GFR), which can be clinically evaluated from increased serum creatinine and decreased creatinine clearance. Cumulative exposure to

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cisplatin can cause acute tubular necrosis and may lead to glomerular damage (Fujieda et al., 2009; Miller et al., 2010; Tezcan et al., 2013).

Cisplatin nephrotoxicity may be reduced, but cannot be completely prevented, through various strategies such as dose fractionation; actively screening for renal abnormalities; slower rate of infusion; enforced diuresis with diuretics and hydration (Tiseo et al., 2007; Moon et al., 2011; Arunkumar et al., 2012). Although many hydration protocols for cisplatin are available, some components such as volume and duration of hydration remain controversial. Furthermore, there is no standard regimen for cisplatin hydration (Santoso et al., 2003; Tiseo et al., 2007; Muraki et al., 2012). Other factors known to increase the risk of cisplatin-induced nephrotoxicity are genetic variation, race, gender, age, comorbidity, smoking, and hypoalbuminemia (de Jongh et al., 2003; Tan et al., 2011; Khrunin et al., 2012; Lavole et al., 2012). Currently cisplatin is still the standard drug at DNCH for treating several cancers such as nasopharyngeal cancer, lung cancer and ovarian cancer. Therefore, it is very important to know the incidence of cisplatin-induced nephrotoxicity and factors affecting it.

## Materials and Methods

This research was a cross-sectional study with data obtained from medical records of cancer patients at DNCH. We retrospectively reviewed adult cancer patients (minimum age of 19 years old) treated with cisplatin  $\geq 60 \text{ mg/m}^2$  for at least four consecutive chemotherapy cycles from August 2011 to November 2013. Nephrotoxicity was defined as renal function decline characterized by creatinine clearance  $< 60 \text{ ml/min}$  (Tiseo et al., 2007; FDA, 2010; Leu and Baribeault, 2010). Creatinine clearance is an estimated glomerular filtration rate (eGFR) calculated by the Cockcroft-Gault (CG) equation. Creatinine clearance using the CG equation is good enough to estimate impaired renal function due to the use of nephrotoxic drugs because this equation takes into account patient's body weight in each chemotherapy cycle besides patient's age and gender (Thomas and Thomas, 2009).

Variables studied as risk factors of renal function decline were age ( $< 50$  years old and  $\geq 50$  years old), gender, cisplatin dose ( $< 75 \text{ mg/m}^2$  and  $\geq 75 \text{ mg/m}^2$ ), hydration volume ( $< 6000 \text{ ml}$  and  $\geq 6000 \text{ ml}$ ), comorbidities (hypertension and diabetes mellitus), the use of other nephrotoxic drugs (paracetamol, NSAIDs, ACE inhibitors, ARBs, cephalosporin, ciprofloxacin), previous treatment with chemotherapy and the number of chemotherapy cycles. Hydration volume was the total volume of hydration fluid given 24 hours before, during, and 24 hours after administration of chemotherapy.

Statistical analysis was conducted by Statistiale Products Social Science (SPSS) 18 for Windows. Paired T-test was used to observe the difference between creatinine clearance before and after chemotherapy, followed by linear regression test to analyze the effect of the number of chemotherapy cycles on creatinine clearance after chemotherapy administration. Chi-Square

test and its alternative, Fisher's exact test was used to analyze the relationship between risk factors (age, gender, cisplatin dose, hydration volume, comorbidities, the use of other nephrotoxic drugs, and previous treatment with chemotherapy) and nephrotoxicity incidence after four chemotherapy cycles. The probability ratio of nephrotoxicity was assessed by Odds Ratio test (OR). Finally, multivariate analysis with logistic regression test was used to analyze the risk factors for nephrotoxicity in patients taking cisplatin. A two-sided p value of  $< 0.05$  was considered statistically significant.

## Results

In this study, a total of 88 subjects were recruited in accordance with the criteria of subject recruitment (Figure 1). Patients who received cisplatin for four cycles were 88 people, and only 56 subjects completed up to six cycles. Nephrotoxicity occurred in 30 subjects (34.1%) after four cycles and occurred in 29 subjects (51.8%) after six cycles of cisplatin chemotherapy. However, statistical analysis was only performed for subjects who completed four cycles of chemotherapy.

