

# Effect of Mannitol Hydration as Renoprotective on Cisplatin Induced Nephrotoxicity (CIN) in Head and Neck Cancer Patients

Mareta Rindang, Andarsari<sup>1</sup>, Yunita Dyah, Kusumaningrum<sup>2</sup>, Rosy Nurlita, Hapsari<sup>3</sup>,  
Dwi Hari, Susilo<sup>4</sup>, Dewi Wara, Shinta<sup>1</sup>

<sup>1</sup>Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia,

<sup>2</sup>Postgraduate Student of Magister of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia, <sup>3</sup>Department of Pharmacy, Dr. Soetomo Hospital, Surabaya, Indonesia, <sup>4</sup>Division Head and Neck Surgery, Department of Surgery, Faculty of Medicine, Universitas Airlangga / Dr. Soetomo Hospital, Surabaya, Indonesia

## Abstract

**Background:** Cisplatin is a cytostatic agent used as treatments in head and neck cancer patients. Nephrotoxicity is one of cisplatin major side effects. This study aimed to evaluate the renoprotective effect of mannitol-hydration administration in head and neck cancer patients who receive cisplatin chemotherapy. **Methods:** This was a cohort observational study to analyze the renal function of head and neck cancer patients who receives cisplatin before and after mannitol-hydration administration in IRNA Surgery and Soekardja Room of Chemotherapy at RSUD Dr. Soetomo Surabaya during June – September 2018. The data obtained were BUN, SCr, and eCICr Cockroft-Gault of each cycle. **Result:** A total of 52 patients were evaluated. The average value of creatinine serum, creatinine clearance, and BUN at each cycle were fluctuate. However, the average value of creatinine serum and BUN were within the normal limit. The result of statistical analysis using paired t-test in those parameters at each cycle were not statistically significant ( $p > 0,05$ ) after mannitol administration except during first cycle to second cycle the SCr increased significantly and eCICr was decreased significantly ( $p$ -value 0,024; 0,006, CI 95% respectively ). At fourth cycle the eCICr also decreased significantly ( $p$  value 0,008, CI 95%). **Conclusion:** The renoprotective effect of mannitol in head and neck cancer patients who receive cisplatin chemotherapy is sufficiently adequate which can maintain the value of BUN and creatinine serum of patients at each cycle within the normal limit.

**Key words:** cisplatin, mannitol, nephrotoxicity, prevention

## Introduction

In 2018, the prevalence of head and neck cancer around the world was ranked at seventh of most common cancer with new cases more than 850,000 and deaths around 450,000<sup>1</sup>. Management therapy of head and neck cancer based on NCCN Guideline can be surgery, radiotherapy, and/or chemotherapy. Cisplatin is the preferred chemotherapy agent which can be used along with radiation as a chemoradiotherapy regimen usually given in high dose (100 mg/m<sup>2</sup> every 21 days for three cycles)<sup>2,3</sup>. Nephrotoxicity is the renowned major side effect (around 28-36%) in the form of

both acute or chronic renal insufficiency which also becomes major consideration in giving cisplatin therapy. Cisplatin is mainly eliminated through kidneys (> 90%) approximately 25% is excreted in urine within the first 24 hours after administration<sup>4,5</sup>. Patients treated with cisplatin about 20% - 30% will experience nephrotoxicity after 10 days administration<sup>6,7</sup>.

A study by Arunkumar et al<sup>8</sup> evaluated the renal injury in several patients at stage IIA to stage IVA with various types of cancer who received a 40-50 mg/m<sup>2</sup> cisplatin regimen and reported the incident of renal injury in patients like hypomagnesemia, hypokalemia,

hypocalcemia, hypophosphatemia, increased of BUN and creatinine serum. Kidera et al<sup>9</sup> also assessed the effect of cisplatin on renal who received cisplatin with doses > 60 mg/m<sup>2</sup> for the first time and this study reported that 32% of patients experience nephrotoxicity which characterized by increase value of creatinine serum. Cisplatin nephrotoxicity is dose-dependent toxicity, it's maybe prevented by hydration and other supplementation strategies like magnesium and mannitol. Mannitol as an osmotic diuretic agent has been widely used for renal protection because it can reduce the contact time between fluid and the tubular epithelium, this way is believed to protect against renal injury by accelerating the removal of renal toxin<sup>10,11</sup>.

