ORIGINAL RESEARCH

Correlation Between Higher Cumulative Dose of Cisplatin for Concurrent Chemoradiation and Acute Kidney Disease Incidence Among Nasopharyngeal Carcinoma Patients: A Comparative Study

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Introduction: Nasopharyngeal carcinoma (NPC) is the most malignant cancer in the head and neck area. According to the stage, the management of NPC includes radiation, chemotherapy, or a combination of both. The standard agent for radiosensitizing chemotherapy is cisplatin. Among the several effects of cisplatin administration, nephrotoxicity raises the most concern, especially in high doses. Acute kidney disease (AKD) is a condition in which an acute kidney injury occurs at >7 days but <90 days. This study aimed to assess whether there is a significant difference in the incidence of AKD between NPC patients who received a cumulative dose of cisplatin up to (≤) 200 mg/m^2 and patients who received more than (>) 200 mg/m^2.

Methods: This is a cohort retrospective study conducted in the radiotherapy unit of Cipto Mangunkusumo General Hospital. Medical records of 540 patients from January 2014 to December 2018 were collected and sorted. After sorting, 120 of the records were analyzed.

Results: The analysis showed that 38.4% of patients who received >200 mg/m^2 cumulative dose of cisplatin experienced AKD, whereas 38.3% of the patients who received ≤200 mg/m^2 cumulative dose of cisplatin experienced AKD.

Conclusion: This study found that in patients with locally advanced NPC who received cisplatin chemoradiation, there was no significant difference in the incidence of AKD, recovery of renal function, or progression of chronic kidney disease between patients receiving a cumulative dose of cisplatin ≤200 mg/m^2 and those receiving >200 mg/m^2.

Keywords: cisplatin, nasopharyngeal cancer, acute kidney disease, chemoradiation

Background

Nasopharyngeal carcinoma (NPC) emerges in the nasopharynx, the area above the throat and behind the nose, showing mild or ultrastructural microscopic squamous differentiation.[1] Nasopharyngeal carcinoma (NPC) is the most malignant tumor in the head and neck region. Based on GLOBOCAN 2018, worldwide, there are 129,079 new cases every year and 72,987 deaths due to NPC.[2] Indonesia is the country with the second-highest prevalence of NPC, after China. Compared to the NPC incidence (17,992/year), the mortality rate (11,204/year) is relatively high in Indonesia.[2] This is because 80% of patients diagnosed with NPC have entered the locally advanced stage.[3]

NPC is a complex disease caused by the interaction of genetic factors, chronic infection such as Epstein–Barr virus (EBV), and environmental factors. A definite

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diagnosis is carried out using endoscopic biopsy of the primary nasopharyngeal tumor.[4] The management of NPC includes radiation, chemotherapy, or a combination of both, according to the stage. Chemotherapy can be administered as neoadjuvant (induction), concurrent (concurrent with radiotherapy), or adjuvant (post-definitive) therapy.[5] Combination of chemoradiation as a radiosensitizer is mainly administered to patients with T2–T4 and N1–N3 NPC. Chemotherapy as a radiosensitizer is administered six times using platinum-based preparations of 30–40 mg/m^2, once a week, 2.5–3 hours before radiation. The standard agent used for concurrent chemoradiation is cisplatin, which has been shown to improve survival, tumor control, and metastasis.[4]

Several concurrent chemoradiation protocols have been used worldwide, including cisplatin 100 mg/m^2 administered every 3 weeks in the USA,[6] cisplatin 20 mg/m^2 per day for 4 days administered at weeks 1 and 5 in Taiwan,[7] and cisplatin 40 mg/m^2 per week in Hong Kong.[8] The center in the current study, Cipto Mangunkusumo General Hospital/RSUPN Dr. Cipto Mangunkusumo (RSCM), adopts a concurrent chemoradiation protocol with cisplatin 40 mg/m^2 per week. The optimal cumulative cisplatin dose for NPC has not acquired global or national consensus. One study showed that patients with >200 mg/m^2 cumulative cisplatin dose have better 5-year overall survival than those who receive 200 mg/m^2,[9] while other studies had different results.[10–12] Our center's chemotherapy protocol states that the minimum cumulative cisplatin dose for NPC is 200 mg/m^2.

According to the National Comprehensive Cancer Network (NCCN) guideline, the primary treatment choice for patients with locally advanced NPC is cisplatin-based concurrent chemoradiation.[13] Cisplatin is a broad-spectrum anticancer therapy.[14] It is used in the treatment of various types of cancer, such as head and neck cancer, soft tissue sarcomas, small and non-small lung cancer, breast cancer, cervical cancer, gastric cancer, bone cancers, testicular cancer, ovarian cancer, bladder cancer, Hodgkin and non-Hodgkin lymphoma, neuroblastoma, melanoma, and mesothelioma.[15]

The main target of platinum agents is the DNA inside the nucleus. These drugs inhibit transcription and replication and also result in apoptosis. The most common cisplatin toxicities are nephrotoxicity, neurotoxicity, and ototoxicity. Among these side effects, nephrotoxicity is the most frequent adverse effect, which can limit subsequent use of this agent. A direct manifestation of nephrotoxicity is acute kidney injury (AKI), which can progress to acute kidney disease (AKD).[16–18]

AKI, AKD, and chronic kidney disease (CKD) lie on a spectrum of impaired kidney function, where AKI is a sudden disruption/decrease in kidney function within <7 days, CKD is a decrease in kidney function occurring in >90 days, and AKD is a condition in which AKI stage 1 or more occurs >7 days after initiating AKI but <90 days.[17,19] The degree of AKI, depending on the number of chemotherapy lines and the dose, can be reversible or irreversible. Data from the M.D. Anderson Cancer Center in the USA showed that that AKI occurred in 45% of all cancer patients during the first 2 days and 55% subsequently.[20] Meanwhile, in Indonesia, Prasaja et al[21] found that AKI occurred in 34% of all cancer patients receiving cisplatin.

