ANALYSIS OF NACL-MANNITOL HYDRATION ON RENAL FUNCTION OF HEAD AND NECK CANCER PATIENTS RECEIVING HIGH-DOSE CISPLATIN CHEMOTHERAPY COMBINATION

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ABSTRAK

*Cisplatin (cis-diamminedichloroplatinum(II), CDDP) merupakan salah satu obat sitostatika golongan platinum yang efektif pada terapi kanker solid, salah satunya adalah kanker kepala dan leher. Efek samping yang perlu diperhatikan pada penggunaan cisplatin adalah nefrotoksitas akut atau kronik. Akumulasi cisplatin di sel epitel tubular proximal mencapai 5 kali konsentrasi serum. Paparan platinum pada sel tubular ginjal membentuk suatu kompleks sehingga menstimulasi faktor-faktor inflamasi yang mengakibatkan apoptosis dan nekrosis sel. Nefrotoksisitas cisplatin dapat dicegah dengan modifikasi metode pemberian atau hidrasi yang agresif. Penelitian ini bertujuan menganalisis efek hidrasi NaCl-Manitol terhadap fungsi ginjal (BUN, serum kreatinin, eClCr) pasien kanker kepala leher yang mendapat kemoterapi cisplatin dosis 100 mg/m2 yang dikombinasi dengan 5FU atau paclitaxel. Metode penelitian ini adalah observasi kohor pada 16 pasien yang mendapat regimen kemoterapi cisplatin dosis 100 mg/m2 baik yang dikombinasi dengan paclitaxel atau 5FU yang sesuai kriteria inklusi BUN 7-18 mg/dl serta serum kreatinin < 2 mg/dl pada siklus berapapun. Fungsi liver, jantung, ginjal dan paru pasien adalah normal. Dilakukan pemeriksaan baseline (pre-kemoterapi) serta minggu ke-3 post-kemoterapi yaitu BUN, serum kreatinin, dan perhitungan eClCr. Pasien mendapatkan hidrasi infus hidrasi NaCl dan manitol. Dari hasil penelitian dapat disimpulkan bahwa pemberian hidrasi NaCl-Manitol sudah cukup adekuat yang ditunjukkan oleh hasil nilai BUN dan serum kreatinin dalam batas normal yaitu pada kelompok kombinasi kemoterapi cisplatin dan 5FU, nilai BUN pre-hidrasi (11,99 + 4,62) mg/dl dan nilai BUN post-hidrasi (12,14 + 4,74) mg/dl serta nilai serum kreatinin pre-hidrasi (0,97 + 0,34) mg/dl dan nilai serum kreatinin post-hidrasi (1,02 + 0,37) mg/dl. Sementara itu pada kelompok kombinasi kemoterapi cisplatin dan paclitaxel, nilai BUN pre-hidrasi (10,19 + 2,58) mg/dl dan nilai BUN post-hidrasi (10,43 + 2,31) mg/dl serta nilai serum kreatinin pre-hidrasi (0,95 + 2,89) mg/dl dan nilai serum kreatinin post-hidrasi (0,98 + 0,26) mg/dl.**(FMI 2017;53:64-74)***

Kata kunci: *Hidrasi, Cisplatin, Nefrotoksisitas, Serum Kreatinin, BUN*

ABSTRACT

*Cisplatin is one of platinum cytostatic drug for the medication of solid cancers, one of which is head and neck cancer. Adverse event that resulted during drug treatment was acute or chronic nephrotoxicity. Cisplatin concentration in proximal tubular epithelial cells is about 5 times the serum concentration. Platinum exposure on renal tubular cells bonding covalent complex which stimulate production of inflammatory factors that lead to apoptosis and necrosis cell. Cisplatin nephrotoxicity can be prevented by aggressive hydration or alternate method of administration. The aim of this study was to analyze the effectiveness of NaCl-Mannitol hydration on renal function of head and neck cancer patients receiving cisplatin 100 mg/m2 chemotherapy combination with 5FU or paclitaxel. This was a cohort, prospective, and observational study to analyze renal function of head and neck cancer patients receiving cisplatin 100 mg/m2 chemotherapy combination with 5FU or paclitaxel. Inclusion criteria were BUN 7-18 mg/dl and serum creatinine < 2 mg/dl of any cycle. All patients received infuse NaCl-Mannitol hydration with term that provided in Surgeon Departement of Dr. Soetomo General Hospital. Data obtained were BUN, SCr, and eClCr Cockroft-Gault, each was measured pre- and post-hydration. In cisplatin and 5FU chemotherapy combination value BUN pre-hydration (11,99 + 4,62) mg/dl, value BUN post-hydration (12,14 + 4,74) mg/dl and value serum creatinine pre-hydration (0,97 + 0,34) mg/dl, value serum creatinine post-hydration (1,02 + 0,37) mg/dl. Meanwhile to the combination of cisplatin and paclitaxel chemotherapy, value BUN pre-hydration (10,19 + 2,58) mg/dl, value of BUN post-hydration (10,43 + 2,31) mg/dl and value of serum creatinine post- hydration (0,98 + 0,26) mg/dl. In conclusion, NaCl-Mannitol hydration administration is adequate which is shown by BUN and serum creatinine in pre- and post-hydration data within normal limits. **(FMI 2017;53:64-74)***

Keywords: *hydration, cisplatin, nephrotoxicity, serum creatinine, BUN*

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INTRODUCTION

Head and neck cancer is a cancer that arises from the surface of mucosal cells in the head and neck region and is largely a squamous cell. The incidence of head cancer of the neck exceeds half a million cases each year and in the United States in 2006 reported 40,500 cases of head cancer of the neck (Skeel, 2007; Vokes, 2010). There

were 36,500 new cases and 7,900 deaths estimated in the United States in 2010 caused by oral cavity cancer and pharyngeal cancer (Pfister et al., 2011). In Indonesia, the National Cancer Registry puts head and neck cancer at the fourth of the top ten malignancies in men and women (Wiliyanto, 2006).

