Nephrotoxicity Effects of Post-Cisplatin Paclitaxel Chemotherapy in Severe Head and Neck Tumor

Des Dwiputra Effendy[1], Soeprijadi[1]

[1]Departement of Otolaryngology, Faculty of Medicine, Universitas Airlangga (60131), Indonesia

Abstract

Background: Cisplatin-paclitaxel is a combination of chemotherapy drugs used in the treatment of head and neck malignancy. The main side effect of cisplatin is nephrotoxicity. Nephrotoxicity manifests in decreased glomerular filtration rate (GFR), increased blood urea nitrogen (BUN) and creatinine serum, and decreased magnesium and potassium serum. **Objective**: this study aimed to determine the nephrotoxicity effects of post cisplatin-paclitaxel chemotherapy in patients with malignant head and neck tumors.

Method: Patients with malignant head and neck tumor who received cisplatin-paclitaxel chemotherapy were taken consecutively and examined their GFR, BUN, creatinine, magnesium and potassium pre- and post-chemotherapy. The data were statistically analyzed whether nephrotoxicity happened post cisplatin-paclitaxel chemotherapy.

Result: Thirty five samples consisted of 24 men and 11 women. The diagnose were 25 nasopharyngeal carcinoma (71.42%), 3 of each sinonasal carcinoma and laryngeal carcinoma (8.57%), and 1 of each tongue carcinoma, parotid carcinoma, tonsillar carcinoma and MAE carcinoma (2.86%). The average of pre-chemotherapy GFR was 94.43±17.44 ml/min, average of post-chemotherapy GFR was 68.17±17.96. Mostly found decreased mild kidney function in 24 (68.57%) post chemotherapy patients.

Conclusion: There was a nephrotoxicity effects after cisplatin-paclitaxel chemotherapy treatment in patients with head and neck malignant tumors treated

Keywords: *Nephrotoxicity, Chemotherapy, Cisplatin-paclitaxel, Malignant head and neck tumor.*

Introduction

Malignant head and neck tumors are a major problem in ENT unit. Research in Dr. Soetomo General Hospital 1996 - 2000 by got 2119 patients with malignant head and neck tumors. New patients in 2009 - 2012 that underwent treatment in ENT outpatient unit Dr. Soetomo General Hospital were 1479 patients of 15867 total visits [1]. In the United States, 5% of all malignancies in 2006, was found 500,000 new cases. The majority of malignancies in head and neck (>75%) are squamous cell carcinomas, which are relatively radiosensitive. Approximately one-third still has an early stage and two-thirds are in locally advanced stage at the time of treatment [2].

Chemotherapy is one of the alternative options in malignant head and neck tumors advanced. The most commonly chemotherapy used in Lotus inpatient unit Dr. Soetomo General Hospital Surabaya is a combination of cisplatin - paclitaxel (cisplatin based), 31% of 2013 patients who received chemotherapy in 2009-2012. The use of cisplatin alone reached 55% in combination with other regimens in chemotherapy of head and neck malignancy [3].

The nephrotoxicity of cisplatin had been recognized since 25 years ago, but since no other drug had been found to be as effective and less toxic, cisplatin continues to be used. Cisplatin nephrotoxicity in experimental animals

Corresponding author:
Bakti Surarso
Departement of Otolaryngology, Faculty of Medicine, Universitas Airlangga (60131), Indonesia
E-mail & phone: unairbakti@gmail.com, +62315020251

was first discovered in 1971 showing a histopathologic change in the form of acute tubular necrosis accompanied by azotemia. Acute kidney failure due to cisplatin occurs 14-100% of patients, with varied incidents according to dose. Renal insufficiency was found in 20-30% of patients. Onset of renal insufficiency usually occured on day 3 to 5 after cisplatin consumption, which was indicated by an increase of creatinine serum and BUN levels. Hypomagnesemia, hypocalcemia, hypophosphatemia and hypokalemia commonly happened, especially after repeated doses of cisplatin characterized by decreased GFR [4].

Cisplatin chemotherapy led to a significant increase of creatinine (44.87%), and an insignificant increase of BUN (8.71%) compared to before treatment. At electrolyte serum examination there was a significant decrease of magnesium (7.18%), potassium (6.44%), phosphate (16.44%) and calcium (5.94%), significant increase of sodium (1.35%) and chloride (3.85%) compared to before treatment [5]. Another study in India reported 15 patients (20.5%) with acute renal injury characterized by a significant increase in creatinine serum levels within the first 48 hours after cisplatin chemotherapy [6]. A study in the United States comparing nephrotoxicity increased in 11 patients receiving cisplatin-paclitaxel combination chemotherapy with 14 cisplatin-treated patients alone had decreased creatinine clearance in 9 patients (81%) who received cisplatin-paclitaxel combination and only 4 (29%) of 14 patients treated with cisplatin alone [7].