A study by Morgan et al, reported the outcomes in patients who receive mannitol improved and a 2.6 increased probability of developing acute kidney injury among adults who did not receive mannitol<sup>12</sup>. Another study by McKibbin et al, in head and neck cancer patients who are using cisplatin 100 mg/m<sup>2</sup> showed that the addition of mannitol decreased the incidence of grade 3 acute kidney injury compared to saline only group<sup>13</sup>. Williams et al<sup>14</sup> also assessed the impact of mannitol administration, patients who acquired mannitol administration has lower average increase of creatinine serum (mg/dl) and experienced less frequent grade 2 or higher nephrotoxicity compared with patients who did not acquire it. Meanwhile, study by Beeler et al reported that the addition of mannitol to saline pre-hydration in patients who receive cisplatin therapy did not change the outcome of renal function decline measured by BUN/Cr ratio, GFR, creatinine, and BUN and the decline of renal function is limited to grade 1 and most patients recover<sup>15</sup>.

Based on the description above, we undertook a study to evaluate the renoprotective effect of mannitol 20% 500 ml administration with saline hydration in head and neck cancer patients who receive cisplatin chemotherapy by observing the renal function (seen from laboratory data BUN and creatinine serum value).

## Material and Methods

This was a cohort observational study that evaluated the renal function of head and neck cancer patients before and after cisplatin combination chemotherapy administration. The patients were given the combination of mannitol (20% 500 ml) and saline hydration one time after cisplatin combination chemotherapy at each cycle. Laboratory examination according procedure established by RSUD DR. Soetomo including BUN, creatinine serum and estimated creatinine clearance with Cockcroft-Gault formula were carried out before patients received cisplatin combination chemotherapy as the baseline data (pre-data). The change of renal function was observed at the start of the next cycle of chemotherapy.

The study subject were patients diagnosed with head and neck cancer who received cisplatin combination chemotherapy in IRNA Surgery and Soekardja Room of Chemotherapy at RSUD Dr. Soetomo Surabaya during June – September 2018. Patients were included if they aged between 21 years old up to 80 years old and had normal function of liver, heart, kidney and lungs. Another important inclusion criteria was patients voluntarily to be involved in this study by signing the informed consent. Meanwhile, patients were excluded in this study if they were allergic to cisplatin and received another therapy that can also induced nephrotoxicity such as aminoglycoside, cyclophosphamide, and others.

The normality of the data distributions was assessed using the One Sample Kolmogorov-Smirnov test before analysis. Comparison of the patient renal function before and after mannitol-hydration administration was performed using the paired t-test if the data were normally distributed and Wilcoxon signed-rank test if the data were not. The differences of renal function between patients with cisplatin-5FU regimentation and cisplatin-paclitaxel regimentation were also evaluated using independent t-test if the data were normally distributed or Mann-Whitney test if the data were not. P-values  $\leq 0.05$  were considered statistically significant. The obtained data were recorded in a special form and then processed through SPSS version 24.0 for Windows

with confidence interval 95%.

## Result and Discussion

### *Patients characteristic*

A total of 52 patients were included in this study between June - September 2018 with sample characteristics shown in Table 1. The percentage of male patients (67 %) was higher than female patients (37%). Head and neck cancer is more common and affected significantly in males rather than females with a ratio 2:1 to 4:1<sup>1,16</sup>. In this study, the patient's mean age range is between 41-64 years (mean 51,92 years), several studies reported that patients with age  $\geq$  50 years had a higher incidence of cisplatin-related nephrotoxicity<sup>17,18</sup>. Most of the patients suffering from nasopharyngeal cancer (33%) and then followed by squamous cell carcinoma (23%) and tongue cancer (18%). Nasopharyngeal cancer is the most common site type of head and neck cancer.