Therapy for head and neck can be surgical, radiation and chemotherapy. Single therapy with radiation or surgery is generally recommended for 30% to 40% of patients with early-stage cancer (stage I or II). At a later stage, chemoradiation (radiation along with chemo-therapy) or combination chemotherapy (Pfister et al., 2013) may be used. According to BC Cancer Agency (BCCA), the use of single chemotherapy has not been proven to remove cancer cells, but when used in conjunction with radiation has been shown to improve disease control and improve the quality of life of head and neck cancer patients (BCCA, 2008).

Cisplatin (cis-diamin dichloro platinum (II)/CDDP) is one of the most effective and potent platinum cytostatics in solid cancer therapy. The side effects of cisplatin in the form of nephrotoxicity, both acute and chronic renal insufficiency, are a major consideration in providing this therapy (BCCA, 2008).

Cisplatin is eliminated by urine of> 90% and as much as 25% is excreted within the first 24 hours after administration. The concentration of cisplatin in proximal tubular epithelial cells reached 5 times the serum concentrations (Stewart et al., 1985; Kuhlmann et al., 1997; Yao et al., 2007). The accumulation of large cisplatin in the kidney is what can induce the occurrence of nephrotoxicity (Arany & Safirstein, 2003; Yao et al., 2007). Exposure to renal tubular cells forms a complex that results in cell damage or death. This stimulates the production of inflammatory factors that exacerbate the damage. Cisplatin also affects renal vascularization resulting in decreased blood flow and ischemia resulting in decreased Glomerular Filtration Rate (GFR) (Pabla & Dong, 2008). The recovery of renal function takes between 2 - 4 weeks (Miller et al., 2010). A study suggests that the incidence of nephrotoxicity can occur in about 50-75% of patients receiving cisplatin chemotherapy (Cornelison & Reed, 1993; Zhang et al., 2006). In addition, about 20-30% of patients were also found to experience signs of acute kidney injury (AKI (Miller et al., 2010).

Since the onset of use, cisplatin nephrotoxicity is known to be dose-related, cumulative, and generally reversible, with effects primarily on the decrease in glomerular filtration rate (GFR) and renal blood flow (RBF) clinically evaluated by increased serum creatinine (SCr) and blood Urea nitrogen (BUN) which affects the decrease in creatinine clearance (ClCr). Increased SCr and BUN can be detected within 6-7 days after cisplatin administration and occurs for approximately 3 weeks. In addition, acute nephrotoxicity is also characterized by decreased mitochondrial function, decreased ATPase activity; Changes in cell cation composition, transport solute interruption; As well as electrolyte disturbances in the form of sodium, magnesium, potassium, calcium, and persistent water loss (Cornelison & Reed, 1993; Tiseo et al., 2007; Arunkumar et al., 2011).

Bitran et al conducted a study that looked at the effect on the kidney as a result of single cisplatin dosage of 30-50 mg/m2 with patients of various cancers. The study showed that 14 patients who met the inclusion criteria were known to experience severe proximal tubular dysfunction characterized by increased excretion of calcium, magnesium and amino acids in urine (Bitran et al., 1982). Another study was conducted by Arunkumar et al by observing BUN, serum creatinine, electrolytes in several cancer patients of different types but at stage IIA to stage IVA who received a 40-50 mg/m2 cisplatin chemotherapy regimen. Observations made during these 4 cycles showed patients receiving cisplatin chemotherapy doses of 40-50 mg/m2 experienced hypomagnesemia, hypokalemia, hypocalce-mia, hypopospatemia and increased BUN and serum creatinine (Arunkumar et al., 2011). Kidera et al also conducted a multivariate analysis study to determine the effect of cisplatin on the kidney with serum creatinine parameters. Cisplatin is given at doses> 60 mg/m2. The results of this study note that of 402 patients, there were 127 patients experiencing nephrotoxicity characterized by increased serum creatinine (Kidera et al., 2014).

Cisplatin nephrotoxicity may be prevented by modification of aggressive administration methods, hydration, drug administration or nephroprotective substances and the development of other platinum analogs that improve their therapeutic index (Vacher, 2008). The infusion of sodium chloride (NaCl) in certain amounts becomes the main strategy of reducing the effects of cisplatin nephrotoxicity (Miller, 2010). Various hydration regimens that can be used include infusion of NaCl, hypertonic saline infusion, with the addition of mannitol or furosemide to induce diuresis (BCCA, 2008).

Mannitol is an osmotic diuretic that is actively filtered by the glomerulus and is not reabsorbed to cause water withdrawal and trigger fluid diuresis. The presence of water withdrawal by mannitol can lead to an increase in urine volume. Furthermore, the condition causes an increase in urine flow rate and contact time between the fluid and tubular epithelium decreased so as to reduce reabsorption of water and salt (Katzung et al., 2009).

In addition to mannitol, furosemide is one of the diuretics that can be used as a hydration regimen. Furosemide increases the water and salt expression. Furosemide is eliminated in the kidneys and infiltrated by the glomerulus. Furosemide inhibits NAKCC2 (Na/K/2Cl) which is a tranporter in the thick ascending limb (TAL) in the loop of henle. The presence of resistance to this transporter causes a decrease in NaCl reabsorption and a positive lumen potential decrease in K +. The existence of these conditions leads to an increase in excretion of magnesium and calcium which, if it occurs continuously, can lead to hypomagnesemia and hypocalcemia conditions. This hypomagnesemia and hypocalcemia conditions can be prevented or reduced by administering furosemide along with NaCl infusion (Katzung et al., 2009). In addition, the use of high-dose furosemide (1-3.4 grams/day) may increase the risk of muscle oxicity. Furosemide secreted in the kidneys and high doses can increase serum concentrations in patients with AKI (Ho et al., 2006).