AKI, which is marked by increased serum creatinine and blood urea nitrogen, can occur within a few days after cisplatin administration.[22,23] A study by Hayes et al[24] found that the increase in serum creatinine occurs on days 6–7 and remains high for 3–4 weeks after cisplatin administration. AKI can be partially reversible, progressive, or permanent, especially with repeated cisplatin administration.[25–28]

Based on a literature search conducted by the authors, it turns out that no studies have examined the relationship between AKD incidence and cumulative dose of cisplatin in NPC patients who received concurrent chemoradiation. The existing studies primarily looked at AKI incidence (not AKD), using different doses and protocols from those used in RSCM.[29–32] This study aimed to confirm whether the incidence of AKD was significantly different between the cumulative doses of ≤200 mg/m^2 and >200 mg/m^2. It is hoped that this study will serve as a guide for determining the optimal cumulative dose of cisplatin to produce beneficial antitumor effects with tolerable toxicity.

Methods
Study Participants

This retrospective cohort study was conducted in the radiotherapy unit of Cipto Mangunkusumo General Hospital. The target population of this study was adult patients with NPC. Data were collected from patients' medical records. The inclusion criteria were NPC patients 18–65 years of age, who received concurrent chemoradiation therapy with cisplatin 30–40 mg/m^2 weekly, with a performance status score

of at least 80 using the Karnofsky scale or at least 1 using the Eastern Cooperative Oncology Group (ECOG) scale, and a glomerular filtration rate (GFR) >60 mL/min/1.73 m². The staging of NPC is based on the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) staging system. Adverse effects are defined according to the Common Terminology Criteria for Adverse Events (CTCAE). The exclusion criteria were incomplete records, uncontrolled hypertension with a diastolic blood pressure of ≥100 mmHg, urinary tract obstruction, diabetes, congestive heart failure, CKD, severe infections/sepsis, receiving furosemide, pregnant women, patients who had received cisplatin in the past/before their current treatment, patients with a history of hospitalization during chemoradiation, and patients with a history of hemodialysis.

Data from January 2014 to December 2018 were collected in July to August 2019. Data analysis was carried out using SPSS version 23.0. Bivariate analysis was conducted using a 2×2 table to determine the odds ratio (OR) for the probability of AKD between patients receiving cisplatin with a cumulative dose of >200 mg/m² and those with a cumulative dose of ≤200 mg/m².

Acute Kidney Injury and Acute Kidney Disease

The diagnostic criteria for AKI consist of an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or increased serum creatinine to ≥1.5 times baseline, occurring within 7 days, or a decrease in urine output to <0.5 mL/kg/hour for 6 hours.[33] AKI is then divided into stages 1, 2, and 3 based on the serum creatinine increase or urine output. AKD is a condition in which AKI stage 1 or more persists for more than 7 days but less than 90 days.[33] GFR was calculated using the CKD-EPI formula, which consists of four variables: gender, race, age, and serum creatinine.

AKD is typically divided into stages 0–3. Compared to the baseline creatinine level, stage 1 AKD is defined as an increase in serum creatinine level to 1.5–1.9 times, stage 2 AKD is defined as an increase in serum creatinine level to 2.0–2.9 times, and stage 3 AKD is defined as an increase in serum creatinine level to ≥3 times, all of which persist for 7–90 days after the initial AKI event.[19,34] Stage 0, also known as subacute AKD, is further divided into A, B, C, and B/C, depending on specific clinical findings. "A" is defined as no sign of injury and not fitting "B" or "C". "B"

is defined as evident prolonged kidney injury with several biomarkers indicating loss of renal reserve. "C" is defined as an increase in serum creatinine <1.5 times baseline level that does not return to the baseline value.[19,34]

In this study, serum creatinine levels were evaluated periodically, whereby the initial serum creatinine measurement was collected before cisplatin-based chemotherapy was initiated. Subsequent serum creatinine measurements were taken after each chemotherapy cycle between 1 week post-chemotherapy and the day before the next cycle. For the last cycle, creatinine measurement was taken between 1 week and 90 days after chemotherapy.

Premedication and Hydration Protocols

Standard premedication for cisplatin chemotherapy consists of 50 mg of intravenous ranitidine, 8 mg of intravenous ondansetron, 10 mg of intravenous diphenhydramine, and 5–10 mg of intravenous dexamethasone. Patients were also administered 1–2 L of intravenous saline hydration before chemotherapy administration. Normal saline hydration was then continued at 100 mL/hour until 3 days after chemotherapy. Hydration protocols for subjects in this study did not include mannitol.

Concurrent Chemoradiation

The chemotherapeutic agent used as radiosensitizers in RSCM is 40 mg/m² cisplatin once a week (on Mondays), 2.5–3 hours before radiation. Chemotherapy may be administered until week 7. Radiation therapy was delivered using two-dimensional intensity-modulated radiation therapy (IMRT) with a radiation dose of 70–70.2 Gy (1.8–2.0 Gy/fraction) every Monday to Friday for 7 weeks.