All patients in this study receive chemotherapy minimally for three cycles and up to six cycles for

several patients with chemotherapy regimentation were combination of cisplatin-5fluorouracil in 42 patients and combination of cisplatin-paclitaxel in 10 patients. Both of them are included as recommended regimens or first-line systemic therapy for advanced head and neck cancer patients<sup>2</sup>. However, a study by Gibson et al<sup>19</sup> showed that there were no statistically significant difference of overall survival or response rate and toxicity between cisplatin-5FU regimentation compared with cisplatin-paclitaxel in head and neck cancer patients.

The dose of cisplatin received by the patient varies from 35 mg/m<sup>2</sup> up to 100 mg/m<sup>2</sup> and the most frequently used was 100 mg/m<sup>2</sup>. A study by Kidera et al and Prasaja et al showed that cisplatin-induced nephrotoxicity occurred in patients who received doses  $>$  60 mg/m<sup>2</sup> in around 32% and 34,1% respectively<sup>9,17</sup>. Therefore, the dose of cisplatin is one of risk factors that affect cisplatin nephrotoxicity. Hydration frequency in cisplatin-5 fluorouracil regimen was 166 times and in cisplatin-paclitaxel regimen was 47 times, so hydration frequency in this study overall was 213 times.

**Table 1: The characteristics of sample**

Characteristic of Sample	Total Patients (n = 52)	Percentage (%)
<b>Gender</b>		
Males	33	63
Females	19	37
<b>Age (years)</b>		
21-40	10	19
41-60	28	54
61-80	14	27
Mean	51,92 $\pm$ 11,32 (41 – 64)	
<b>Types of Head and Neck Cancer</b>		
Nasopharyngeal cancer	17	33
Squamous cell carcinoma	12	23
Tongue Cancer	9	18
Group of Other Types of Head and Neck Cancer	7	14
Maxilla Cancer	4	8
Mandibula Cancer	2	4

**Cont... Table 1: The characteristics of sample**

<b>The Number of Patients in Every Cycles</b>		
First cycle – Third cycle	52	100
Fourth cycle	26	50
Fifth cycle	21	41
Sixth cycle	10	19
<b>Chemotherapy Regimentation (patients)</b>		
Cisplatin - 5FU	42	81
Cisplatin – Paclitaxel	10	19
<b>Cisplatin Dosage (mg/m2)</b>		
Note = 1 patient might experience change in dosage so can receive more than one kind of dose		
30 – 50	11	17
> 50 – 70	5	8
> 70 – 90	18	27
> 90 – 100	32	48
<b>Hydration Frequency</b>		
Frequency 3x	26	50
Frequency 4x	5	10
Frequency 5x	11	21
Frequency 6x	10	19

*Change in SCr, eClCr, and BUN in patients during cisplatin combination chemotherapy*

The change of creatinine serum, creatinine clearance, and BUN value in all patients on each chemotherapy cycle were shown in figure 1 until figure 3 respectively. The average value of those three parameters were fluctuating. Based on analysis using independent t-test, there were no statistically significance difference on patient renal function (SCr p-value 0,223; eGFR p-value 0,418; and BUN p-value 0,677, CI 95 %) between cisplatin-5 fluorouracil group and cisplatin-paclitaxel group.

Several previous studies evaluated the effect of mannitol on cisplatin-related nephrotoxicity. Three studies by Morgan et al, McKibbin et al, and Williams et al revealed that mannitol administration with cisplatin concomitantly has a significant protective effect that allows patients to receive cisplatin therapy with low risk of nephrotoxicity<sup>12-14</sup>. Even though in this study patients had already received saline-mannitol 20% 500 ml hydration combination one time after each cycle, the average value of patient renal function like SCr, eClCr, and BUN were fluctuating. However, the average value of creatinine serum and BUN were within the normal limit.

