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Cisplatin-induced Nephrotoxicty and its Predisposing Factors for Unrecovered Kidney Injury: A Report from Indonesia National Cancer Center

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Abstract

BACKGROUND: Cisplatin-induced nephrotoxicity is the most common and devastating side effects which affects long-term outcome. It may be reversible in some patients but may also cause permanent kidney injury.

AIM: This research aims to evaluate risk factors of cisplatin nephrotoxicity and unrecovered kidney function at national cancer hospital in Indonesia.

METHODS: This is a retrospective and cohort study conducted at Dharmais National Cancer Hospital, Jakarta, Indonesia. All cancer patients aged 18 years old and above, who received cisplatin-based regimen as the first-line chemotherapy and completing all cycles with at least four cycles, were included in the study. Demographic data were collected and kidney function was evaluated using estimated glomerular filtration rate (eGFR) before, 3 times during chemotherapy, 1 and 3 months after the last dose.

RESULTS: A total of 177 patients were included in the analysis, with mean age of 45.80 ± 11.75 years old, majority diagnosed with nasopharynx cancer (58.8%), and have baseline eGFR of 102.76 ± 20.68 mL/min 1.73m^2. Nephrotoxicity is occurred in 80 (45.2%) patients with 27 (15.3%) toxicity occurred after the first cycle. Age above 50, hypertension and non-steroidal anti-inflammatory drugs (NSAID) use associated with increased risk of cisplatin-induced nephrotoxicity. Nephrotoxicity risk factors include age above 50 (OR 4.18, 95% CI 2.11–8.28; p < 0.0001), hypertension (OR 2.03, 95% CI 1.03–4.01; p = 0.040), and NSAID use (OR 2.34, 95% CI 1.22–4.93; p = 0.025). Risk factors of patients who unrecovered above 75% eGFR baseline were hypertension (OR 0.47, 95% CI 0.17–0.56; p = 0.001) and gender (OR 0.018, 95% CI 0.03–0.95; p = 0.043).

CONCLUSION: Nephrotoxicity occurs in 45.2% patients throughout cisplatin-based chemotherapy cycles. Risk factors of nephrotoxicity includes age above 50, hypertension, and NSAID while hypertension and female gender are risk factor for not recover above 75% eGFR baseline after cisplatin cycles.

Introduction

Regardless of the advancement of oncology therapeutic scope, cisplatin, a platinum agent, continues to be the cornerstone due to its most potent effect. It is one of the most potent cancer that is used for broad types of cancer such as head and neck, testicular, ovarian, cervical, non-small cell lung carcinoma, and many other types of cancer [1]. Unfortunately, it is also count as one of the most nephrotoxic drugs. Cisplatin nephrotoxicity is dose-dependent and by discontinuation of the drug it is reversible [2].

Nephrotoxicity is a rapid deterioration in the kidney function due to toxic effect of medications and chemicals that may affect renal function in more than one way [3].

Despite the potentially lifesaving impact, cisplatin can cause side effects in normal tissue, including neurotoxicity, ototoxicity, emetogenicity, and nephrotoxicity. Lately, many studies have attempted to look for preventive strategies to minimize its side effects, such as hydration to reduce cisplatin half-life, concentration in urine and proximal tubule transit time; magnesium supplementation as a nephroprotectant and forced diuresis in selected patients [1], [4]. However, renal toxicity still occurs even with such hydration, subjecting the need for more effective preventive measurements [5].

In particular, the nephrotoxic side effects of cisplatin might be severe and are often reduced or discontinued, thus limiting the effectiveness of the treatment, increasing the risk of relapse or progression of the cancer. It is reported that cisplatin nephrotoxicity occurred in between 5% and 45% of patients who have received the drug. The prevalence varies due to differences in defining the renal injury [6].

Cisplatin's nephrotoxicity is attributed to two main factors: Higher degree accumulation of cisplatin in the kidney than other organs through mediated transports, where about 90% of cisplatin undergoes urinary excretion and the adverse impacts on the renal

transport system [7], [8]. In addition, nephrotoxicity occurs within 10 days after cisplatin administration, and it is evidenced by the reduction in glomerular function, increased serum creatinine, and lower levels of magnesium and potassium [1]. The pathophysiological mechanisms involved in cisplatin nephrotoxicity are proximal tubular injury, oxidative stress, inflammation, and vascular injury in the kidney. There is predominantly acute tubular necrosis and also apoptosis in the proximal tubules [9].