Statistical Analysis

The collected data were analyzed using SPSS version 23.0. The primary characteristics of the subjects are presented in Table 1. Mean and standard deviation evaluations were performed on quantitative data. Bivariate analysis using a 2×2 table was conducted to evaluate the odds ratio (OR) of AKD between the subjects receiving a cumulative dose of cisplatin >200 mg/m² and those receiving ≤200 mg/m². Chi-squared analysis was performed to determine the p-value. For categorical variables, p values were also determined using chi-squared analysis. Multivariate analysis and logistic regression were conducted on variables with p<0.250.

Table I Characteristics of the Study Subjects

Characteristics	Cumulative Cisplatin Dose		Total	p
	>200 mg/m² (n=73)	≤200 mg/m² (n=47)		
Age (years)				0.846
Mean ± SD	44.86±13.98	45.43±12.35	45.08±12.9	
Max	70	71	71	
Min	10	21	18	
Sex, n (%)				0.222
Male	57 (78.1%)	32 (68.1%)	89 (74.2%)	
Female	16 (21.9%)	15 (31.9%)	31 (25.8%)	
Body mass index, n (%)				1.000
<18.5 kg/m²	12 (16.4%)	9 (19.1%)	21 (17.5%)	
18.5–22.9 kg/m²	34 (46.6%)	19 (40.4%)	53 (44.2%)	
≥23 kg/m²	27 (37.0%)	19 (40.4%)	46 (38.3%)	
Body mass index (kg/m²)				0.468
Mean ± SD	21.86±3.87	22.65±4.27	22.17±4.04	
Min–Max	(13–32)	(15–32)	(13–32)	
ECOG score				0.094
0	47 (64.4%)	37 (78.7%)	84 (70.0%)	
I	26 (35.6%)	10 (21.3%)	36 (30.0%)	
eGFR, n (%)				0.589
60–90 mL/min/1.73 m²	17 (23.3%)	13 (27.7%)	30 (25.0%)	
>90 mL/min/1.73 m²	56 (76.7%)	34 (72.3%)	90 (75.0%)	
Cancer stage (AJCC), n (%)				0.089
I	0 (0%)	0 (0%)	0 (0%)	
II	0 (0%)	0 (0%)	0 (0%)	
III	21 (28.8%)	14 (29.8%)	35 (29.2%)	
IVA	27 (37.0%)	25 (53.2%)	52 (43.3%)	
IVB	25 (34.2%)	8 (17.0%)	33 (27.5%)	
Histology, n (%)				1.000
WHO type 1	2 (2.7%)	0 (0%)	2 (1.7%)	
WHO type 2	0 (0%)	0 (0%)	0 (0%)	
WHO type 3	70 (95.9%)	45 (95.7%)	115 (95.8%)	
Mixed type 2 and 3	1 (1.4%)	2 (4.3%)	3 (2%)	
Age, n (%)				0.791
≥40 years	48 (65.8%)	32 (68.1%)	80 (66.0%)	
<40 years	25 (34.2%)	15 (31.9%)	40 (33.3%)	
Hypertension, n (%)				0.714
Yes	18 (24.7%)	13 (27.7%)	31 (25.8%)	
No	55 (75.3%)	34 (72.3%)	89 (74.2%)	

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum; eGFR, estimated glomerular filtration rate; ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; WHO, World Health Organization.

Ethical Approval

This study has been approved by the Ethical Committee of the Faculty of Medicine, University of Indonesia (ethical approval number KET-718/UN2.F1/ETIK/PPM.00.02/ 2019). It was decided by the committee that individual patient consent was not required as long as confidentiality could be maintained. This waiver was granted because this study did not apply any intervention, and complete anonymity is maintained. Patient confidentiality is protected and maintained in compliance with the Declaration of Helsinki.

Results

In this study, 120 subjects were eligible for data analysis. Out of 120 subjects, 89 were male (74.2%), and the subjects' age ranged from 18 to 71 years old (mean: 45.08 years old). About 33% were <40 years old, while 66.7% were over 40. Most patients were in stage IVA (43.3%), with the most common histopathological classification being WHO type 3 (95.8%). The subjects' ECOG status was mainly in a fair condition (ECOG 1=70%). The characteristics of the subjects are shown in Table 1.

All subjects had good renal function before chemotherapy. Patients who received a cumulative dose of cisplatin >200 mg/m^2 had a mean pre-chemotherapy GFR of 103.58 mL/min/1.73 m^2 and 86.35 mL/min/1.73 m^2 post-chemotherapy. Those who received a cumulative dose of ≤200 mg/m^2 had a mean pre-chemotherapy GFR of 99.92 mL/min/1.73 m^2 and 84.19 mL/min/1.73 m^2 post-chemotherapy. Hydration was more aggressive in those who received cisplatin >200 mg/m^2 compared to those who received cisplatin ≤200 mg/m^2 (median total hydration volume 9000 mL vs 7500 mL, respectively). Table 2 shows the clinical characteristics of the subjects' pre- and post-chemoradiation therapy.

It can be seen that the decrease in renal function (seen from the mean estimated GFR [eGFR]) is more apparent in those who received >200 mg/m^2 cisplatin cumulative dose. The mean eGFR of both groups for each cycle of chemotherapy administered can be seen in Figures 1 and 2. The figures show a slight improvement in eGFR in the fifth cycle for both groups (Figures 1 and 2).