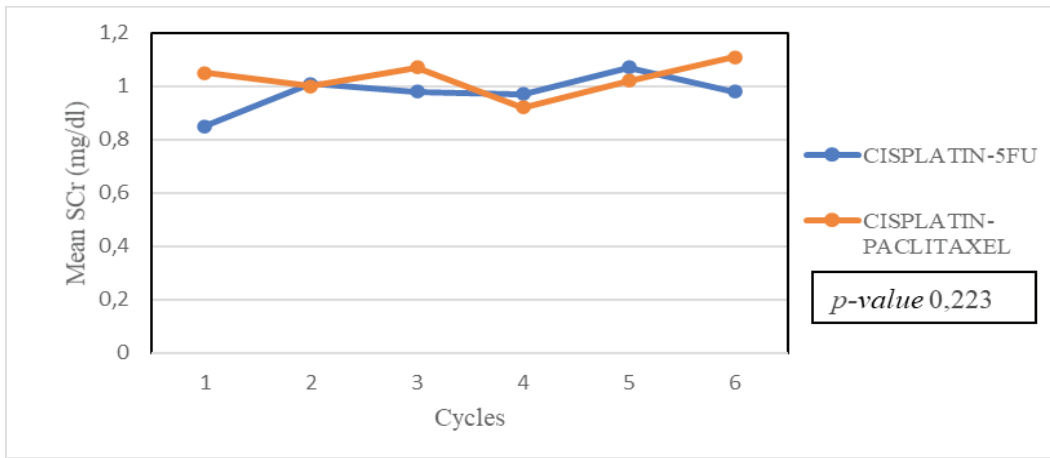


Figure 1: The average creatinine serum (SCr) value of patients from 1<sup>st</sup> to 6<sup>th</sup> cycles

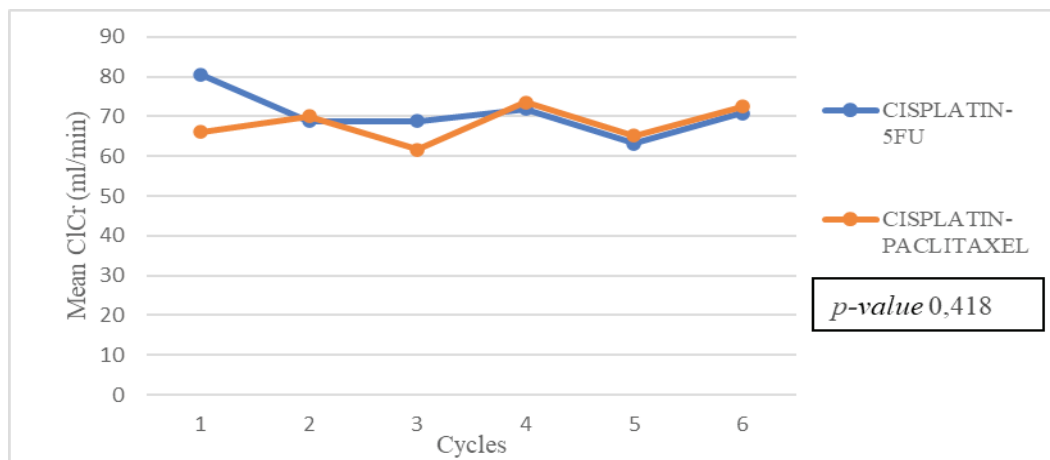


Figure 2: The average creatinine clearance (ClCr) value of patients from 1<sup>st</sup> to 6<sup>th</sup> cycles