The administration of hydration fluid and diuretics in some protocols includes the addition of Electrolytes of Potassium Chloride (KCl) and Magnesium Sulfate (MgSO4) to balance the electrolyte balance as a manifestation of renal reabsorption disorders. The amount of hydration, diuretics and doses of electrolyte administered depends on the dose of cisplatin (mg/m2) described (BCCA, 2008).

The non-comparative study by Hayes is the first study to observe hydration with diuretics mannitol in patients receiving cisplatin chemotherapy. Although in this study the definition of nephrotoxicity was not clearly stated, from 52 patients receiving cisplatin doses of 3-5 mg/kg, 42 patients showed a temporary increase in serum creatinine with levels <2.0 mg/dL. The remaining ten patients showed serum creatinine levels> 2.0 mg/dL of which 9 had renal impairment prior to receiving chemotherapy making them at high risk for nephrotoxic effects. A prospective, randomized, phase 2 study in 33 patients randomized by Al-Sarraf et al evaluated the effect of renal toxicity on the administration of high-dose cisplatin (100 mg/m2) accompanied by single hydration compared with hydration with the use of mannitol. The incidence of nephrotoxicity in the single hydration group was 39% compared with the hydration and mannitol group of 32% (Al-Sarraf et al, 1982).

Sufficient hydration at the time of administration of cisplatin (up to 12 hours thereafter) will induce diuresis of at least 100 mL/hr. If within 3 hours of urine production does not reach 300 mL then hydration fluid is increased to 300 mL/h for 3 h and if urine production <300 mL in the next 3 h period can be added diuretic furosemide 1x20 mg to induce diuresis. Evaluation of renal function of the patient is done routinely before cisplatin chemotherapy of the next cycle through serum BUN laboratory tests, creatinine serum or creatinine clearance, and urine 24 hours. From the serum creatinine data it can be estimated that glomerular filtration rate (GFR) and creatinine clearance through the Modified of Diet in Renal Disease (MDRD) or Cockcroft-Gault formula are used as a modified dose of therapy calculations when there are signs of renal impairment. Serum creatinine can be examined on days 3 - 5 after cisplatin administration to determine an acute increase in serum creatinine (Vacher, 2008).

Hydration method applied in Head and Neck Surgery RSUD Dr. Soetomo Surabaya in head and neck cancer patients who received a combination of high doses of cisplatin chemotherapy using NaCl and Mannitol hydration. Volume of hydration given in Head and Neck Surgery is NaCl 3350 ml and Manitol 500 ml. The volume of hydration is the total volume administered to the patient in a single cycle of chemotherapy. The success of hydration is assessed from the production of urine contained >100 ml/h which is expected to reduce the risk of occurrence of nephrotoxicity. Until now the hydration has not been evaluated in depth. This study is a prospective observational study by analyzing the hydration of NaCl-Mannitol in head neck cancer patients who received a combination of high-dose cisplatin chemotherapy by observing renal function (seen from laboratory data BUN and serum creatinine) pre- and post-chemotherapy.

MATERIALS AND METHODS

The method of this study was cohort observation in 16 patients receiving cisplatin chemotherapy dose of 100 mg/m2 either combined with paclitaxel or 5FU according to inclusion criteria of BUN 7-18 mg/dl and serum creatinine <2 mg/dl in any cycle. The liver, heart, kidney and lung function of the patient is normal. The study was conducted in IRNA Surgery and Chemotherapy Room of Soekardja Dr. Soetomo Surabaya from December 2015 to April 2016. A baseline (pre-chemotherapy) and post-chemotherapy 3-week, BUN, serum creatinine, and eClCr calculations were performed. Patients get hydration according to the established protocol in IRNA Surgery RSUD Dr. Soetomo is a hydration infusion of NaCl and mannitol.

RESULTS

There were 20 patients consisting of 16 patients who met the inclusion criteria, 3 excluded patients, and 1 patient dropped out. Patients excluded because the

patient had abnormal liver and kidney function, and 1 patient dropped out for not performing chemotherapy on a predetermined schedule. Of 16 patients who met the inclusion criteria, hydration frequency was found 44 times in cisplatin and 5FU chemotherapy regimen and hydration frequency 21 times in cisplatin and paclitaxel chemotherapy regimens.

In Table 1. It is possible to know the characteristics of the samples categorized by age, weight, gender, head neck type, chemotherapy combination regimen type, chemotherapy cycle, hydration frequency, average BUN, serum creatinine, and eCrCl Cokroft-Gault Pre-hydration. Based on Table 1, the baseline study (Pre-Hydration) data is recorded and the recording of BUN value, serum creatinine and eClCr Cockroft-Gault initial patient is given hydration. For baseline BUN baseline values were 11.99 + 4.62 in patients with cisplatin and 5FU chemotherapy and 9.28 + 3.79 in patients with cisplatin and paclitaxel chemotherapy. The mean serum creatinine values were 0.97 + 0.34 for patients with cisplatin and 5FU chemotherapy and 1.87 + 2.89 in patients with cisplatin and paclitaxel chemotherapy. On the average data value of eClCr Cockroft-Gault baseline was 61.43 +18.60 in patients with cisplatin and 5FU chemotherapy and 71.58 + 15.38 in patients with cisplatin and paclitaxel chemotherapy. The results of BUN data analysis, serum creatinine, and the estimated GFR of post-hydration can be seen in Tables 2 and 3. The results showed an increase in BUN, serum creatinine, and post-hydration eClCr decrease.