Effect of Cumulative Cisplatin Dose on AKD

Of the subjects receiving cisplatin >200 mg/m^2, 28 patients (38.4%) experienced AKD, while among subjects receiving ≤200 mg/m^2 cisplatin, 18 experienced AKD (38.3%). The mean cumulative dose in the first group was 200 mg/m^2. In the higher dose group, the mean cumulative cisplatin dose was 246.31 mg/m^2. The occurrence of AKD post-chemotherapy can be seen in Table 3. Among those who experienced AKD, most of the subjects had grade 1 AKD. The proportions of AKD grades of the subjects can also be seen in Table 3.

Potential Confounding Factors and Their Correlation with AKD Post-Chemoradiation

Some notable confounding factors in this study were age, sex, grade 2 mucositis, hypertension, initial GFR, vomiting, and ECOG performance status. The correlation of these factors with AKD can be seen in Table 4.

Multivariate Analysis

Variables with a *p*-value <0.25 were analyzed further for multivariate analysis: grade 2 mucositis, vomiting, and sex. The results can be seen in Table 5. Here, it is seen that grade 2 mucositis, vomiting, and sex are not confounding factors for a cumulative dose of cisplatin with the occurrence of AKD because the change in OR is less than 10%.

Table 2 Clinical Characteristics of the Subjects, Before and After Chemoradiation

	Before Starting Chemoradiation			After Complete Cycle of Chemoradiation		
	Cisplatin >200 mg/m^2	Cisplatin ≤200 mg/m^2	*p*	Cisplatin >200 mg/m^2	Cisplatin ≤200 mg/m^2	*p*
eGFR (mL/min/1.73 m^2) Mean±SD	103.58±17.36	99.92±18.64	0.277	86.36±22	84.19±24.61	0.602
<60 60–90 >90	0 (0%) 17 (23.3%) 56 (76.7%)	0 (0%) 13 (27.7%) 34 (72.3%)	0.589	9 (12.3%) 30 (41.1%) 34 (46.6%)	9 (19.1%) 20 (42.6%) 18 (38.3%)	0.990
Total hydration, before and after chemoradiation (mL) Median (min–max)	9000 (6000– 10,500)	7500 (6000– 10,000)				

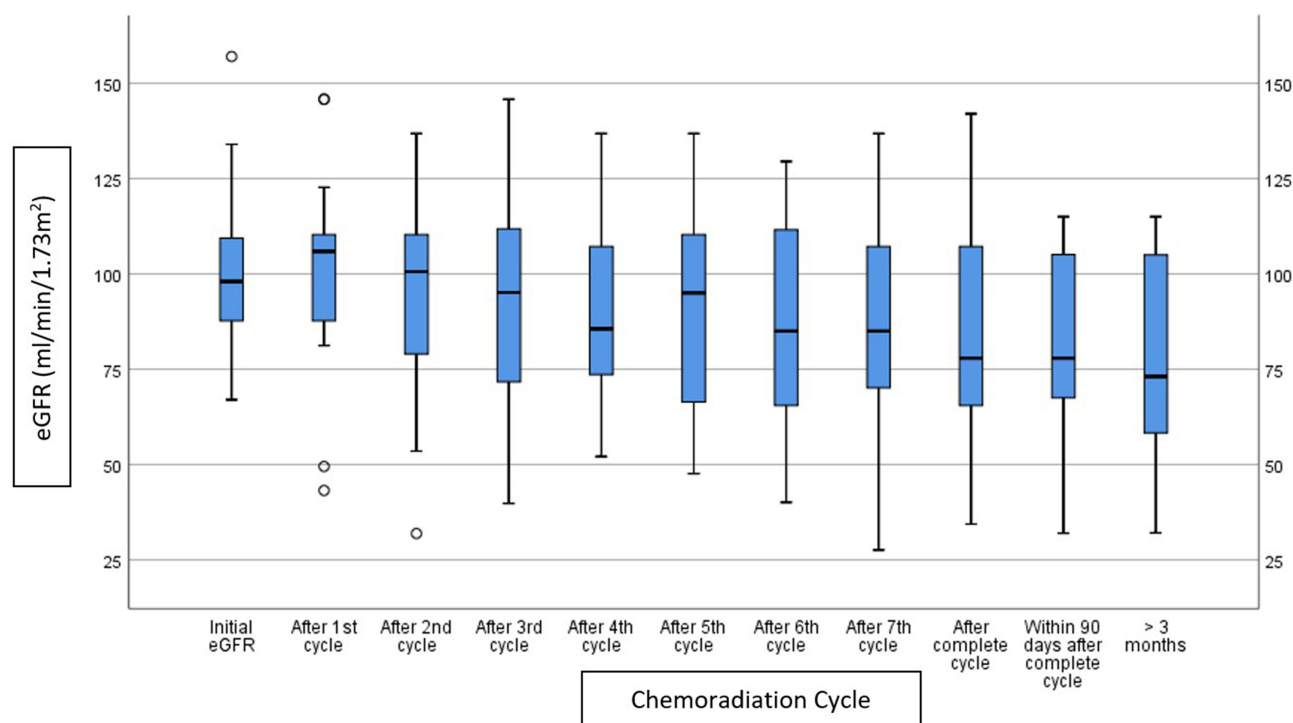**Abbreviations**: SD, standard deviation; eGFR, estimated glomerular filtration rate.