For some individuals, nephrotoxicity can be reversible, but for others become permanent kidney injury, chronic progressive renal failure, or renal tubule function impairment. Nephrotoxicity is a major threat to increase burden in cancer patients. It affects long-term outcome [10] and studies had reported that acute kidney injury was associated with increased long-term risk of chronic kidney disease, end-stage renal disease, cardiovascular events, and majorly impact to quality of life, increases the costs of hospitalization and the worst is death [11], [12], [13], [14]. Hereby, we conduct a study to assess risk factors toward cisplatin nephrotoxicity and its recovery at national cancer hospital in Indonesia.

Methods

Study design

We retrospectively analyzed the data of patients who received cisplatin-based regimen chemotherapy as the first-line chemotherapy in Dharmais National Cancer Hospital between January 2019 and December 2021. Data collection was conducted January–April 2022. We collected clinical information for patients aged 18 years old and above with all types of malignancies, completing all chemotherapy cycles with at least four cycles. Baseline estimated glomerular filtration rate (eGFR) was the value within and closes to 14 days before the start of cisplatin. The eGFR value after the first, middle, and last cycle was the laboratory results maximum within 14 days after each cycle is completed. For the follow-up period, eGFR data on 1 and 3 months after the last administration of cisplatin are also recorded. In this study, renal insufficiency was clinically evaluated from decreased creatinine clearance below 60 mL/min/1.73 m^2. The study was conducted after obtaining approval from the Ethical Committee at Dharmais National Cancer Hospital, Jakarta, Indonesia.

Patient population

Any cancer patients aged 18 years or older, who had completed cisplatin-containing regimen with minimum of four cycles with complete laboratory results, from January 2019 to December 2021 at the Dharmais National Cancer Hospital, were included in the study. Exclusion criteria are those who did not complete all the chemotherapy cycles, creatinine clearance of <60 mL/min/1.73 m^2 (estimated by the Cockroft-Gault equation) before the first chemotherapy, prior chemotherapy history, incomplete laboratory results, and other medical records data that are needed.

Measurements

Demographic data include age, sex, weight, height, operation status, chemotherapy cycles, chemotherapy regimen, cancer type and stage, and presence of comorbidities. Laboratory results consist of eGFR was derived from the clinical laboratory database of the patient that conducted before their first chemotherapy, after the first chemotherapy, after the mid-cycle, after the last cycle of chemotherapy, 1 and 3 months after the last cycle of chemotherapy. The criterion used for nephrotoxicity is any occasion when the creatinine clearance is below 60 mL/min/1.73 m^2. The national kidney foundation recommended that clinicians should not use serum creatinine concentration to assess level of kidney function [15]. The recovery status was categorized based on creatinine clearance into: Recovered to 25% baseline and below, between 25% and 75% of baseline, and to 75% of baseline and above.

Statistics

All recorded data were written in Microsoft Excel. Statistical analysis of the data was done with SPSS version 25.0. Demographic data of the subjects were presented quantitatively. Differences in characteristics between two groups were assessed using Chi-square, with $p < 0.05$ were regarded as statistically significant**.** Bivariate and multivariate logistic regression model was used to evaluate predictor of nephrotoxicity by including potential variables. Hazard ratios with 95% confidence intervals were calculated.