Table 1. Characteristics of the sample

Characteristics	Total Patients (n=16)	%	Mean (Range)
Age (Year)			
21-30	0	0	
31-40	3	19	
41-50	3	19	
51-60	6	37	
61-70	4	25	
Rata-rata			53.13 ± 10.36 (31-68)
Body weight (Kg)			
Rata-rata			52.25 ± 6.89 (39-65)
Sex			
Male	9	56	
Female	7	44	
Types of Head-Neck Cancer			
Squamous cell carcinoma	3	18	
Nasopharyngeal cancer	8	50	
Gingival cancer	2	13	
Parotid cancer	1	6	
Tongue cancer	2	13	
Types of Chemotherapy Combination Regiments			
Cisplatin + Paclitaxel	6	38	
Cisplatin + 5FU	10	62	
Chemotherapy Cycles			
Cycle I to II	1	6	
Cycle I to III	1	6	
Cycle I to IV	1	6	
Cycle I to VI	11	69	
Cycle IV to VI	2	13	
Hydration Frequency			
Frequency 1x	1	6	
Frequency 2x	3	19	
Frequency 3x	1	6	
Frequency 5x	11	69	
BUN (mg/dL) Pre-Hydration			
BUN in combination cisplatin + 5FU			11.99 ± 4.62 (5-32)
BUN in combination cisplatin + paclitaxel			10.19 ± 2.58 (7-11)
Creatinine Serum (mg/dL) Pre-Hydration			
SCr in combination cisplatin + 5FU			0.97 ± 0.34 (0.5-1.9)
SCr in combination cisplatin + paclitaxel			0.95 ± 2.89 (0.7-1.9)
eClCr *Cockroft-Gault* (ml/menit) Pre-Hydration			Mean (Range)
eClCr in combination cisplatin + 5FU			61.43 ± 18.60 (38.80-135.7)
eClCr in combination cisplatin + paclitaxel			71.58 ± 15.38 (60.21-105.61)

Table 2. BUN examination results, serum creatinine, eClCr Cockroft-Gault Pre- and Post-Hydration with cisplatin chemotherapy regimen

Patient's Initial	Cycles (n=44)	Pre			Post		
		BUN (mg/dl)	SCR (mg/dl)	E ClCr CG (ml/min)	BUN (mg/dl)	SCR (mg/dl)	E ClCr CG (ml/min)
Mr. Ta	I	18	1.1	55.15	23	1.6	37.92
	II	23	1.6	37.92	19	1.3	46.67
Mr. Tar	I	10	0.9	77.4	16	1.0	69.6
	II	16	1.0	69.6	9	1.0	69.6
	III	9	1.0	69.9	10	1.1	63.31
	IV	10	1.1	63.31	9	1.0	69.6
	V	9	1.0	69.6	11	0.9	77.4
Ms. Su	I	8	0.5	109.08	11	0.7	77.92
	II	11	0.7	77.92	11	0.5	109.08
	III	11	0.5	109.08	10	0.5	109.08
	IV	10	0.5	109.08	11	0.7	77.92
	V	11	0.7	77.92	11	0.7	77.92
Mr. Ya	I	12	1.1	58.08	11	0.9	71.00
	II	11	0.9	71.00	11	1.0	58.08
	III	11	1.0	58.08	13	0.7	91.27
	IV	13	0.7	91.27	10	1.0	58.08
	V	10	1.0	58.08	11	0.9	71.0
Ms. P	I	12	0.9	66.67	13	1.0	51.00
	II	13	1.0	51.00	10	0.9	66.67
	III	10	0.9	66.67	11	0.9	66.67
	IV	11	0.9	66.67	9	1.0	51.0
	V	9	1.0	51.0	10	1.1	46.36
Mr. E	I	18	1.2	52.50	32	1.8	35.00
	II	32	1.8	35.00	16	1.6	39.38
	III	16	1.6	39.38	12	1.9	33.16
	IV	12	1.9	33.16	12	1.9	33.16
	V	12	1.9	33.16	22	1.9	33.16
Ms. Sar	I	13	0.8	61.6	11	0.8	61.6
	II	11	0.8	61.6	17	0.7	70.4
	III	17	0.7	70.4	15	0.9	54.78
	IV	15	0.9	54.78	13	1.2	41.08
	V	13	1.2	41.08	11	1.0	49.30
Ms. Aw	I	5	1.2	42.3	7	1.2	42.3
	II	7	1.2	42.3	6	1.0	50.76
Mean		11.99	0.97	61.43	12.14	1.02	58.64
SD		4.62	0.34	18.60	4.74	0.37	18.36

Based on the result of statistical analysis, the significance value of each parameter of serum creatinin (p = 0,276), BUN (p = 0,950) and eCrCl Cockroft-Gault (p = 0,205) with cisplatin and 5FU chemotherapy regimen and serum creatinine (p = 0.666), BUN (p = 0,560), and eCrCl Cockroft-Gault (p = 0.401) with cisplatin and paclitaxel chemotherapy regimens. This shows that there is no significant difference (p> 0.05) in BUN, SCr, and eClCr Cockroft-Gault levels between pre-hydration data and post-hydration data on administration of both types of cisplatin chemotherapy regimens.

Analysis of BUN data, serum creatinine, and pre- and post-chemotherapy cisplatin GFR estimation can be seen in Table 4 and Table 5. One cycle of chemotherapy is 3 weeks (21 days). The value of n (number of samples) used is the number of patients receiving cisplatin chemotherapy. From the observation, there was a change of BUN value, Serum creatinine, and eClCr Cockroft Gault between before chemotherapy and post-chemotherapy on cisplatin chemotherapy regimen with 5FU and cisplatin with paclitaxel. Increase or decrease in each cycle of chemotherapy on the BUN value, serum creatinine and eCrCl Cockroft-Gault can be seen in Fig.s 1, 2, and 3.