Figure 1 Mean eGFR for each chemoradiation cycle in subjects receiving >200 mg/m^2 cumulative dose of cisplatin.
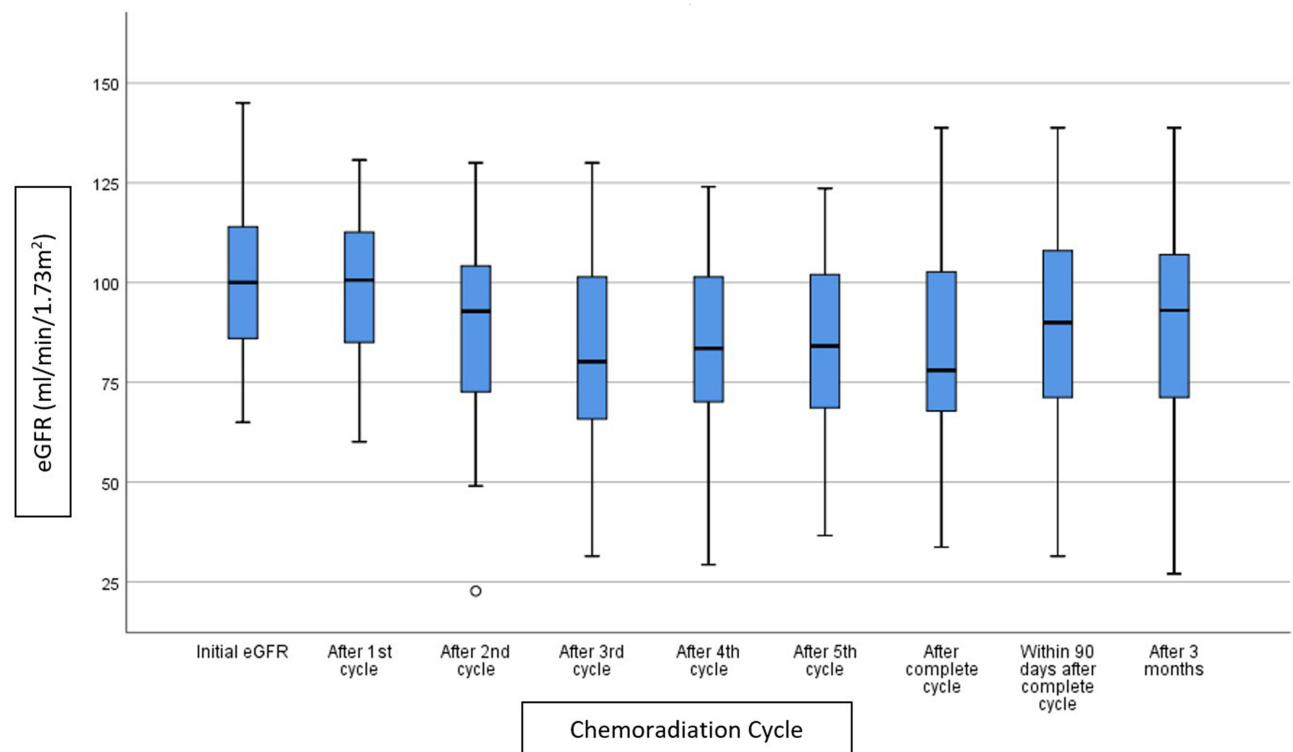

Figure 2 Mean eGFR for each chemoradiation cycle in subjects receiving ≤200 mg/m^2 cumulative dose of cisplatin.

Table 3 Occurrence of AKD After Completion of Chemotherapy Cycle

	AKD					No AKD: 74 (61.7%)	OR*	95% CI*	p
	Total: 46 (38.3%)	Grade 0: 9 (7.5%)	Grade 1: 24 (20%)	Grade 2: 12 (10%)	Grade 3: 1 (0.8%)				
Cisplatin cumulative dose									
>200 mg/m^2	28 (38.4%)	6 (8.2%)	17 (23.3%)	5 (6.9%)	0 (0%)	45 (61.6%)	1.002	0.472–2.131	0.995
≤200 mg/m^2	18 (38.3%)	3 (6.4%)	7 (14.9%)	7 (14.9%)	1 (2.1%)	29 (61.7%)			

Note: *Odds ratio and confidence interval were calculated using Total AKD vs No AKD.
Abbreviations: AKD, acute kidney disease; OR, odds ratio; CI, confidence interval.

Table 4 Potential Confounding Variables

	AKD After Complete Cycle of Chemotherapy (%)				
	Yes	No	OR	95% CI	p
	46 (38.3%)	74 (61.7%)			
Age (years)					
≥40, n (%)	30 (37.5%)	50 (62.5%)	0.900	0.413–1.959	0.791
<40, n (%)	16 (40.0%)	24 (60.0%)			
Sex					
Female, n (%)	17 (54.8%)	14 (45.2%)	2.512	1.090–5.789	0.028
Male, n (%)	29 (32.6%)	60 (67.4%)			
Hypertension					
Yes, n (%)	12 (38.7%)	19 (61.3%)	1.022	0.441–2.366	0.960
No, n (%)	34 (38.2%)	55 (61.8%)			
Mucositis					
Yes, n (%)	41 (39.4%)	63 (60.6%)	1.463	0.463–4.423	0.531
No, n (%)	5 (31.3%)	11 (68.8%)			
Initial eGFR (mL/min/1.73 m^2)					
60–90, n (%)	14 (46.7%)	16 (53.3%)	1.587	0.687–3.663	0.278
>90, n (%)	32 (35.6%)	58 (64.4%)			
Age (years)					
≥65, n (%)	2 (33.3%)	4 (66.7%)	0.796	0.140–4.526	0.796
<65, n (%)	44 (38.6%)	70 (61.4%)			
Grade 2 mucositis					
Yes, n (%)	11 (73.3%)	4 (26.7%)	5.500	1.633–18.521	**0.003***
No, n (%)	35 (33.3%)	70 (66.7%)			
Vomiting					
Yes, n (%)	18 (54.5%)	15 (45.5%)	2.529	1.114–5.739	**0.024***
No, n (%)	28 (32.2%)	59 (67.8%)			
ECOG score					
1, n (%)	34 (40.5%)	50 (59.5%)	1.360	0.600–3.083	0.461
0, n (%)	12 (33.3%)	24 (66.7%)			

Note: *Values in bold denote statistically significant results.
Abbreviations: AKD, acute kidney disease; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; CI, confidence interval.