Results

After excluding 10 patients due to prior history of chemotherapy, a total of 177 patients were included in the study analysis. The patient demographic characteristic is shown in Table 1. Most patients are male (62.3%), had been operated before the chemotherapy (58.2%), receive concurrent radiation (65.5%), diagnosed as nasopharynx cancer (58.8%), received docetaxel as combination with cisplatin (39.5), have hypertension as comorbidity (37.9), not receiving non-steroidal anti-inflammatory drugs (NSAID), and having stage 4 cancer (58.2%). The baseline eGFR of all patients were mean of 102.76 ± 20.68 mL/min. However, about quarter of our study population (27.7%)

Table 1: Demographic of subjects

Variables	n (%) (n = 177)
Age (mean ± SD, years)	45.80 ± 11.75
BMI (mean ± SD, kg)	
Obesity	53 (29.9)
Not obese	124 (70.1)
Gender	
Female	65 (36.7)
Male	112 (63.3)
Medical record year	
2019	53 (29.9)
2020	53 (29.9)
2021	71 (40.1)
Operated	
Yes	74 (41.8)
No	103 (58.2)
Radiation	
Yes	116 (65.6)
No	61 (34.4)
Type of cancer	
Nasopharynx	104 (58.8)
Lung	29 (16.4)
Breast	9 (5.1)
Others	35 (19.7)
Combination drug	
Docetaxel	70 (39.5)
Docetaxel + 5FU	40 (22.6)
Pemetrexed	17 (9.6)
5FU	13 (7.3)
Others	37 (20.9)
Comorbidities	
Hypertension	51 (28.8)
Diabetes mellitus	17 (9.6)
Obesity others	53 (29.9)
NSAID use	
Yes	44 (24.9)
No	133 (75.1)
Cancer stage	
Stage 4	103 (58.2)
Stage 3	44 (24.9)
Stage 2	6 (3.4)
Unstaged	24 (13.6)

BMI: Body mass index, NSAID: Non-steroidal anti-inflammatory drugs.

have baseline under 90 mL/min. After the first cycle, nephrotoxicity was found in 27 patients (15.3%). After the mid and last cycle of chemotherapy, the number of patients that had renal insufficiency increased to 30 (16.9%) and 57 (32.2%) patients, respectively. In total, renal insufficiency occurred in 80 (45.2%) patients. Throughout the chemotherapy treatment, there were 76 (95%) patients that had to change the cisplatin regimen into carboplatin due to renal insufficiency.

Based on the demographic data, the majority of those who experience renal insufficiency throughout the chemotherapy cycles are aged above 50 (53.8%), male (56.3%), not obese (70.0%), had history of cancer operation (55.4%), receive radiotherapy (70.0%), not receive NSAID (75.1%). Table 2 describes demographic characteristics of those with and without nephrotoxicity. It was observed that there are two patients who experienced nephrotoxicity right after the first cycle of the chemotherapy whose creatinine clearance stay below 60 mL/min. Each patient is female and male, diagnosed as salivary gland cancer and nasopharynx cancer, receiving chemotherapy combination of 5-fluorouracil (5-FU) and docetaxel, respectively. Both aged above 50 years old, have hypertension, have eGFR baseline under 90 mL/min and got carboplatin replacement until the last sixth cycle.

Few factors were found to be associated with increased risk eGFR below 60 mL/min during chemotherapy. On bivariate analysis, age above 50 years old, hypertension, and NSAID use, had history

Table 2: Characteristic of the subjects with and without nephrotoxicity

Variables	Normal (n = 97)	Nephrotoxicity (n = 80)	OR (95%CI)	p-value
Age (mean ± SD, years)				
Below 50	73 (74.2)	37 (46.3)	1	<0.0001*
Above 50	24 (25.8)	43 (53.7)	3.34 (1.77–6.30)	
Sex				
Female	30 (30.9)	35 (43.7)	0.57 (0.31–1.067)	0.078
Male	67 (69.1)	45 (56.3)	1	
Hypertension				
Yes	32 (32.9)	46 (57.5)	1.55 (0.80–2.97)	0.001
No	65 (67.0)	34 (42.5)	1	
Diabetes				
Yes	5 (5.2)	12 (15.0)	2.59 (0.87–7.68)	0.084
No	92 (94.8)	85 (15.0)		
Obesity				
Yes	27 (27.8)	26 (32.5)	1.24 (0.65–2.37)	0.500
No	70 (72.2)	54 (67.5)	1	
Operation				
Yes	33 (37.9)	41 (55.4)	2.03 (1.11–3.74)	0.021*
No	64 (62.1)	39 (44.6)	1	
Radiation				
Yes	60 (61.8)	56 (70.0)	1.27 (0.83–1.93)	0.257
No	37 (38.1)	24 (30.0)	1	
NSAID use				
Yes	17 (17.5)	27 (33.7)	2.39 (1.1–04.82)	0.013*
No	80 (82.5)	53 (66.3)	1	

