original reports abstract

The Effect of Intravenous Mannitol Combined With Normal Saline in Preventing Cisplatin-Induced Nephrotoxicity: A Randomized, Double-Blind, Placebo-Controlled Trial

Panot Sainamthip, MD[1]; Siriwimon Saichaemchan, MD[1]; Bancha Satirapoj, MD[2]; and Naiyarat Prasongsook, MD, MS[1]

PURPOSE Nephrotoxicity is a major dose-limiting toxicity among patients with cancer who were treated with cisplatin. Although no standard approach is available to prevent cisplatin-induced nephrotoxicity, administering intravenous isotonic saline is recommended. Additionally, mannitol combined with hydration has been evaluated, but none of them have been established. Our study aimed to determine the efficacy of mannitol combined hydration to prevent cisplatin-induced nephrotoxicity.

PATIENTS AND METHODS This study was a phase II, randomized, placebo-controlled design. All patients with solid cancers who were treated with cisplatin (n = 48) were randomly assigned to receive either placebo (n = 25) or 20 g of mannitol (n = 23) after completing 2 L of prehydration and receiving cisplatin. Serum creatinine, blood urea nitrogen, electrolyte, and glomerular filtration rate (GFR) were measured at baseline and days 2 and 7. Moreover, GFR was calculated based on the 24-hour urine creatinine clearance rate to assess renal function at baseline and 48 hours after receiving cisplatin. Severity of nausea and vomiting was evaluated using Common Terminology Criteria for Adverse Events.

RESULTS No difference was found regarding baseline characteristics between the two groups. Seven of 23 patients (37.4%) in the mannitol group and 10 of 25 patients (40%) in the placebo group increased serum creatinine level ≥ 0.3 mg/dL at 48 hours after intervention (*P* value = .48). Patients receiving mannitol exhibited significantly lower incidence of 24-hour urine GFR below 60 mL/min/1.73 m than those in the placebo group (13.6% *v* 48.0% in the placebo group; *P* value = .012). Univariate analysis showed the greatest benefit for administering mannitol among patients receiving cisplatin > 80 mg/m^2, or patients receiving concomitant radiation.

CONCLUSION Mannitol combined with hydration significantly prevented cisplatin-induced nephrotoxicity. Additionally, mannitol should be particularly considered among patients with cancer, treated with cisplatin > 80 mg/m^2, or patients receiving concomitant radiation.

JCO Global Oncol 8:e2100275.

INTRODUCTION

Cisplatin-induced nephrotoxicity is a major adverse event (AE), and the incident rate is approximately 30%.[1-3] Three basic mechanisms lead to cisplatin-induced nephrotoxicity, that is, tubular cell toxicity, renal microvasculature vasoconstriction, and proinflammatory effects.[3] Several factors are associated with increased risk of cisplatin-induced nephrotoxicity including high peak plasma free platinum concentration, pre-existing kidney damage, and concomitant use of other nephrotoxic agents.[1-4]

The mainstay approach to prevent cisplatin-induced nephrotoxicity is administering intravenous (IV) hydration with isotonic saline to increase renal blood flow, and decline in half-life of cisplatin and urinary cisplatin concentration.[5] Additionally, many other agents have been studied, such as mannitol, N-acetylcysteine, and furosemide. However, no agents have been established.

Mannitol is an osmotic diuretic. Regarding its mechanism of action, mannitol is independently filtered by the glomerulus of the kidneys, and is poorly absorbed from renal tubules, leading to increased osmolarity of glomerular filtration, and inhibited renal tubular reabsorption of sodium, chloride, and other solutes, and then promoting diuresis.[4,6,7] Mannitol may be used to prevent cisplatin-induced nephrotoxicity because of the proposed mechanism underlying a potential nephroprotective effect.

Regarding the lack of standard guidelines for cisplatin-induced nephrotoxicity, few systematic studies have been conducted in clinical practice.[1,4] Therefore, our study aimed to evaluate the clinical benefit of mannitol

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 24, 2022 and published at ascopubs.org/journal/go on April 18, 2022: DOI https://doi.org/10.1200/GO.21.00275

CONTEXT

Key Objective

Does mannitol combined with hydration prevent cisplatin-induced nephrotoxicity among patients with cancer receiving cisplatin?