Method

The samples were taken by consequtive sampling. The independent variable in this study was cisplatin-paclitaxel and dependent variables were nephrotoxicity effects assessed by GFR, BUN, serum creatinine, magnesium (Mg^{++}), potassium (K^{+}) blood plasma [8].

Administration of cisplatin-paclitaxel is the process of incorporating chemotherapy drugs consisting of cisplatin and paclitaxel into the body. The dose of cisplatin in this study was 100 mg/m^2 of body surface and paclitaxel dose in this study was 200 mg/m^2 of body surface. The effect of nephrotoxicity is a condition that indicates renal impairment due to chemicals characterized by decreased GFR, increased BUN and creatinin, and decreased Mg^{++} and K^{+} in 10 days' post-cisplatin-paclitaxel chemotherapy [9]. The data collected in sheet was arranged in table then analyzed descriptively and analytically. Normal distribution test on the data used Shapiro-Wilk, while the analytical test used t 2 paired samples if the data were ratio scale and normal distribution, if the requirement was not met, it would use Wilcoxon test [10].

Results

It was obtained 35 samples with age distribution of 17-25 years (8.57%), 26-35 years (17.14%), 36-45 years (25.71%), 46-55 years (42.86%), 56-65 years (5.72%). Sex distribution obtained 24 males (68,57%) and 11 females (31,43%). Ethnicity distribution obtained Java was 28 (80%), Madura was 5 (14.28%), Batak and Dayak was 1 each (2.86%). The diagnosis obtained were 25 nasopharyngeal carcinoma (71.42%), 3 of each sinonasal carcinoma and laryngeal carcinoma (8.57%), and 1 of each tongue carcinoma, parotid carcinoma, tonsillar carcinoma and MAE carcinoma (2.86%).

GFR examination was done pre-chemotherapy and post-chemotherapy of cisplatin-paclitaxel. The average of pre-chemotherapy GFR was 94.43±17.44 ml/min, average of post-chemotherapy GFR was 68.17±17.96 ml/min (Table 1). Decreased mild kidney function with GFR values range of 56-90 ml/min was 24 (68.57%) patients. Decreased moderate kidney function with GFR value range of 35-55 ml/min was 6 (17.14%) patients. Severe kidney dysfunction patients with GFR <35 ml/min was 2 (5.72%) (Table 2).

The average of pre-chemotherapy BUN level was 9.11±3.27 mg/dl and post-chemotherapy BUN level was 14.94±13.88 mg/dl (table 3). The average of pre-chemotherapy creatinin serum levels was 0.84±0.15 mg/dl and post-chemotherapy creatinin serum level was 1.20±0.54 mg/dl (Table 3). The average of pre-chemotherapy Mg^{++} levels was 2.20±0.31 mg/dl and post-chemotherapy Mg^{++} level was 1.93±0.35 mg/dl (Table 3). Patients with hypomagnesium in post cisplatin-paclitaxel chemotherapy were 8 (22.86%), 26 (74.28%) patients had normal Mg^{++} levels, and 1 (2.86%) patient had hypermagnesium (Table 4). The average of pre-chemotherapy K^{+} level was 4.08±0.42 mmol/l, while post chemotherapy was 3.55±0.52 mmol/l (Table 5).

Table 1. The result of GFR examination pre and post cisplatin-paclitaxel chemotherapy.

Parameter	Pre-chemotherapy		Post-chemotherapy		P
	Average	SD	Average	SD	
GFR	94.43	17.44	68.17	17.96	0.000

Table 2. Frequency of renal function decrease post cisplatin-paclitaxel chemotherapy

Renal function decrease	**Total**	**%**
Mild Moderate Severe	24 6 2	68.57 17.14 5.72
Total	32	91.43

Table 3. Result of Laboratory finding of pre and post cisplatin-paclitaxel chemotherapy

Parameter	**Pre-chemotherapy**		**Post-chemotherapy**		**P**
	Average	**SD**	**Average**	**SD**	
BUN	0.84	0.15	1.20	0.54	0.000
Creatinin Serum	0.84	0.15	1.20	0.54	0.000
Mg^{++}	2.20	0.31	1.93	0.35	0.001