Based on different test of paired t-test of BUN value, serum creatinin, and eCrCl Cockroft-Gault in cisplatin and 5FU chemotherapy regimen it can be concluded that there is no statistically significant difference (p> 0,05) on different test of BUN content, serum creatinine , And eClCr Cockroft-Gault data pre- compared to the 2nd cycle until the 6th cycle. Meanwhile, based on different paired t-test in cisplatin and paclitaxel chemotherapy regimens it can be concluded that there was statistically significant difference (p <0.05) on different test of creatinine serum level (p = 0,037) pre-data compared with cycle 4 and at the level of eClCr Cockroft-Gault (p = 0,019) pre-data compared to the 4th cycle.

Table 3. BUN examination results, serum creatinine, eClCr Cockroft-Gault Pre- and Post-Hydration with a cisplatin chemotherapy regimen of 100 mg/m2 and paclitaxel

Patient's Initial	Cycles (n=44)	Pre			Post		
		BUN (mg/dl)	SCR (mg/dl)	E ClCr CG (ml/min)	BUN (mg/dl)	SCR (mg/dl)	E ClCr CG (ml/min)
Mr. Alf	I	7	0.8	75.26	7	1.0	60.21
	II	7	1.0	60.21	8	0.8	60.21
	III	8	0.8	60.21	10	0.9	66.90
	IV	10	0.9	66.90	11	0.9	66.90
	V	11	0.9	66.90	10	0.8	75.26
Ms. Sw	I	13	0.9	81.0	15	1.0	72.90
	II	15	1.0	72.90	17	1.9	38.37
	III	17	1.9	38.37	12	1.3	56.08
	IV	12	1.3	56.08	11	1.0	72.90
	V	11	1.0	72.90	12	1.0	72.90
Ms. Kar	I	8	0.7	105.61	11	0.7	105.61
	II	11	0.7	105.61	10	1.0	73.93
	III	10	1.0	73.93	9	0.9	82.14
	IV	9	0.9	82.14	11	0.9	82.14
	V	11	0.9	82.14	11	1.0	73.93
Mr. Suk	I	11	0.8	70.31	10	1.0	56.25
	II	10	1.0	56.25	8	0.8	70.31
Mr. JP	I	9	0.7	79.44	8	0.9	61.79
	II	8	0.9	61.70	9	0.8	69.51
	III	9	0.8	69.51	10	1.0	55.61
Mr. Ma	I	7	1.1	65.91	9	1.0	72.50
Mean	10.19	0.95	71.58	10.43	0.98	68.87	
SD	2.58	2.89	15.38	2.31	0.26	13.22	

Table 4. BUN examination results, serum creatinine, eClCr Cockroft-Gault Pre- and Post-Chemotherapy with cisplatin chemotherapy regimen 100 mg/m2 and 5FU

No	Cycle I (Pre-)			Cycle II (Post-)			Cycle III (Post-)			Cycle IV (Post-)			Cycle V (Post-)			Cycle VI (Post-)		
	BUN	SCR	eClCr	BUN	SCr	eClCr	BUN	SCr	eClCr	BUN	SCr	eClCr	BUN	SCr	eClCr	BUN	SCr	eClCr
1	12	0.6	57.55	12	0.7	49.33	13	0.7	49.33	8	0.7	49.33	12	0.8	43.16	8	0.7	49.33
2	7.36	0.7	74.86	5	0.9	58.23	9	0.8	65.50	8	0.8	65.50	12	0.9	58.23	13	1.7	30.83
3										18	1.1	55.15	23	1.6	37.92	10	1.3	46.67
4	10	0.9	77.4	16	1.0	69.60	9	1.0	69.60	10	1.1	63.31	9	1.0	69.60	11	0.9	77.40
5	8	0.5	109.08	11	0.7	77.92	11	0.5	109.08	10	0.5	109.08	11	0.7	77.92	11	0.7	77.92
6	12	1.1	58.08	11	0.9	71	11	1.0	58.08	13	0.7	91.27	10	1.0	58.08	11	0.9	71.00
7	12	0.9	66.67	13	1.0	51	10	0.9	66.67	11	0.9	66.67	9	1.0	51.00	10	1.1	46.36
8	18	1.2	52.50	32	1.8	35.00	16	1.6	39.38	12	1.9	33.16	12	1.9	33.16	22	1.9	33.16
9	13	0.8	61.6	11	0.8	61.6	17	0.7	70.4	15	0.9	54.78	13	1.2	41.08	11	1.0	49.30
10										5	1.2	42.30	7	1.2	42.30	6	1.0	50.76
Mean	11.55	0.84	69.72	13.88	0.98	59.21	12.00	0.90	66.00	11.00	0.98	63.06	11.80	1.13	51.25	11.30	1.12	53.27
SD	3.31	0.24	18.09	7.94	0.35	13.91	3.07	0.33	20.49	3.74	0.39	22.55	4.34	0.37	14.52	4.22	0.40	16.80

Table 5. BUN examination results, Creatinine Serum, eClCr Cockroft-Gault Pre- and Post-Chemotherapy with chemotherapy regimen cisplatin 100 mg/m2 and paclitaxel