Table 1 describes general and clinical characteristics

**Table 1. General and Clinical Characteristics of Subjects**

Characteristics	Frequency	(%)
Gender		
Male	37	42
Female	51	58
Age		
$< 50$ years old	55	62.5
$\geq 50$ years old	33	37.5
Comorbidity		
Diabetes Mellitus	5	5.7
Hypertension	25	28.4
Type of cancer		
Nasopharyngeal cancer	35	39.8
Ovarian cancer	17	19.3
Breast cancer	18	20.5
Other head and neck cancer	14	15.9
Lung cancer	4	4.5
Cisplatin dose		
$< 75 \text{ mg/m}^2$	15	17
$\geq 75 \text{ mg/m}^2$	73	83
Hydration volume		
$< 6000 \text{ ml}$	43	48.9
$\geq 6000 \text{ ml}$	45	51.1
The use of other nephrotoxic drugs		
No	33	37.5
Yes	55	62.5
Previous treatment with chemotherapy		
No	70	79.5
Yes	18	20.5
Chemotherapy combination		
Paclitaxel	18	20.5
Pemetrexed	1	1.1
Docetaxel	19	21.6
Docetaxel, 5 FU	33	37.5
Etoposid, Bleomisin	2	2.3
5 FU	12	13.6
Siklofosamid	1	1.1
Doxorubicin, Siklofosamid	2	2.3

of the study subjects. The number of male and female subjects was almost equal (42.0% vs. 58.0%). The mean age of subjects was 44.28±12.03 years old, the youngest was 19 years old and the oldest was 68 years old. Almost one-third of the subjects had hypertension (28.4%), whereas only five subjects had diabetes mellitus (5.7%). The most common cancer among study subjects was nasopharyngeal cancer. Cisplatin doses in

this research were 60, 75, and 100 mg/m<sup>2</sup>, depending on combination chemotherapy. Hydration volume per cycle for four chemotherapy cycles had a mean value of 7712.41±4177.80 ml (2,475-16,070 ml).

Table 2 shows the incidence of renal function decline induced by cisplatin from the first cycle to the sixth cycle. Paired T-test showed a significant difference between creatinine clearance before and after 4 cycles of cisplatin (n=88, p=0.000, p<0.05). In addition, the percentage of decline in creatinine clearance after six chemotherapy cycles was greater than the percentage in the previous cycles. Based on linear regression, a strong correlation between the number of chemotherapy cycles and creatinine clearance mean of each cycle was characterized by r=-0.946, indicating that creatinine clearance mean became more decreased with increasing number of chemotherapy cycles. The coefficient of determination (r<sup>2</sup>) of 0.895 indicated that 89.50% variation in creatinine clearance mean was affected by the number of cycles, whereas 10.50% was influenced by unknown variables.

Table 3 shows factors affecting cisplatin-induced nephrotoxicity in subjects. Age (p=0.008, OR=3.433, 95%CI=1.363-8.645) and hypertension (p=0.026,

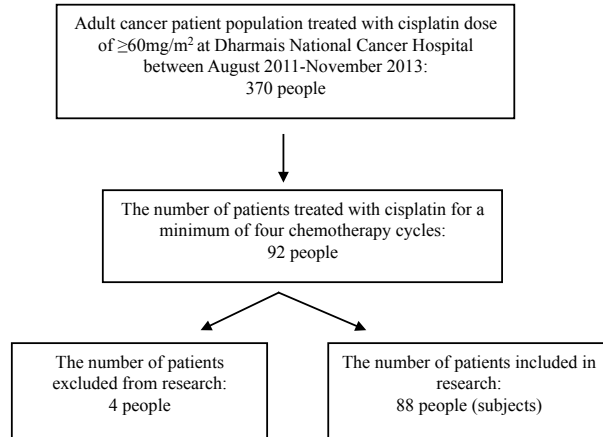


Figure 1. The Recruitment of Subjects

Table 2. Decreased Creatinine Clearance During Chemotherapy Administration

Creatinine clearance (Ccr)	Before* chemotherapy	After chemotherapy cycles					
		1*	2*	3*	4*	5*	6*
Mean (ml/min)	103.61±30.77	85.29±27.12	84.48±27.14	82.56±28.47	75.33±27.83	73.16±26.06	61.00±24.08
% Decrease (%)	-	15.44	16.79	18.58	26.52	29.29	40.97

\*Before: Creatinine clearance (Ccr) 1-3 days before chemotherapy administration; 1: Ccr 1-3 weeks after the first cycle; 2: Ccr 1-3 weeks after the second cycle; 3: Ccr 1-3 weeks after the third cycle; 4: Ccr 1-3 weeks after the fourth cycle; 5: Ccr 1-3 weeks after the fifth cycle; 6: Ccr 1-3 weeks after the sixth cycle