Table 4. Hypomagnesium frequency pre and post cisplatin-paclitaxel chemotherapy

Mg^{++}	**Total**	**%**
Hypomagnesium Normal Hypermagnesium	8 26 1	22.86 74.28 2.86
Total	35	100.00

Table 5. Result of K^+ pre and post cisplatin-paclitaxel chemotherapy

Parameter	**Pre- chemotherapy**		**Post-chemotherapy**		**Changes**		**T**	**p**
	Average	**SD**	**Average**	**SD**	**Average**	**SD**		
K+	4.08	0.42	3.55	0.52	0.53	0.53	5.906	0.000

Discusion

Cisplatin is a strong cellular toxin especially in the low chloride state. In the cell, the chloride atoms in cisplatin will be replaced by water molecules. This hydrolysis product is believed to be an active species that reacts with glutathione in cytoplasm and the DNA nucleus of renal tubular cell. More than 50% of these drugs are excreted in the urine within the first 24 hours after administration, platinum concentrations reach the renal cortex faster than plasma or other organs. Cisplatin primarily damages S3 segment of the proximal tubules causing a decrease in GFR [11].

Factors that increase the risk of nephrotoxicity include female, old age, smoking, hypoalbuminemia, and renal insufficiency. Age affects renal function because along with age it will also be followed by decreased renal function [12]. Patients (>40 years) have a greater risk of decreased renal function. This is caused by nephron loss at that age. Decreased renal function estimation on the basis of each decade increase is about 10 ml/min/1.73 m^2. At the age of the fourth decade or 40 years there has been a decline in renal function about 10% of renal ability. Patients in advanced age are more susceptible to get drug side effects due to their physiological condition that has decreased [13].

Cisplatin nephrotoxicity can occur in a variety of signs and symptoms, one of the most commonly found is acute renal injury with the most common incidence of renal insufficiency. The onset of renal insufficiency occurs a few days after cisplatin consumption, which is indicated by increased creatinine serum and BUN levels. Cisplatin can cause damage to the renal blood vessels resulting in ischemia that may interfere with renal blood perfusion and consequently an increase in creatinine serum [14]. Creatinine serum will increase significantly after 5 days of cisplatin administration. There will be a change in the partial glomerular atrophy of some tubular cells. The distal and proximal tubules exhibit partial degeneration and destruction of epithelial cells. Increased creatinine serum may be the final indicator of renal injury due to cisplatin chemotherapy because renal failure can occur without increase creatinine serum [15].

Hypomagnesemia is one of clinical manifestations that occur in patients who received cisplatin chemotherapy. Persistent exhalation of magnesium as a result of decreased magnesium levels indicates that hypomagnesemia occurs due to renal impairment in reabsorbing magnesium [4]. Cisplatin causes magnesium receptors damage in the ascending branch of Henle curve and distal tubules, causing tubular cell necrosis resulting in disruption of magnesium reabsorption mechanism. It was found 1 (2.86%) patient who experienced post-chemotherapy hypermagnesemia. Hypermagnesemia is a rare condition except in renal failure or after parenteral Mg^{++} administration. This condition can cause central nervous system depression as well as heart function and sometimes hypermagnesemia itself may be an indication for dialysis [16].

Hypokalemia is a common electrolyte disorder occurring during cisplatin treatment, causing by increased renal reabsorption ability in response to reduced potassium absorption. Hypomagnesium can also cause damage of Mg^{++} dependent Na, K-ATPase due to high loss of sodium in cells, if it was combined with a decrease in renal potassium causing hypokalemia [17]. The results showed a significant decrease in glomerular filtration rate (GFR), significant increase in blood urea nitrogen (BUN) levels, significant increases in creatinine serum levels, significant decreases in magnesium (Mg^{++}), and significant decrease in potassium (K^{+}) levels. Thus the hypothesis of this study was proven [7].

Conclusion

There was a nephrotoxicity effect of 27,80% glomerulus filtration rate (GFR), increased blood urea nitrogen (BUN) level of 63.94%, increased serum creatinine of 41.80%, decrease magnesium (Mg^{++}) level of 12.30%, decreased potassium (K^{+}) level of 13% after cisplatin-paclitaxel chemotherapy treatment in patients with malignant head and neck tumors.