Knowledge Generated

Mannitol combined with intravenous hydration demonstrated significantly declining incidence of acute kidney injury among patients with cancer who were treated with cisplatin in combination regimen. Clinical benefits were observed in mannitol combined with hydration among patients receiving cisplatin (> 80 mg/m^2) once every three weeks, and patients receiving concomitant radiation by univariate analysis.

Relevance

Mannitol combined with hydration significantly prevented cisplatin-induced nephrotoxicity. Therefore, mannitol should be considered among patients with cancer, treated with cisplatin, especially among patients receiving cisplatin (> 80 mg/m^2) once every three weeks, or patients receiving concomitant radiation.

combined with hydration to prevent cisplatin-induced nephrotoxicity among patients with cancer receiving cisplatin.

PATIENTS AND METHODS

Study Design

This study was a randomized, double-blind, placebo-controlled phase II screening trial combining hydration with or without mannitol among patients with cancer receiving cisplatin (1:1 randomization ratio). Computer-generated permuted blocks were used, and investigators, nurses, and participants were blinded. Random assignment was stratified by doses of cisplatin (≤ 80 mg/m^2 or > 80 mg/m^2) once every 3 weeks and concomitant radiation.

The primary objective was to determine the clinical benefit of mannitol combined with hydration in terms of preventing cisplatin-induced acute kidney injury. The secondary end point was incidence of estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 at 7 days after receiving cisplatin between the two groups. The study was conducted in an inpatient setting at a single institution (Phramongkutklao Hospital, Bangkok, Thailand) and was compliant with Good Clinical Practice Guidelines. The protocol was approved by the Institutional Review Board at Phramongkutklao College of Medicine. This study was registered at clinicaltrials.gov under the identification number NCT04251689. All patients provided written informed consent before enrolling in the study. This initiative study was received funding from Office of Research Development, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Royal Thai Army Medical Department, Bangkok, Thailand.

Main Eligibility Criteria

Patients were eligible if they had histologically confirmed solid malignancies with an Eastern Cooperative Oncology Group performance status score ≤ 2 and planned to receive chemotherapy with either cisplatin in combination, or cisplatin alone. All patients had adequate renal function—(glomerular filtration rate [GFR] > 60 mL/min/1.73 m^2), hepatic or hematologic function, and had no contraindication for IV hydration administration. Patients who had any prior acute or chronic kidney disease, history of nephrectomy, or had taken nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, antidiuretic, for example, furosemide, aminoglycoside, or amphotericin B were excluded. No chemotherapy with concomitant nephrotoxic potential of anticancer therapy was allowed, for example, cyclophosphamide, ifosfamide, or methotrexate. In addition, patients with cardiac disease such as chronic heart failure, cirrhosis, or any immune deficiency disease were excluded.

Treatment

At baseline, the full history, physical examination, and blood tests (serum creatinine, serum electrolyte, other standard metabolic panel, and complete blood count) were performed. In addition, 24-hour urine samples were collected for the measurement of volume and creatinine.

At treatment, all enrolled patients received 2-L IV infusion of normal saline at the rate of 80 mL/h, and routine local practice for antiemetic regimen once every 3 weeks (olanzapine 10 mg oral, ondansetron 16 mg IV, and dexamethasone 12 mg IV). Cisplatin was administered at doses of 40-100 mg/m^2, and 1-L volume with normal saline containing 10 mL of 10% magnesium sulfate, and 20 mEq of potassium chloride was subsequently administered over 6 hours. In addition, 100 mL of 20% mannitol solution (20 g) or matching placebo was administered IV over 30 minutes. Thereafter, all enrolled patients received another 2-L IV infusion of normal saline at the rate of 80 mL/h. In addition, patients who received cisplatin combination chemotherapy regimen were delivered additional IV fluids, whereas patients who received single-agent cisplatin were not. For example, 500 mL of IV fluids were added for etoposide preparation. Moreover, oral fluid and oral nutritional supplement intakes were permitted in both groups.