Table 3. Factors Affecting Renal Function Decline Induced by Cisplatin

Variable	After 4 cycles (n=88)							
	Creatinine Clearance				p	OR	95%CI	
	<60 ml/min		≥ 60 ml/min				Min	Max
	n	%	n	%				
Gender								
Female	18	35.3	33	64.7	0.780**	1.136	0.464	2.785
Male	12	32.4	25	67.6		Reff*		
Age (years)								
≥50	17	51.5	16	48.5	0.008**	3.433	1.363	8.645
<50	13	23.6	42	76.4		Reff*		
Diabetes Mellitus (DM)								
Yes	1	20	4	40	0.657†	0.466	0.05	4.361
No	29	34.9	54	65.1		Reff*		
Hypertension								
Yes	13	52	12	48	0.026**	2.931	1.12	7.67
No	17	27	46	73		Reff*		
Cisplatin dose (mg/m <sup>2</sup> )								
≥ 75	25	34.2	48	65.8	0.946**	1.042	0.321	3.381
<75	5	33.3	10	66.7		Reff*		
Hydration volume (ml)								
<6000	13	30.2	30	69.8	0.455**	0.714	0.294	1.733
≥6000	17	37.8	28	62.2		Reff*		
The use of other nephrotoxic drugs								
Yes	19	34.5	36	65.5	0.908**	1.056	0.424	2.629
No	11	33.3	22	66.7		Reff*		
Previous treatment with chemotherapy								
Yes	6	33.3	12	66.7	0.939**	0.958	0.32	2.871
No	24	34.3	46	65.7		Reff*		

\* reff=reference; \*\* analyzed by Chi-Square test; † analyzed by Fisher Exact test

OR=2.931, 95%CI=1.120-7.670) had a significant relationship with renal function decline after four cycles of cisplatin chemotherapy (n=88). Multivariate analysis using logistic regression showed that age (p=0.016, OR=3.192, 95%CI=1.240-8.217) had a significant association with renal function decline after four chemotherapy cycles, while hypertension had no statistically significant relationship with renal function decline (p=0.055, OR=2.661, 95%CI=0.979-7.232).

## Discussion

Nephrotoxicity of cisplatin is a restrictive factor for its clinical use in treating solid tumors (Yamada et al., 2011; Morgan et al., 2012). Unbound cisplatin is eliminated by kidney through glomerular filtration and tubular secretion, then accumulates in renal parenchymal cells (Miller et al., 2010). Cisplatin enters renal tubular cells via passive diffusion and a mechanism mediated by transporters such as OCT2 (Organic Cation Transporter 2) and Ctr1 (Copper Transporter 1) (Pabla and Dong, 2008). It is metabolized into nephrotoxin in proximal tubule (Yao et al., 2007; Perazella, 2009). Cisplatin affects gene regulation; causes direct cytotoxicity through increased oxidative stress (Reactive Oxygen Species); activates mitogen-activated protein kinase; induces apoptosis; causes mitochondrial dysfunction; then stimulates inflammation and fibrogenesis (Yao et al., 2007; Naughton, 2008; Miller et al., 2010). These events cause tubular damage leading to electrolyte disturbances (Arunkumar et al., 2012; BC Cancer Agency, 2013). Most patients have acute kidney injury but others can experience chronic renal failure (Miller et al., 2010; Lacy et al., 2011). The early stage of renal disorder generally does not cause symptoms. Functional impairment is only detected when GFR is <60 ml/min/1.73m<sup>2</sup>. In this condition, renal impairment is more difficult to treat (Thomas and Thomas, 2009). Approximately 90% of renal function might be lost before clinical symptoms appear (Bell et al., 2013). Therefore, monitoring renal function is necessary to detect early renal impairment.

Researchers observed that renal function decline had occurred since the first cycle of cisplatin administration. This was consistent with the research of Prasetyaningrum (2013) and Tezcan et al. (2013), which reported that cisplatin causes impaired renal function since the first cycle of chemotherapy, characterized by decreased creatinine clearance or glomerular filtration rate. Furthermore, the reduction of renal function got worse with increasing number of chemotherapy cycles, indicated by creatinine clearance mean that became more decreased after each cycle. Successive cisplatin therapy may induce permanent and progressive nephrotoxicity despite the application of preventive strategies (Miller et al., 2010). Tezcan et al. (2013) reported that when the number of chemotherapy cycles increases, changes in renal function may be permanent. If serum creatinine of patients taking cisplatin is >1.5 mg/dL, chemotherapy should be stopped, cisplatin dose should be lowered, or regimen should be changed because the recovery period of renal function is lengthy (about 5-6 months) (Moon et al., 2011).