Table 5 Crude RR and Adjusted RR with 95% CI of Cumulative Dose Towards AKD Post-Chemotherapy with Gradual Addition of Confounding Factors

Variable	RR (95% CI)	p	RR Changes with Confounding Factors
Crude RR	1.002 (0.472–2.131)	0.995	
Adjusted RR			
+Grade 2 mucositis	0.948 (0.433–2.075)	0.894	$\frac{(0.948-1.002)}{0.948} \times 100\% = 5.69\%$
+Vomiting	0.956 (0.432–2.115)	0.912	$\frac{(0.956-0.948)}{0.956} \times 100\% = 0.84\%$
+Sex	1.045 (0.463–2.359)	0.915	$\frac{(1.045-0.956)}{1.045} \times 100\% = 8.51\%$

Abbreviations: RR, relative risk; CI, confidence interval; AKD, acute kidney disease.

Analysis of Progression and Subject Recovery from AKD Post-Chemotherapy

Subjects who had AKD were observed to see whether there were further progressions or recovery. The proportions of progressions and recovery from AKD can be observed in Table 6. Furthermore, it can be seen that of all the subjects with AKD who received >200 mg/m^2 cumulative dose of cisplatin, three (10.7%) experienced recovery, while of those who received ≤200 mg/m^2 only one (5.6%) achieved recovery. Recovery in the following months can be seen in Table 6.

Of the subjects from the group that received >200 mg/m^2 cumulative dose of cisplatin who experienced AKD, 10 subjects (35.7%) progressed to CKD, while seven (38.9%) progressed to CKD from the other group (Table 7).

Discussion

In this study, the mean age of the patients with NPC was 45.08 years. The mean ages of subjects in the groups with a cumulative dose of cisplatin >200 mg/m^2 and ≤200 mg/m^2 were relatively the same. These characteristics are similar to those in another study conducted in Indonesia by Prasaja et al.[21] In contrast, in studies in other countries the subjects were older, as reported by Faig et al in the USA[32] and Driessen et al in the Netherlands,[17] where the mean ages (± standard deviation) were 54±10.8 years and 55.3±7.6 years, respectively.

In this study, there were more male patients than female patients, with a ratio of 7:3. There was a higher proportion of men than women in both groups. According to the data from GLOBOCAN 2021, head and neck cancer is more common in men than in women, with a ratio of 2–3:1.[35] A large number of men experience head and neck cancer cases; this is associated with the microendocrine milieu, which is rich in the hormone testosterone.[36]

Most of the subjects in this study had stage IVA cancer (43.3%). This is in accordance with a study by Faiza et al[37] in Western Indonesia, where most subjects were stage IVA and IVB (31.82% and 31.82%, respectively). The most common histopathological result in our study was WHO type 3 (95.8%). This is similar to a study by Adham et al,[38] which was also conducted in Indonesia. There were no significant differences in the histopathological type of cancer between patients receiving cisplatin ≤200 mg/m^2 and those receiving >200 mg/m^2.[38]

Most of the patients had good performance and nutritional status. These data are important because poor nutritional status may influence the result of the serum creatinine

Table 6 Subjects Who Experienced Recovery After AKD

	Recovery					
	Yes: 4 (8.7%)				No: 42 (91.3%)	p*
	3 mo	6 mo	12 mo	Total		
Cumulative dose of cisplatin						
>200 mg/m^2, n (%)	2 (66.6%)	1 (33.3%)	0 (0%)	3 (10.7%)	25 (89.3%)	0.545
≤200 mg/m^2, n (%)	0 (0%)	0 (0%)	1 (100%)	1 (5.6%)	17 (94.4%)	

Note: *p value between recovery and no recovery.
Abbreviations: AKD, acute kidney disease; mo, months.

Table 7 Proportions of Subjects with AKD Who Experienced Progression Towards CKD

	Progression		
	Yes: 17 (37%)	No: 29 (63%)	p
Cumulative cisplatin dose >200 mg/m^2, n (%) ≤200 mg/m^2, n (%)	10 (35.7%) 7 (38.9%)	18 (64.3%) 11 (61.1%)	0.828

Abbreviations: AKD, acute kidney disease; CKD, chronic kidney disease.

examination, affecting the eGFR values. Moreover, as many as 25.8% of the patients had hypertension. Hypertension is a known factor for kidney disease. Other comorbidities, such as diabetes mellitus, heart disease, CKD, and severe infections, have been excluded. There was no significant difference in hypertension between the two groups.

In this study, all patients had good kidney function before the administration of chemotherapy. Mean baseline eGFR was comparable with the results of the studies by Driessen et al[17] and Faig et al.[32]

Mucositis affected the fluid intake of the patients in this study. Almost all patients in this study had mucositis, mostly grade 1. However, mucositis in this study was less frequent and less severe than that in the study by Faig et al,[32] where all of the patients had mucositis, which varied from grade 1 to grade 4. This may be because the cisplatin dose in Faig's study was higher, ie, 100 mg/m^2 per cycle. It is known that cisplatin is cytotoxic to all cells, so that the greater the cisplatin dose, the greater the damage, including mucositis. Apart from mucositis, 27.5% of the patients in this study experienced vomiting.