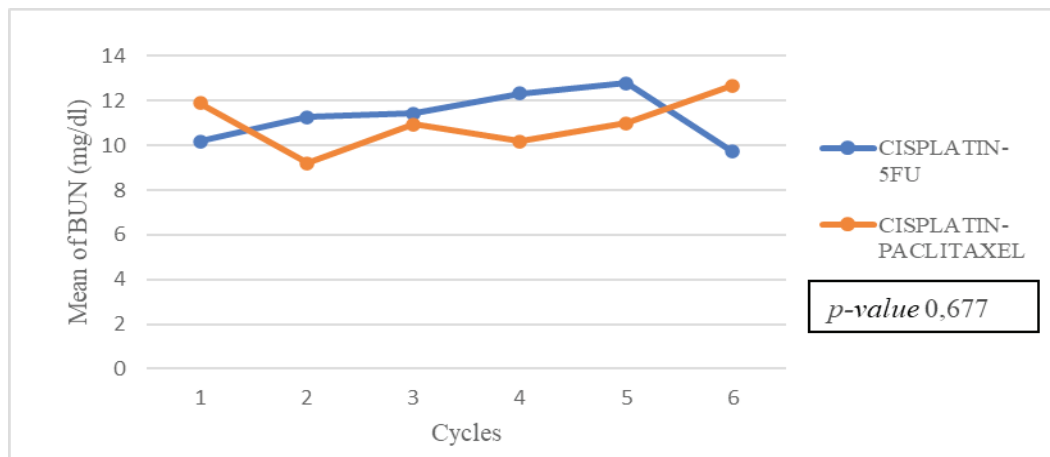


Figure 3: The average BUN value of patients from 1<sup>st</sup> to 6<sup>th</sup> cycles

**Table 2: Statistical analysis result of renal function in all 52 patients who receive cisplatin combination chemotherapy**

Variable		Total Patients (n)	Creatinine Serum (mg/dl)			Creatinin Clearance (ml/min)			BUN (mg/dl)		
			Mean ± SD		p-value	Mean ± SD		p-value	Mean ± SD		p-value
Pre	Post		Pre	Post		Pre	Post		Pre	Pre	
Cycle I	Cycle II	52	0,89 ± 0,26	1,01 ± 0,40	0,024	77,80 ± 31,41	69,06 ± 27,35	0,006	10,52 ± 3,87	10,87 ± 5,25	0,964
Cycle II	Cycle III	52	1,01 ± 0,40	0,99 ± 0,29	0,745	69,06 ± 27,35	67,42 ± 22,19	0,550	10,87 ± 5,25	11,35 ± 4,03	0,335
Cycle III	Cycle IV	26	0,98 ± 0,29	0,95 ± 0,25	0,660	69,31 ± 20,41	72,26 ± 22,84	0,450	11,20 ± 3,55	11,74 ± 3,56	0,449
Cycle IV	Cycle V	21	0,94 ± 0,26	1,05 ± 0,29	0,082	73,18 ± 24,35	63,83 ± 22,56	0,008	11,92 ± 3,49	12,19 ± 4,06	0,707
Cycle V	Cycle VI	10	0,97 ± 0,12	1,02 ± 0,22	0,253	73,74 ± 23,68	71,33 ± 21,81	0,368	12,00 ± 2,45	10,60 ± 2,80	0,177

**Table 3: Statistical analysis result of renal function patients who receive combination cisplatin-5fluorouracyl regimen**