NSAID: Non-steroidal anti-inflammatory drugs.

of operation, eGFR baseline under 90 mL/min, had significant p-value on bivariate analysis. However, only age above 50 (OR 4.18, 95% CI 2.11–8.28; p < 0.0001), had hypertension (OR 2.03, 95% CI 1.03–4.01; p = 0.040), and NSAID use (OR 2.34, 95% CI 1.22–4.93; p = 0.025) are significant on the multivariate analysis. More details are shown in Table 3.

Table 3: Risk factors of nephrotoxicity during cisplatin combination chemotherapy

Factors	Bivariate		Multivariate	
	OR (95% CI)	p-value	OR (95%CI)	p-value
Age, above 50	3.34 (1.77–6.30)	<0.0001	4.18 (2.11–8.28)	<0.0001
Hypertension	2.74 (1.48–5.07)	0.001	2.03 (1.03–4.01)	0.040
NSAID use	2.39 (1.19–4.82)	0.013	2.34 (1.22–4.93)	0.025
Gender (female)	0.57 (0.31–1.06)	0.078		
Operation	2.03 (1.11–3.74)	0.021		
eGFR baseline >90	2.18 (1.12–4.28)	0.022		
Diabetes	2.59 (0.87–7.68)	0.084		
Radiation	1.43 (0.76–2.70)	0.257		
Obesity	1.24 (0.65–2.37)	0.500		

eGFR: estimated glomerular filtration rate, NSAID: Non-steroidal anti-inflammatory drugs.

In this study population, docetaxel is the most used chemotherapy as combination to cisplatin. The top three regimens with the highest percentage of renal insufficiency incidents were a combination of cisplatin with pemetrexed in 13 out of 17 (76%) patients, 5-FU in 9 out of 13 (69%) patients, docetaxel in 31 out of 70 (44%) patients, followed by docetaxel and 5-FU, gemcitabine and etoposide. More detailed results are presented in Figure 1.

A total of 48 patients were followed-up until 3 months after the last cycle of chemotherapy (Table 4). We also observed that the majority of those who experienced renal insufficiency recovered between 25% and 75% of creatinine clearance baseline, on the 1 (77.1%) and 3 (70.8%) month follow-ups. On the bivariate and multivariate analysis of risk factors of patients who did not recover to above 75% eGFR baseline, only hypertension (OR 0.47, 95% CI 0.17–0.56; p = 0.001) and gender (OR 0.018, 95% CI 0.03–0.95; p = 0.043) are significant in both analyses (Table 5).

Discussion

The present, retrospective, and cohort study reported that nephrotoxicity is found in almost one third of the population, 45.2% of those who received cisplatin combination chemotherapy. This number is higher to the study by Kidera *et al*. from Japan and Isiiko *et al*., from Uganda [5], [16], reported a cisplatin-induced nephrotoxicity in 32% and 35.9% patients. Two studies from Netherlands found higher prevalence, 53.7% and 69% in head-and-neck cancer patients that treated with high-dose cisplatin. While in other Japanese, lung cancer population reported was only in 6.1% population [17]. Cisplatin-induced nephrotoxicity varies between studies, due to differences in defining nephrotoxicity method, specific combination of regimen, and type of cancer population. This study use eGFR to determine nephrotoxicity, due to decreased creatinine clearance, was found to be more sensitive than the elevates serum creatinine level [15].

We reported that almost one-third of the population have renal insufficiency. The creatinine clearance of 27.7% studied population falls between 60 and 90 mL per minute, a Stage 2 renal insufficiency according to KDIGO definition. This finding is lower than IRMA study which found 57.4% in solid tumor patients [15]. The main issue for patients with eGFR within 90–60 mL/min is drug nephrotoxicity. The previous studies also demonstrated that pre-existing abnormal renal function is a risk factor for drug-induced nephrotoxicity [15].