Researchers found that older patients (≥50 years) had higher risk of nephrotoxicity from four cycles of cisplatin administration. In general, old age is one of many factors that increase the risk of drug nephrotoxicity (Perazella, 2009). Some studies showed that older age is a risk factor for the development of cisplatin nephrotoxicity due to reduced number and volume of tubules, as well as increased synthesis of reactive oxygen compounds and inflammation in the ageing kidney (Caglar et al., 2002; de Jongh et al., 2003; Mathe et al., 2011; BC Cancer Agency, 2013). Geriatric patients tend to have chronic kidney disease despite having no comorbidities (Stevens et al., 2010) and the prevalence of renal impairment is high in elderly cancer patients (Thomas and Thomas, 2009; Aapro and Launay-Vacher, 2012). The risk of cisplatin-nephrotoxicity is 26% in patients <48 years old, 35% in patients 48-62 years old, and 41% in patients >62 years old (de Jongh et al., 2003). Moreover GFR decreases by 10 ml/min every 10 years after 40 years old (Bell et al., 2013) and the elderly has an annual GFR decline of <1 ml/min/1.73 m<sup>2</sup> (Thomas and Thomas, 2009). If GFR decreases more than 3 ml/min/1.73 m<sup>2</sup> in one year, the risk factor of mortality is increased regardless of baseline GFR (Thomas and Thomas, 2009).

A comorbidity, hypertension, could also influence renal function decline caused by cisplatin. Mathe et al. (2011) and Lavole et al (2012) reported that cardiovascular diseases (hypertension and ischemic heart disease) and diabetes mellitus increase the risk of nephrotoxicity in lung cancer patients. In this study, diabetes mellitus did not influence the occurrence of nephrotoxicity. The difference of these results might be due to fewer number of diabetic patients in the study. In addition, there were differences in cisplatin dose, hydration protocol, type of cancer and nephrotoxicity criteria. First, Mathe et al. (2011) and Lavole et al (2012) examine nephrotoxicity induced by cisplatin ≥75 mg/m<sup>2</sup> in lung cancer patients with one type of hydration protocol. Nephrotoxicity criteria by Lavole et al. (2012) is defined as ≥grade 1 according to NCIC common toxicity criteria. In contrast, subjects in the present study were patients with various cancer types, using cisplatin ≥60 mg/m<sup>2</sup>, in more diverse chemotherapy combinations and hydration protocols. Prehydration fluid in this protocol consisted of 0.9% NaCl (Normal Saline, NS) or dextrose 5% in NS or a combination of NS, dextrose 5%, KCl solution in NS, and mannitol. Posthydration fluid were NS solution or dextrose 5% in NS or a combination KCl solution in NS and MgSO<sub>4</sub> solution in NS. Some research reported that diabetic animals have reduced gene and protein expression of OCT (Organic Cation Transporter) isotopes, thus lowering the risk of cisplatin nephrotoxicity (Kroning et al., 2000; Grover et al., 2004; Yao et al., 2007). In addition, the site of renal damage caused by cisplatin is different from that caused by hypertension and diabetes mellitus. Hypertension and diabetes mellitus destruct renal glomerulus (Corwin, 2008) while cisplatin causes destruction mainly in the renal proximal tubule (Yao et al., 2007). However, hypertension can cause ischemic glomerulosclerosis, which further stimulates interstitial fibrosis and tubular atrophy, the main target of cisplatin nephrotoxicity (Hill, 2008; Fine



and Norman, 2008; Perazella, 2009).

Limitation of this study was a cross-sectional design that did not describe the disease course and could not determine any causal relationships (Ghazali et al., 2011). Although this study used total sampling method and obtained 88 subjects, researchers hardly find any relationship between risk factors and renal function decline due to the use of cisplatin. However, we observed the profile of nephrotoxicity induced by high-dose cisplatin and analyzed factors that influence it. Hopefully these results can be used as a reference or comparison material for further research.

Further prospective research is needed to study factors affecting cisplatin nephrotoxicity in patients with one type of cancer and one type of chemotherapy combination. The sample size should be larger in order to represent the population. In addition, further research is needed regarding the type and volume of hydration that is more effective in alleviating cisplatin nephrotoxicity.

In conclusion, renal function decline induced by cisplatin  $\geq 60$  mg/m<sup>2</sup> was affected by patient's age and hypertension, and occurred in the majority of adult cancer patients although hydration had been given.

## Acknowledgements

We are grateful to Dharmas National Cancer Hospital for allowing us to conduct this retrospective research. We thank Leovinna Widjaja, MD and Reni Indardini, S.Si. for revision of the manuscript. This research was self-funded and there is no conflict of interest.

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