Variable		Total Patients (n)	Creatinine Serum (mg/dl)			Creatinin Clearance (ml/min)			BUN (mg/dl)		
			Mean ± SD		p-value	Mean ± SD		p-value	Mean ± SD		p-value
Pre	Post		Pre	Post		Pre	Post		Pre	Pre	
Cycle I	Cycle II	42	0,85 ± 0,23	1,01 ± 0,42	0,008	80,58 ± 31,92	68,84 ± 23,78	0,001	10,19 ± 3,60	11,26 ± 5,67	0,358
Cycle II	Cycle III	42	1,01 ± 0,42	0,98 ± 0,31	0,429	68,84 ± 23,78	68,80 ± 23,58	0,985	11,26 ± 5,67	11,44 ± 3,90	0,789
Cycle III	Cycle IV	19	0,96 ± 0,31	0,97 ± 0,28	0,945	70,54 ± 22,48	71,79 ± 25,41	0,793	11,15 ± 3,64	12,32 ± 3,71	0,196
Cycle IV	Cycle V	14	0,94 ± 0,31	1,07 ± 0,35	0,212	72,99 ± 28,35	63,15 ± 26,21	0,053	12,79 ± 3,58	12,79 ± 4,77	1,000
Cycle V	Cycle VI	7	0,93 ± 0,09	0,98 ± 0,21	0,407	73,89 ± 28,49	70,86 ± 26,60	0,388	12,29 ± 2,69	9,71 ± 2,69	0,042

**Table 4: Statistical analysis result of renal function patients who receive combination cisplatin-paclitaxel regimen**

Variable		Total Patients (n)	Creatinine Serum (mg/dl)			Creatinin Clearance (ml/min)			BUN (mg/dl)		
			Mean ± SD		p-value	Mean ± SD		p-value	Mean ± SD		p-value
Pre	Post		Pre	Post		Pre	Post		Pre	Post	
Cycle I	Cycle II	10	1,05 ± 0,33	1,00 ± 0,32	0,612	66,11 ± 27,60	69,96 ± 40,74	0,559	11,90 ± 4,82	9,22 ± 2,40	0,143
Cycle II	Cycle III	10	1,00 ± 0,32	1,07 ± 0,21	0,536	69,96 ± 40,74	61,60 ± 14,49	0,507	9,22 ± 2,40	10,95 ± 4,74	0,258
Cycle III	Cycle IV	7	1,04 ± 0,22	0,92 ± 0,17	0,262	65,99 ± 14,21	73,54 ± 15,32	0,293	11,35 ± 3,57	10,18 ± 2,75	0,220
Cycle IV	Cycle V	7	0,92 ± 0,17	1,02 ± 0,12	0,025	73,54 ± 15,32	65,18 ± 14,35	0,014	10,18 ± 2,75	11,00 ± 1,73	0,274
Cycle V	Cycle VI	3	1,05 ± 0,17	1,11 ± 0,27	-	73,39 ± 9,38	72,44 ± 3,99	-	11,33 ± 2,08	12,67 ± 2,08	-

*Effect of mannitol-saline administration in the change of SCr, eCICr and BUN of patients*

The differences in patients renal function value (SCr, eCICr, and BUN) in each cycle before and after mannitol-hydration administration were shown in Table 2. Furthermore, the differences in patients renal function during each cycle of chemotherapy before and after mannitol-hydration administration in both cisplatin-5fluorouracyl group and cisplatin-paclitaxel group listed in Table 3 and Table 4. In cisplatin-paclitaxel regimentation group, the number of samples that receive chemotherapy up to fifth cycle and sixth cycle only 3 patients so it did not meet the requirements for differential statistical analysis using paired t-test. Based on the statistical analysis result in all 52 patients, it seems renal function impairment had occurred after first cycle cisplatin combination chemotherapy administration which is characterized by increased creatinine serum and decreased creatinine clearance significantly (p-value

0,024; 0,006, CI 95% respectively). It's only occurred in group of patients with cisplatin-5FU regimentation therapy (p-value <0,05) but not in group of patients with cisplatin-paclitaxel regimentation (p-value >0,05).