Ethical Clearance: This research process involves participants in the survey using a questionnaire that was accordant with the ethical research principle based on the regulation of research ethic committee. The present study was carried out in accordance with the research principles. This study implemented the basic principle ethics of respect, beneficence, nonmaleficence, and justice.

Conflict of Interest: The author reports no conflict of interest of this work.

Source of Funding: This study is paid by authors'money only.

References

1. Sari GM. THE EFFECT OF LONG TERM ADMINISTRATION OF GLUCOCORTICOID TO BONE LINING CELLS APOPTOSIS. Folia Medica Indones. 2017;52(4):251–7.
2. Fahmi MZ, Haris A, Permana AJ, Wibowo DLN, Purwanto B, Nikmah YL, et al. Bamboo leaf-based carbon dots for efficient tumor imaging and therapy. RSC Adv. 2018;8(67):38376–83.
3. Damayanti A, Werdiningsih I. Classification of tumor based on magnetic resonance (MR) brain images using wavelet energy feature and neuro-fuzzy model. In: Journal of Physics: Conference Series. IOP Publishing; 2018. p. 12027.
4. Bonaventura A, Vecchié A, Carbone S, Montecucco F, Abbate A. Comment on Hypoglycemia and hyperglycemia are risk factors for falls in the hospital population by Berra et al. Acta Diabetol. 2019;1–2.
5. Hadiyanti N, Hasmono D, Islam MS. Analysis of Differences of Serum Thromboxane B2 Level after Taking Acetosal in Acute Thrombotic Stroke with Diabetes Mellitus and Non-Diabetes Mellitus. Folia Medica Indones. 2018;54(1):53–8.
6. Veen G, Giltay EJ, DeRijk RH, van Vliet IM, van Pelt J, Zitman FG. Salivary cortisol, serum lipids, and adiposity in patients with depressive and anxiety disorders. Metabolism. 2009;58(6):821–7.
7. Schirmer SH, Sayed MMYA, Reil J-C, Ukena C, Linz D, Kindermann M, et al. Improvements in Left Ventricular Hypertrophy and Diastolic Function Following Renal Denervation. J Am Coll Cardiol. 2013;63(18):1916–23.
8. Efendi F, Nursalam N, Ulfiana E, Fauziningtyas R. Situational Analysis of Career Choices among Indonesian Nurses Returnees. Indian J Public Heal Res Dev. 2019;10(2).
9. Nursalam N, Octavia M, Tristiana RD, Efendi F. Association between insomnia and social network site use in Indonesian adolescents. In: Nursing forum. Wiley Online Library; 2019. p. 149–56.
10. Bramantoro T, Karimah N, Sosiawan A, Setijanto RD, Berniyanti T, Palupi R, et al. Miswak users' behavior model based on the theory of planned behavior in the country with the largest Muslim population. Clin Cosmet Investig Dent. 2018;10:141.
11. Jenei-Lanzl Z, Meurer A, Zaucke F. Interleukin-1β signaling in osteoarthritis–chondrocytes in focus. Cell Signal. 2018;
12. Vellas BJ, Wayne SJ, Romero LJ, Baumgartner RN, Garry PJ. Fear of falling and restriction of mobility in elderly fallers. Age Ageing. 1997;26(3):189–93.
13. Li Y, Zhang J, Liu H, Yuan J, Yin Y, Wang T, et al. Curcumin ameliorates glyoxylate-induced calcium oxalate deposition and renal injuries in mice. Phytomedicine. 2019;61:152861.
14. Koutny LB, Schmalzing D, Taylor TA, Fuchs M. Microchip electrophoretic immunoassay for serum cortisol. Anal Chem. 1996;68(1):18–22.
15. Pan Y, Cai X, Jing J, Meng X, Li H, Wang Y, et al. Stress hyperglycemia and prognosis of minor ischemic stroke and transient ischemic attack: the CHANCE study (clopidogrel in high-risk patients with acute nondisabling cerebrovascular events). Stroke. 2017;48(11):3006–11.
16. Milan A, Zocaro G, Leone D, Tosello F, Buraioli I, Schiavone D, et al. Current assessment of pulse wave velocity: comprehensive review of validation studies. J Hypertens. 2019;
17. Pimentel GD, Lira FS, Rosa JC, Oller do Nascimento CM, Oyama LM, Harumi Watanabe RL, et al. High-fat fish oil diet prevents hypothalamic inflammatory profile in rats. ISRN Inflamm. 2013;2013.