We also found that hypertension is an independent predisposing factor to renal insufficiency. Renal vascular abnormalities are basically observed in hypertensive patients and an independent risk factor for renal disease in general. Subclinical kidney damage due to hypertension could constitute a predisposed ground for cisplatin nephrotoxicity thus it can worsen the renal function during cisplatin treatment [18]. In the present study, diabetes is not one of the risk factors, while in other retrospective study, Máthé *et al*., found a link [19]. This could be explained by the lack of samples with diabetes in our study, by considering that diabetes alone can increase risk of renal impairment in general, authors suggest that cancer patients with diabetes should have more consideration.

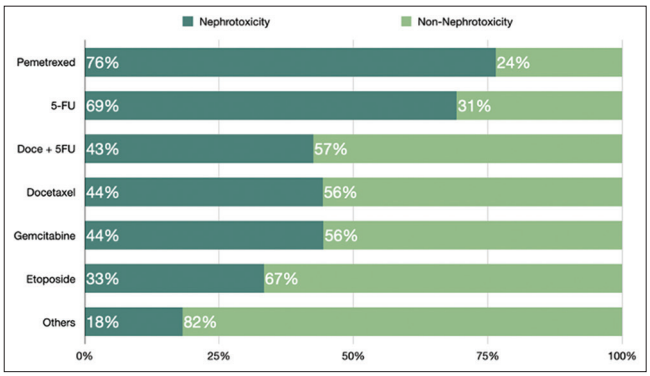

Figure 1: *Nephrotoxicity prevalence based on chemotherapy regimen*

In line with other studies, this study found that concurrent NSAID use increased risk of cisplatin nephrotoxicity [20], [21]. The study from Korea found that NSAID was found to be a risk factor in terms of permanent renal toxicity [22]. Non-selective cyclooxygenase inhibition by NSAIDs decreases prostaglandin synthesis and induces vasoconstriction and renal ischemia [23].

Multivariate analysis showed that age 50 and older is an independent risk factor of cisplatin-induced nephrotoxicity. The incidence of nephrotoxicity gradually increased with age [23]. The study in China reported that age 50 and older is associated with cisplatin-induced nephrotoxicity, increased risk up to 11 times [24]. The finding is similar to the result of other study done in Uganda [16]. Older age has higher risk of nephrotoxicity, supported by the fact that older patients are more susceptible due to specific anatomical and functional changes, including kidney vasculature, filtration, and tubulointerstitial function [25]. Association toward sex are varies. Some studies found that sex was not associated with greater risk of cisplatin nephrotoxicitiy [6], [26], but other studies stated that female patient has increased risk [23].

Our result supports that cisplatin nephrotoxicity is reversible. Most of our studied population recover within 25–75% of eGFR baseline in 3-month follow-up. However, higher recovery found in other study, with 88.9% population recovered to above 75% baseline on 6-month follow-up period [23]. It is observed that the earlier nephrotoxicity occurs and the lower the cumulative dose, the more quickly the patient will recover [22].

This study found the most prevalent renal insufficiency incidence found in cisplatin combination regimen with premetrexed (76%). It is primarily eliminated by renal excretion and there is now accumulating evidence for the nephrotoxic potential of

Table 4: Demographic characteristics based on patients recovery

eGFR Recovery						
Variables	1 month			3 month		
	<25%	25–74.9%	>75%	<25%	25–74.9%	>75%
Number of patients	2 (4.2)	37 (77.1)	9 (18.8)	3 (6.3)	34 (70.8)	11 (22.9)
Age	40.0 ± 14.14	48.37 ± 11.13	50.88 ± 5.34	41.0 ± 12.16	48.85 ± 11.24	50.36 ± 5.39
Sex ratio (F: M)	2:0	0.94 (18:19)	0.50 (3:6)	2.0 (2:1)	1.12 (18:16)	0.37 (3:8)
BMI	28.08 ± 8.52	23.72 ± 3.87	22.99 ± 3.68	25.02 ± 8.02	23.99 ± 4.05	22.71 ± 2.71
eGFR	42.65 ± 22.16	55.07 ± 15.04	72.55 ± 11.62	29.86 ± 5.29	56.50 ± 14.07	92.18 ± 37.17

eGFR: Estimated glomerular filtration rate, BMI: Body mass index.