Furthermore, the average value of creatinine clearance also decreased significantly after the fourth cycle of chemotherapy (p-value 0,008, CI 95%). It's only occurred in patients with cisplatin-paclitaxel regimentation which was also accompanied by a significant increase in creatinine serum otherwise it did not occur in the group of patients with cisplatin-5FU regimentation. This result was consistent with the study by Tezcan et al and Prasaja et al. that state renal function reduction occurred after first cycle of cisplatin administration<sup>17,20</sup>. Based on those two studies, renal impairment function will be worsened along with increasing numbers of chemotherapy which characterized by creatinine clearance decline after each cycle and it might be permanent.

The average BUN value of all 52 patients who received cisplatin combination chemotherapy was increase after each cycle but not statistically significant ( $p$ -value  $> 0,05$ ) and remained within the limit of the reference value. However, after fifth cycle those value was decline but also not statistically significant. It's happened because in the group patients with cisplatin-5FU regimentation had statistically significant decrease of average BUN value after fifth cycle ( $p$ -value 0,042, CI 95%). A study by Arunkumar et al and Teczan et al, reported that BUN value parameter will increase after cisplatin chemotherapy treatment, it's just that in the study by Arunkumar et al the increase was not statistically significant as well as in this study<sup>8,20</sup>.

This study result was consistent with the study by Leu and Baribeault which performed in patients using 40 mg/m<sup>2</sup> of cisplatin ( $n= 92$ ) showed that there were no statistically significant differences in average eClCr decrease ( $p = 0.09$ ) in patients received either mannitol-hydration ( $n=46$ ) or hydration alone ( $n=46$ )<sup>21</sup>. A similar result also showed in a study by Beeler et al, that there were no statistically significant difference ( $p > 0,05$ ) of BUN/Cr ratio, GFR, creatinine, and BUN between patients received mannitol-saline ( $n=25$ ) and saline alone ( $n=23$ ) during 14 days during cisplatin therapy<sup>15</sup>.

### Conclusion

In conclusion, the renoprotective effect of mannitol in head and neck cancer patients who receive cisplatin chemotherapy is sufficiently demonstrated in this study. Mannitol administration can maintain the value of BUN and creatinine serum of patients at each cycle within the normal limit. Although the average value of the patient renal function (SCr, eClCr, and BUN) at each cycle were fluctuating and the result of statistical analysis using paired t-test in those three parameters were not statistically significant ( $p > 0,05$ ) except on first cycle and on fourth cycle that eClCr decreased significantly. Several risk factors like cisplatin dosage and patient age might affect cisplatin-related nephrotoxicity which can also affect the effectiveness of mannitol therapy as renoprotector.

**Acknowledgements:** We would like to thank Dr. Soetomo General Hospital for granting permission to use the data provided in this study

**Ethical Clearance:** Taken from Dr. Soetomo Hospital's Ethics Committee

**Statement conflict of Interest:** The authors disclose no potential conflicts of interest.

**Funding:** This study funded by Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia.

### References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;**68**(6):394–424.
2. Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and neck cancers, version 2.2020. *JNCCN J Natl Compr Cancer Netw.* 2020;**18**(7):873–98.
3. Möller T. Head and neck cancer. *Acta Oncol (Madr).* 1996;**35**(SUPPL. 7):22–45.
4. Pabla N, Dong Z. Cisplatin nephrotoxicity: Mechanisms and renoprotective strategies. *Kidney Int.* 2008;**73**(9):994–1007.
5. BC Cancer Agency. Drug Name: Cisplatin. *BC Cancer Agency Cancer Drug Man.* 2010;(July):1–11. Available from: [http://www.bccancer.bc.ca/drug-database-site/Drug\\_Index/Cisplatin\\_monograph.pdf](http://www.bccancer.bc.ca/drug-database-site/Drug_Index/Cisplatin_monograph.pdf)
6. Peres LA Ibert. B, da Cunha AD anta. Acute nephrotoxicity of cisplatin: molecular mechanisms. *J Bras Nefrol.* 2013;**35**(4):332–40.
7. Higuchi K, Yanagawa T. Evaluating dose of cisplatin responsible for causing nephrotoxicity. *PLoS One.* 2019;**14**(4):1–10.
8. Arunkumar PA, Viswanatha GL, Radheshyam N, Mukund H, Belliyappa MS. Science behind cisplatin-induced nephrotoxicity in humans: A clinical study. *Asian Pac J Trop Biomed.* 2012;**2**(8):640–4.
9. Kidera Y, Kawakami H, Sakiyama T, Okamoto K, Tanaka K, Takeda M, et al. Risk factors for cisplatin-induced nephrotoxicity and potential of magnesium supplementation for renal protection.