No	Cycle I (Pre-)			Cycle II (Post-)			Cycle III (Post-)			Cycle IV (Post-)			Cycle V (Post-)			Cycle VI (Post-)		
	BUN	SCR	eClCr	BUN	SCr	eClCr	BUN	SCr	eClCr	BUN	SCr	eClCr	BUN	SCr	eClCr	BUN	SCr	eClCr
1	7	0.8	75.25	7	1.0	60.21	8	0.8	75.26	10	0.9	66.90	11	0.9	66.90	10	0.8	75.26
2	13	0.9	81.00	15	1.0	72.90	17	1.9	38.37	12	1.3	56.08	11	1.0	72.90	12	1.0	72.90
3	8	0.7	105.61	11	0.7	105.61	10	1.0	73.93	9	0.9	82.14	11	0.9	82.14	11	1.0	73.93
4	11	0.8	70.30	10	1.0	56.25	8	0.8	70.31	-	-	-	-	-	-	-	-	-
5	9	0.7	79.44	8	0.9	61.79	9	0.8	69.51	10	1.0	55.61	-	-	-	-	-	-
6	7	1.1	65.91	9	1.0	72.50												
Mean	9.17	0.83	79.59	10.00	0.93	71.54	10.40	1.06	65.48	10.25	1.03	65.18	11.00	0.93	73.98	11.00	0.93	74.03
SD	2.40	0.15	13.94	2.83	0.12	18.00	3.78	0.48	15.34	1.26	0.19	12.45	0.00	0.58	7.68	1.00	0.12	1.18

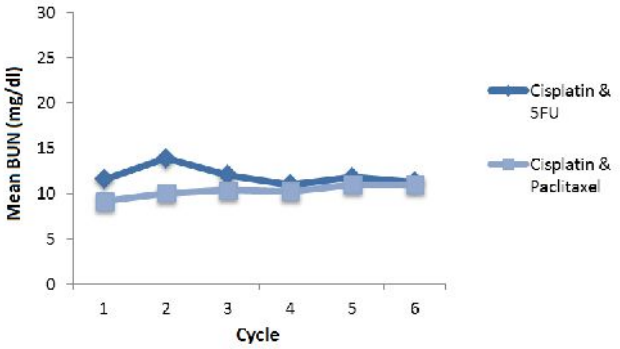

Fig. 1. The average BUN of the 1st cycle (pre-) up to the 6th cycle of cisplatin chemotherapy

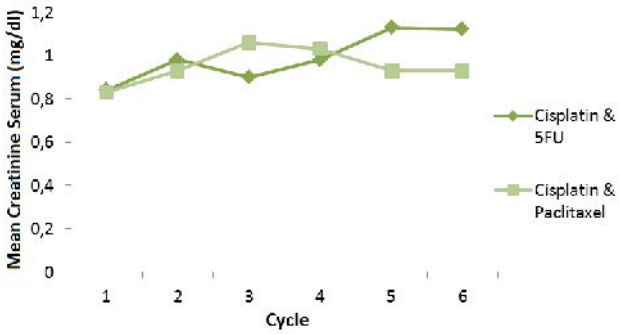

Fig. 2. Mean of 1st cycle Creatinine Serum (Pre-) to 6th cycle of cisplatin chemotherapy

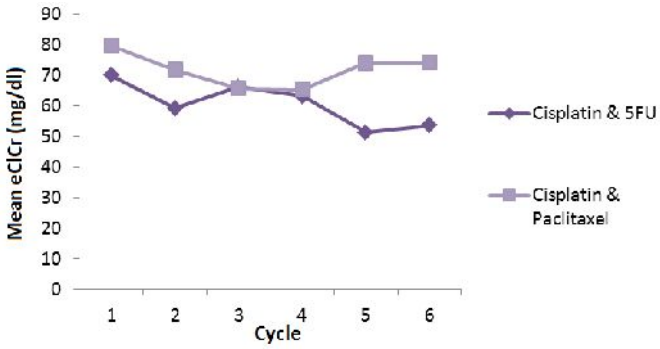

Fig. 3. Average eClCr Cockroft-Gault of the 1st cycle (Pre-) up to the 6th cycle of cisplatin chemotherapy

DISCUSSION

From this study (see table 1) shows the age range of patients with a diagnosis of head cancer of the neck that is between 31-68 years (average 53.13 years). Female gender 7 patients (43.75%) and men 9 patients (56.25%). This suggests that head cancer of the neck is more common in men than women (Riskesdas, 2010). The most common type of histology is nasopharyngeal cancer (50%) and chemotherapy regimens are widely used is a combination of cisplatin with 5FU (62.50%). The combination of cisplatin and 5FU chemotherapy is most widely used because this combination can be used in all types of head cancer of the neck (Pfister et al., 2011). However, based on a study by Gibson et al it was found that resistance or response rates in neck head cancer patients between combination of cisplatin and 5FU chemotherapy compared with cisplatin and paclitaxel were not statistically significant differences (Gibson et al., 2005).

At the time this study takes place based on predetermined inclusion criteria then the patient with any cycle will still do the data retrieval and followed its development in the next cycle. One cycle of cisplatin 100 mg/m2 chemotherapy is 3 weeks (21 days). The most observations were those who underwent cycle I to cycle VI, ie 11 patients (68.75%), and then the patients who underwent IV to VI cycle were 2 patients (12.50%). While the frequency of hydration is the most with 5 times frequency in 11 patients (69%). This happens because at the time of the research many patients who just start chemotherapy for the first time (first cycle) so that the observation on the patient can be done until all cycles are fulfilled as much as 6 cycles, as well as the hydration frequency is met 5 times.