Table 5: Risk factors of not recover above 75% eGFR baseline from nephrotoxicity

Factors	Bivariate		Multivariate	
	OR (95% CI)	p-value	OR (95%CI)	p-value
Hypertension	0.12 (0.02–0.66)	0.015	0.47 (0.17–0.56)	0.01
Gender (female)	0.26 (0.06–1.15)	0.077	0.18 0.03–0.95)	0.043
eGFR baseline<90	0.20 (0.05–0.82)	0.025		
NSAID use	0.35 (0.09–1.36)	0.132		
Age, above 50	0.71 (0.19–2.67)	0.618		
Diabetes	0.70 (0.11–4.24)	0.701		
Stage 4	0.72 (0.35–1.46)	0.367		
Operation	0.63 (0.17–2.39)	0.507		
Radiation	1.16 (0.25–5.35)	0.843		

eGFR: estimated glomerular filtration rate.

pemetrexed [27], [28]. However, the overall percentage should not be generalized due to minimal population in our study (n = 17), a prospective study with larger population is needed to confirm the result. Another observational study found that the prevalence of renal impairment due to pemetrexed alone is 21% [29]. However, the huge gap with our study may be explained that both cisplatin and pemetrexed are nephrotoxic thus it may worsen the nephrotoxicity effects.

Increased oxidative stress, kidney damage, and apoptosis play an important role in the pathogenesis of nephrotoxicity caused by 5-FU [30]. This study reports a higher percentage of renal insufficiency rate in head-and-neck, and gastric cancer patients, with 46% (after one or two cycles) and 43.9% patients, respectively [31]. In contrast, lower incidence (43%) was found in patients received docetaxel and 5-FU, compared to the previous study that occurred in half population of advanced esophageal cancer (51.2%) [32]. Difference rate of renal insufficiency within other studies may be due to the cutoff of nephrotoxicity that varies and there is no cancer-specific population in our study. Figure 1 explains the percentage of renal insufficiency in each chemotherapy combination with cisplatin.

The increased incidence of renal insufficiency in the last cycle of chemotherapy represents that higher number of cisplatin cycles tend to increase risk of renal toxicity [33]. We observed that the renal function during chemotherapy is fluctuating. Renal impairment induced by cisplatin has been found to be transient and reversible [22]. Other studies also found that patients with cisplatin nephrotoxicity are recovering up to 80.5% and 88.9% [22]. We reported that patients are partially recovering but some may last permanently and chronic [18], [34] in the cell model, repeated treatment with low-dose cisplatin induces long-term pathologies with characteristic of chronic kidney disease [35]. Result supports that cisplatin nephrotoxicity is reversible. Most of our studied population recover within 25–75% of eGFR baseline in 3-month follow-up. However, higher recovery found in other study, with 88.9% population recovered to above 75% baseline on 6-month follow-up period [25]. It is observed that the earlier nephrotoxicity occurs and the lower the cumulative dose, the more quickly the patient will recover [19]. The follow-up in our study is limited to 3 months, thus another observational study with longer duration of follow-up should be conducted to confirm the result.

To the best of our knowledge, this study is the first to analyze risk factors of those who unrecovered from cisplatin nephrotoxicity. Our study is also combining many types of cancer who receive various type of cisplatin combinations. Thus, this study could describe well the prevalence of nephrotoxicity despite the regimen combination. The limitation of our study is limited to the duration of follow-up.

Conclusion

Maintaining normal renal function during cisplatin combination chemotherapy is extremely fundamental. As in this study reported that nephrotoxicity could occur as early as after the first cycle and not improve during follow-up. Higher concern should be done in population with risk factors of cisplatin-nephrotoxicity, As in limited-resources health-care facility, we strongly recommend that at least the kidney function check should be done for all cancer patients before, after, on the mid cycle, after the last cycle, 1- and 3-month follow-up after the last chemotherapy to minimize the risk of nephrotoxicity.

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