Kidney disorder induced by cisplatin chemotherapy is characterized by several histological changes, including acute focal necrosis of the proximal convoluted tubules and collecting ducts, dilatation of the collecting tubules, and formation of urinary casts. Cisplatin has a low molecular weight and hence it is freely filtered in the glomerulus and almost entirely excreted in the urine. This drug will penetrate tubular cells and reach high concentrations in proximal tubular cells in the inner renal cortex and outer medulla. High-dose cisplatin can cause injury to the distal tubule and the collecting duct.[21]

Weekly cisplatin is a very effective chemotherapy regimen, but the risk of nephrotoxicity limits its administration. Several mechanisms are responsible for renal dysfunction following cisplatin use. These mechanisms are tubular epithelial cell toxicity, vasoconstriction in the renal microvasculature, and the proinflammatory effects of cisplatin. Exposure of tubular cells to cisplatin is followed by accumulation of the toxic compound in the tubular fluid. These toxic compounds diffuse into tubular cells, which are highly permeable, leading to tubular cell injury and cell death. This tubular epithelial cell toxicity involves various cytotoxic signaling pathways, namely p53, MAPK, and SOR. Cisplatin also causes renal vascular injury, ischemia, cell death, decreased renal blood flow, and decreased GFR. The proinflammatory effects of cisplatin are mainly mediated by the production of tumor necrosis factor (TNF)-alpha, which triggers a series of inflammatory responses.[22,29]

The results showed that the total incidence of AKD in subjects who received chemoradiation with cisplatin >200 mg/m^2 was 38.4%, slightly higher than in the study by Patimarattananan et al in Thailand,[39] which reported an AKD incidence of 27.9%. This difference is thought to be attributed to prophylactic feeding being administered to all patients in the study by Patimarattananan et al,[39] which was not provided in this study. Grade 1 AKD was more commonly discovered among subjects who received a cumulative cisplatin dose of >200 mg/m^2. The incidence of AKD in the group of subjects who received a cumulative dose of cisplatin >200 mg/m^2 was slightly higher than in those who received ≤200 mg/m^2 of cisplatin (38.4% vs 38.3%). Still, there was no statistically significant difference (p=0.995).

In this study, the measurement of renal function was performed in each chemotherapy cycle because several studies have shown variable responses to cisplatin exposure in terms of renal function. One of the studies regarding kidney recovery was conducted by Mizushima et al[40] in rats, where the creatinine value was lower in the rats that received a second cisplatin injection than the creatinine value after receiving the first injection. After the third and fourth injections, the serum creatinine value gradually increased. According to Mizushima et al, this could be due to the host defense response, where some enzymes in the renal epithelium can reduce the renal toxicity of cisplatin.[40] The study by Tezcan et al, in humans, produced similar results, where the GFR was higher after receiving the third chemotherapy session compared to the first and second chemotherapy sessions.[41] Another renal recovery survey was conducted by Sharp and Siskind, who compared the nephrotoxic effect in mice receiving a single high dose of cisplatin versus mice receiving low and repeated doses. This study found that creatinine was more significant in mice receiving cisplatin in a single

high dose. This was due to the increased necrosis caused by increased cleavage caspase-3 in mice that received cisplatin in high doses. Meanwhile, mice that received low and repeated doses tended to develop fibrosis. Inflammatory events predominantly occur at repeated low doses rather than at single high doses. This inflammation will continue in repair activities, which then develop into adaptive or maladaptive repair. Adaptive repair will result in kidney recovery, while the maladaptive repair will progress to fibrosis and lead to CKD.[42]

There is limited published research available regarding AKD. It is known that the greater the cisplatin dose per cycle, the higher the incidence of AKI, as obtained in a study by Morgan et al.[43] Furthermore, a study on AKI by Prasaja et al stated that the higher the cumulative dose, the greater the incidence of AKI.[21] The same results were obtained by Hwan Moon et al.[44] However, our study obtained different results, showing no significant difference between the cumulative dose of ≤200 m[2] and >200 mg/m^{2}, which is in line with the results of Patimarattananan et al.[39] It is stated that high doses of cisplatin will cause destruction of tubular cells directly through the necrosis pathway. In contrast, small doses of cisplatin will cause cells to experience cell death through the apoptotic pathway.[42] In the necrosis pathway, cells will experience death within a few hours, while cells will experience death within a few days in the apoptotic pathway. Hence, cells may still have time to undergo repair in small-dose administrations. The eGFR of the subjects in this study tended to decrease, similarly to Prasaja's study.[21] However, differently from Prasaja's study,[21] both groups showed improvement in the eGFR within a cycle in this study. This may indicate that there is kidney recovery in patients who have AKD.

These results showed that there were significant differences in the incidence of AKD based on sex, grade 2 mucositis, and the incidence of vomiting. However, after adjusting for confounding factors in the multivariate analysis, sex, grade 2 mucositis, and vomiting were no longer confounders.

There was no significant difference in the incidence of AKD based on age. AKD was less common in subjects aged >65 years, consistent with the study by Hrushesky et al.[45] This may be due to several factors, such as a decrease in the ability to concentrate urine and short cisplatin exposure time due to low accumulation of cisplatin in the kidney tubules in old age.[45] In addition, an animal study by Sharp and Siskind[42] found no significant difference between old and young mice in terms of renal function.