- PLoS One*. 2014;**9**(7).
10. Ramin S, Harlan I and DP. Diuretic Agents. In: Katzung BG, editor. Basic and Clinical Pharmacology. 14th ed. United States of America: McGraw Hill; 2018. p. 267–8.
  11. Shawkat H, Westwood MM, Mortimer A. Mannitol: A review of its clinical uses. *Contin Educ Anaesthesia, Crit Care Pain*. 2012;**12**(2):82–5.
  12. Morgan KP, Snaveley AC, Wind LS, Buie LW, Grilley-Olson J, Walko CM, et al. Rates of Renal Toxicity in Cancer Patients Receiving Cisplatin With and Without Mannitol. *Ann Pharmacother*. 2014;**48**(7):863–9.
  13. McKibbin T, Cheng LL, Kim S, Steuer CE, Owonikoko TK, Khuri FR, et al. Mannitol to prevent cisplatin-induced nephrotoxicity in patients with squamous cell cancer of the head and neck (SCCHN) receiving concurrent therapy. *Support Care Cancer*. 2016;**24**(4):1789–93.
  14. Williams RP, Ferlas BW, Morales PC, Kurtzweil AJ. Mannitol for the prevention of cisplatin-induced nephrotoxicity: A retrospective comparison of hydration plus mannitol versus hydration alone in inpatient and outpatient regimens at a large academic medical center. *J Oncol Pharm Pract*. 2017;**23**(6):422–8.
  15. Bradley Beeler, Wilfred P. Delacruz, Frederick L. Flynt, Sandra Terrazzino, Naomi Hullinger, James Aden, Tiffany Byrd, Melissa M. King DAN. Saline alone vs saline plus mannitol hydration for the prevention of acute cisplatin nephrotoxicity: A randomized trial. *J Clin Oncol*. 2018;**36**(30):242.
  16. Lambert R, Sauvaget C, De Camargo Cancela M, Sankaranarayanan R. Epidemiology of cancer from the oral cavity and oropharynx. *Eur J Gastroenterol Hepatol*. 2011;**23**(8):633–41.
  17. Prasaja Y, Sutandyo N, Andrajati R. Incidence of cisplatin-induced nephrotoxicity and associated factors among cancer patients in Indonesia. *Asian Pacific J Cancer Prev*. 2015;**16**(3):1117–22.
  18. Wen J, Zeng M, Shu Y, Guo D, Sun Y, Guo Z, et al. Aging increases the susceptibility of cisplatin-induced nephrotoxicity. *Age (Omaha)*. 2015;**37**(6):1–13.
  19. Gibson MK, Li Y, Murphy B, Hussain MHA, DeConti RC, Ensley J, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): An Intergroup Trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2005;**23**(15):3562–7.
  20. Tezcan S, Izzettin FV, Sancar M, Yumuk PF, Turhal S. Nephrotoxicity Evaluation in Outpatients Treated with Cisplatin-Based Chemotherapy Using a Short Hydration Method. *Pharmacol & Pharm*. 2013;**4**(3):296–302.
  21. Leu L, Baribeault D. A comparison of the rates of cisplatin (cDDP) - Induced nephrotoxicity associated with sodium loading or sodium loading with forced diuresis as a preventative measure. *J Oncol Pharm Pract*. 2010;**16**(3):167–71.