Each patient who received a combination of cisplatin chemotherapy 100 mg/m2 was given infusion of NaCl hydration and mannitol. The hydration volumes given were NaCl 3350 ml and Manitol 500 ml. The given hydration volume is the total volume administered to the patient in a single cycle of chemotherapy. The hydration given to the patient is only NaCl and mannitol alone, without any addition of electrolytes. Meanwhile, based on BCCA protocol (see table 2.11) for cisplatin chemotherapy dose> 80 mg/m2 it is necessary to add electrolyte ie KCl 20 mEq and MgSO4 1 g and a given hydration volume of 4000 ml NaCl. The addition of Electrolytes of Potassium Chloride (KCl) and Magnesium Sulfate (MgSO4) to balance the electrolyte balance as a manifestation of renal reabsorption disorder (BCCA, 2008).

Observations in this study emphasized the evaluation of renal function of patients who received a combination of chemotherapy cisplatin 100 mg/m2 with the provision of hydration protocols NaCl and mannitol. Monitoring performed is to observe the renal function of patients seen from laboratory data BUN and serum creatinine. Examination was performed at baseline (measurement and recording of BUN value, serum creatinine and initial Cockroft-Gault eClCr given hydration), and week 3 post-chemotherapy. In addition, CrCl estimates were calculated using the formula according to Cockroft-

Gault and Modification of Diet in Renal Disease (MDRD).

Based on baseline study data for baseline BUN baseline values ??(11.99 + 4.62) mg/dl in patients with cisplatin and 5FU chemotherapy and (10,19 + 2.58) mg/dl in patients with chemotherapy Cisplatin and paclitaxel. The mean serum creatinine values were (0.97 + 0.34) mg/dl in patients with cisplatin and 5FU chemotherapy and (0.95 + 2.89) mg/dl in patients with cisplatin and paclitaxel chemotherapy. In the mean value data of eClCr Cockroft-Gault baseline (61,43 + 18,60) ml/min in patients with cisplatin and 5FU chemotherapy and (71,58 + 15,38) ml/min in patients with cisplatin chemotherapy and Paclitaxel. Baseline study is important as the preliminary data on the development of eClCr value which is a parameter to see the side effects of cisplatin chemotherapy that is nephrotoxicity. BUN baseline study and serum creatinine data obtained from the study were compared with inclusion criteria ie BUN value of 7-18 mg/dl and serum creatinine <2 mg/dl so that all patients participating in the study were considered to have met the criteria.

Mannitol is an osmotic diuretic that acts by increasing the osmolarity of glomerular filtration, causing fluid excretion and inhibiting electrolyte reabsorption in the renal tubules. The occurrence of diuresis will decrease platinum contact time with renal tubular cells. The half-life of mannitol ranges from 15 - 100 minutes, with onset of diuretics occurring for 1-3 hours (Anderson et al 2002). In this study the effect of mannitol diuretic can not be known because the measurement of urine production is not done observation. Measurements of urine production should be necessary to determine the adequacy of hydration in the administration of cisplatin chemotherapy that will induce diuresis of at least 100 ml/h (Vacher, 2008). Urine production can also be used as a reference to the degree of nephrotoxicity (KDIGO, 2012). However, this study does not measure urine volume because there are several rejections from the patient or the patient's family. In this study also did not check the degrees of dehydration pre- and post-chemotherapy. Patients receiving hydration fluid should be in euvolemic condition. Patients with fluid constraints in hypervolemic conditions such as conditions of congestive heart failure and chronic renal failure, then contraindications receive large amounts of hydration that may aggravate the underlying disease complaint. Conversely, patients with hypovolemic conditions addressed as dehydration therapy by a fluid mechanism will fill in the intravascular space first.

The ideal infusion fluid therapy in this model study is through an infusion pump. With infusion pump the speed of administration can be adjusted accurately so that the conditions received by each subject can be homogeneous. The limitations of this study provide hydration fluid using conventional infusion, so that the rate of administration of each patient may vary.

Cisplatin-induced nephrotoxicity begins with sodium reabsorption disorders in the proximal tubules and decreased water reabsorption in the distal tubule. This results in increased excretion of sodium and water ions. Administration of cisplatin is generally followed by polyuria occurring in 2 different phases. The first phase occurs at 24-48 hours after cisplatin administration characterized by decreased urinary osmolality but the GFR values are within normal limits. The second phase occurs between 72-96 hours after cisplatin administration characterized by increased urinary volume and decreased GFR (Bagnis, 2003., Patzer, 2007., Vacher, 2008). A decrease in renal blood flow occurred 3 hours after cisplatin administration followed by a 23% decrease in GFR. Decreased renal and GFR blood flow is caused by increased renal vascular resistance activated by tubuloglomerular feedback from increased delivery of NaCl to the macula densa in the distal tubule. A decrease in GFR leads to a reduction of the fluid flow rate thus decreasing the reabsorption of water and sodium distal to the nephron. This results in increased water and sodium excretion which is clinically indicated by conditions of polyuria and hyponatremia.

From the observation of 10 patients receiving cisplatin and 5FU chemotherapy there was an increase in BUN and serum creatinine levels and decreased eClCr Cockroft-Gault on post-hydration data compared with pre-hydration data. Based on normality test results known BUN value and serum creatinine distributed is not normal, meanwhile value of eClCr Cockroft-Gault is normal distributed. To determine the significance value of each parameter, Wilcoxon test on BUN value and serum creatinine and Paired T-Test different test on eClCr Cockroft-Gault value. In the Wilcoxon and Paired T-Test tests, there was no statistically significant difference ($p > 0.05$) for BUN value, serum creatinine, and eClCr Cockroft-Gault after hydration compared with before hydration where the mean value of each of the Paired T- BUN (0,950), serum creatinine (0,276) and eClCr Cockroft-Gault (0,205) respectively.