This study found that the incidence of AKD was higher in patients who had hypertension, but this difference was not significant (38.7% vs 38.2%, p=0.960), similarly to the study by Mizuno et al.[46]

In this study, AKD was more common in patients with an initial eGFR of 60–90 mL/min/1.73 m[2] than in those with eGFR >90 mL/min/1.73 m[2], but this difference was not statistically significant (46.7% vs 31.3%, p=0.278). This result is different from the studies by Loh et al[47] and Faig et al,[32] where patients with high GFR were at higher risk of developing AKI. The lack of statistical significance may be due to the limited number of subjects in our study.

There was a significant difference between the incidence of AKD in subjects with and those without grade 2 mucositis. Although, theoretically, solid food intake is preserved in patients with grade 2 mucositis, the presence of painful ulcers may impair their ability to ingest adequate fluid. This result is consistent with the results of a study by Andronesi et al,[48] which found that mucositis increases the risk of AKI.

Moreover, this study also detected no significant difference in the incidence of AKD between the cumulative cisplatin doses of ≤200 mg/m^{2} and >200 mg/m^{2}. However, a slightly higher incidence of AKD was seen in the group receiving cisplatin >200 mg/m^{2}. This may be because the group with a cumulative dose of cisplatin >200 mg/m^{2} had more mucositis (89% vs 84%), which has been proven to increase the incidence of AKD in this study.

Of the subjects with AKD who received a cumulative dose of cisplatin >200 mg/m^{2}, three (10.7%) recovered, while of the subjects who received a cumulative dose of cisplatin ≤200 mg/m^{2}, only one subject (5.6%) recovered. This result is different from the study by Patimarattananan et al,[39] where no one experienced recovery of renal function. The difference arises because subjects in Patimarattananan's study received a higher cumulative cisplatin dose, up to 300 mg/m^{2}. Another study, by Latcha et al, study also reported that none of the subjects experienced recovery; however, in that study the total cumulative cisplatin dose varied widely, with the highest dose reaching >700 mg/m^{2}.[18]

In terms of progressivity of AKD to CKD, there was no significant difference in the number of subjects who experienced progressivity in both groups in this study (38.9% vs 35.7%, p=0.879). This finding suggests that in

those who experienced AKD, the cisplatin cumulative dose does not affect the progression to CKD.

After an episode of AKI, the kidneys can repair their structures back to normal and return to function even though there appears to be severe damage. Recovery of the kidney is then initiated by repopulation of the damaged tubules by regenerating cells.[30] After much debate as to whether the cells involved in this regenerative process are endogenous tubular epithelial cells, mature renal stem cells, or bone marrow-derived stem cells, there is now increasing evidence that repopulation is primarily dependent on endogenous tubular cells, which are still viable with stem cells derived from bone marrow by a paracrine pathway through the secretion of growth factors.[31] In the kidney, adaptive repair can take place, where the condition of the kidney can return to normal or become maladaptive, which leads to the occurrence of CKD.[30,31] Our findings showed that there were no significant differences in terms of recovery of renal function and progression from AKD to CKD in patients receiving cisplatin cumulative doses of ≤200 mg/m^2 versus >200 mg/m^2.

From the above results, considerations can be added to the policy regarding the dosing of cisplatin in chemoradiation. In NPC patients, the choice of administering cisplatin dose >200 mg/m^2 is not associated with significant increase of the incidence of AKD. Results from studies by Loong et al[9] and Gundog et al[49] show that overall survival is better at doses >200 mg/m^2. From the results of those studies, administration of cisplatin with a cumulative dose >200 mg/m^2 produces better outcomes. Another study, by Peng et al,[50] compared the effect of different cumulative cisplatin doses (≥240 mg/m^2 vs <240 mg/m^2) on the long-term survival of patients with NPC receiving concurrent chemotherapy. This study stated that a cumulative cisplatin dose ≥240 mg/m^2 is an independent prognostic factor for disease-free progression in NPC patients receiving cisplatin concurrent chemoradiation.[50]

One limitation of administering high-dose cisplatin is the risk of nephrotoxicity. Our study showed that cisplatin can be administered safely at the recommended dose suggested by the guideline, without significant renal adverse effects compared to lower doses.

Beside the drug cisplatin itself, factors that affect the decline in kidney function after chemotherapy include fluid intake at home and excess fluid loss due to vomiting, which is one of the side effects of cisplatin chemotherapy. This can occur up to days 6–7 after cisplatin chemotherapy (delayed emesis), even though all subjects had received pre-chemotherapy antiemetic premedication followed by oral antiemetic drugs post-chemotherapy. Unfortunately, this study did not obtain data on the incidence of emesis at home or data on patient diuresis at home up to days 6–7 after chemotherapy owing to technical limitations in data collection.

Another limitation of this study is the retrospective design, which took data from medical records. The weaknesses of collecting data from medical records are that there are some incomplete data and there is a possibility of information bias.

Conclusion

This study found that in patients with locally advanced NPC who received cisplatin chemoradiation, there was no significant difference in the incidence of AKD, recovery of renal function, or progression of CKD between patients receiving a cumulative dose of cisplatin ≤200 mg/m^2 and those receiving >200 mg/m^2.

Ethical Approval

Ethical clearance was granted by the Ethics Committee of the Faculty of Medicine, University of Indonesia (ethical approval number: KET-718/UN2.F1/ETIK/PPM.00.02/2019). The ethics committee waived the requirement for individual patient consent because this study did not involve any intervention. Furthermore, full anonymity and confidentiality are maintained in compliance with the Declaration of Helsinki.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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