Based on the results of the study in 6 patients who received cisplatin and paclitaxel chemotherapy, serum creatinine was known to be abnormally distributed, the pre-hydration serum creatinine analysis on post-hydration was conducted by Wilcoxon test. The result of Wilcoxon test was not found any significant difference significantly that is (0,685) ($p > 0,05$). In the BUN and eClCr Cockroft-Gault data are known to be

normally distributed, the pre-hydration data analysis of post-hydration is tested by Paired T-Test. The result of different test of Paired T-test on the 2 parameters is BUN (0,085) and eClCr Cockroft-Gault (0,401) which mean there is no statistically significant difference (p> 0,05). The result of different test on each parameter were BUN, serum creatinin, and eClCr Cockroft-Gault on both combination of cisplatin chemotherapy revealed no statistically significant difference (p> 0,05) because in this research only observation chronic nephrotoxicity is With a 3-week post-chemotherapy cisplatin observation in which time the kidney function has undergone recovery. Recovery of renal function is known within 2-4 weeks (Miller et al., 2010). Proximal and distal renal tubular reabsorption damage as well as increased vascular resistance may occur within 48 to 72 hours after administration of cisplatin. Renal impairment occurring between 72 and 96 hours after cisplatin administration is characterized by a decrease in the value of GFR (Yao et al., 2007). Decreased GFR is usually followed by increased serum creatinine and BUN occurring on days 6-7 after cisplatin (Cornelison, 1993).

The data analysis of the research results was also conducted on each cycle aimed at knowing the condition of increase and decrease of BUN, Serum creatinin, and eClCr Cockroft-Gault on the first cycle data (pre-) until the 6th cycle presented in table 4 and Table 5. Based on the data in table 4 it is known that there is an increase in serum creatinine levels and decreased eClCr Cockroft-Gault data cycle 1 (pre-) compared with the second cycle until cycle 6 on cisplatin and 5FU chemotherapy. The same is also shown in Table 5 which shows an increase in BUN, serum creatinine, and eClCr Cockroft-Gault data on the 1st cycle (pre-) compared to the 2nd cycle until the 6th cycle on chemotherapy cisplatin and paclitaxel . Through the data presented above, it is known that BUN, serum creatinine, and eClCr Cockroft-Gault data are normally distributed, then BUN data analysis, serum creatinine, and eClCr Cockroft-Gault pre-chemotherapy on post-chemotherapy data are tested by different Paired T -Test.

The result of different test of Paired T-Test giving cisplatin and 5FU chemotherapy concluded that there was no statistically significant difference (p> 0,05) on different test of BUN content, serum creatinine, and eClCr Cockroft-Gault data cycle 1 -) compared to the 2nd cycle until the 6th cycle of chemotherapy. In addition, the results of different tests of Paired T-Test BUN data on cisplatin and palitaxel chemotherapy can also be concluded that there was no statistically significant difference (p> 0.05) in the first-cycle data (pre-) compared with cycle To-2 until the 6th cycle of chemotherapy. Meanwhile, on different test of Paired T-Test data of serum creatinine and eClCr Cockroft-Gault on cisplatin and palitaxel chemotherapy, it was concluded that there was statistically significant difference (p <0,05) in serum creatinine pre-chemotherapy data on serum creatinine data The 4th cycle (p = 0,037) and the eClCr Cockroft-Gault pre-chemotherapy data on the 4th Cockroft-Gault eClCr data (p = 0,019).

In this study, although no statistically significant results were found, there was an increase in BUN and serum creatinine as well as impairment of eClCr Cockroft-Gault on Tn. Mj. This condition began to appear at the time of Mr. Mj undergoes 5th cycle chemotherapy so that cisplatin has accumulated large enough in the kidney. The concentration of cisplatin in proximal tubular epithelial cells reached 5 times the serum concentrations (Stewart et al., 1985; Kuhlmann et al., 1997; Yao et al., 2007). The accumulation of large cisplatin in the kidney is what can induce the occurrence of nephrotoxicity (Arany & Safirstein, 2003; Yao et al., 2007). Meanwhile at Ny. Ma is known from the beginning to enter the eClCr Cockroft-Gault value of patients <60 ml/min but the BUN and serum creatinine values are still within the normal range. This may occur because under chronic nephrotoxicity the BUN and serum creatinine levels may increase or fall within the normal range, but the value of GFR will continue to decline (Cornelison & Reed, 1993). Increased or decreased values of BUN, serum creatinine and eClCr Cockroft-Gault in patients can also be seen based on Fig. 5.4, Fig. 5.5, and Fig. 5.6 indicating that there is a tendency for nephrotoxicity in the administration of cisplatin chemotherapy. Similar results also occurred in the study by Kidera et al. Who observed the nephrotoxic effect of 60 mg/m2 cisplatin doses retrospectively showing 127 patients from 402 patients experiencing nephrotoxicity characterized by elevated serum creatinine. However, this study used the NaCl hydration method with the addition of furosemide, KCl, and MgSO4 (Kidera et al., 2014).

CONCLUSION

NaCl-Mannitol hydration is sufficiently demonstrated by the results of BUN and serum creatinine values within normal limits. The combination of cisplatin and 5FU chemotherapy showed a pre-hydration BUN value of 11.99 + 4.62 mg/dl and post-hydration BUN value of 12.14 ± 4.74 mg/dl, sera creatinine sera 0.97 + 0, 34 mg/dl and serum creatinine value of post-hydration 1.02 + 0.37 mg/dl. The combination of cisplatin and paclitaxel chemotherapy showed pre-hydration BUN values of 10.19 + 2.58 mg/dl and post-hydration BUN values of 10.43 + 2.31 mg/dl, pre-hydration serum creatinine 0.95

+ 2, 89 mg/dl and serum creatinine value post-hydration 0.98 + 0.26 mg/dl.

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