TABLE 1. Patient Characteristics (n = 48)

Characteristic	Total (n = 48) No. (%)	Placebo (n = 25) No. (%)	Mannitol (n = 23) No. (%)	*P*
Sex				1.000[a]
Male	43 (89.6)	22 (88.0)	21 (91.3)	
Female	5 (10.4)	3 (12.0)	2 (8.7)	
Age, years				.882
< 50	12 (25.0)	7 (28.0)	5 (21.7)	
50-59	20 (41.7)	10 (40.0)	10 (43.5)	
≥ 60	16 (33.3)	8 (32.0)	8 (34.8)	
Mean ± SD	53.98 (± 10.01)	52.68 (± 11.50)	55.39 (± 8.10)	.620[b]
BMI				.152[a]
< 18.5	15 (31.3)	8 (32.0)	7 (30.4)	
18.5-24.9	26 (54.2)	11 (44.0)	15 (65.2)	
25-29.9	7 (14.6)	6 (24.0)	1 (4.3)	
Mean ± SD	20.07 (± 3.55)	20.25 (± 4.02)	19.88 (± 3.03)	.720[c]
HT				.235
Yes	3 (6.3)	3 (12.0)	0 (0)	
No	45 (93.8)	22 (88.0)	23 (100)	
Cancer				.176[a]
Head and neck	32 (66.7)	17 (68.0)	15 (65.2)	
Lung	2 (4.2)	2 (8.0)	0 (0)	
Esophagus	6 (12.5)	2 (8.0)	4 (17.4)	
Germ cell tumor	3 (6.3)	2 (8.0)	1 (4.3)	
Urothelial cancer	2 (4.2)	2 (8.0)	0 (0)	
Other	3 (6.3)	0 (0)	3 (13.0)	
Osteosarcoma	2 (4.2)	0 (0)	2 (8.7)	
Thymoma	1 (2.1)	0 (0)	1 (4.3)	
Aim				.622[a]
Neoadjuvant	2 (4.2)	2 (8.0)	0 (0)	
Adjuvant	10 (20.8)	4 (16.0)	6 (26.1)	
Palliative	12 (25.0)	6 (24.0)	6 (26.1)	
Curative	24 (50.0)	13 (52.0)	11 (47.8)	
Metastasis				.727[a]
Yes	10 (20.8)	6 (24.0)	4 (17.4)	
No	38 (79.2)	19 (76.0)	19 (82.6)	
TNM stage				.310[a]
I	2 (4.2)	1 (4.0)	1 (4.3)	
II	6 (12.5)	5 (20.0)	1 (4.3)	
III	12 (25.0)	7 (28.0)	5 (21.7)	
IV	28 (58.3)	12 (48.0)	16 (69.6)	
Chemotherapy				.268
Cisplatin alone	27 (56.3)	15 (60.0)	12 (52.2)	
Cisplatin plus etoposide	2 (4.2)	2 (8.0)	0 (0)	
Cisplatin plus fluorouracil	11 (22.9)	4 (16.0)	7 (30.4)	
Cisplatin plus gemcitabine	2 (4.2)	2 (8.0)	0 (0)	

(Continued on following page)

TABLE 1. Patient Characteristics (n = 48) (Continued)

Characteristic	Total (n = 48) No. (%)	Placebo (n = 25) No. (%)	Mannitol (n = 23) No. (%)	*P*
Cisplatin plus other	6 (12.5)	2 (8.0)	4 (17.4)	
Dose cisplatin (mean ± SD)	84.27 (± 23.52)	84.20 (± 24.69)	84.35 (± 22.73)	.945[b]
Dose cisplatin, once every three weeks				1.000
≤ 80	20 (41.7)	10 (40.0)	10 (43.5)	
> 80	28 (58.3)	15 (60.0)	13 (56.5)	
Radiation				1.000
Concurrent	32 (66.7)	17 (68.0)	15 (65.2)	
No	16 (33.3)	8 (32.0)	8 (34.8)	
Cycle				.868[a]
1	36 (75.0)	19 (76.0)	17 (73.9)	
≥ 2	12 (25.0)	6 (24.0)	6 (26.1)	
Route of food intake				.850
Oral	28 (58.3)	14 (56.0)	14 (60.9)	
NG	8 (16.7)	5 (20.0)	3 (13.0)	
PEG	12 (25.0)	6 (24.0)	6 (26.1)	
ECOG PS				.826[a]
0	1 (2.1)	1 (4.0)	0 (0)	
1	42 (87.5)	22 (88.0)	20 (87.0)	
2	5 (10.4)	2 (8.0)	3 (13.0)	
Fluid intake (oral and IV) for 48 hours (mean ± SD)	6,338.97 (± 1,340.43)	6,115.92 (± 1,439.15)	6,581.43 (± 1,208.77)	.88[c]
Urine output for 48 hours (mean ± SD)	5,892.29 (± 2,154.80)	6,007.00 (± 2,303.44)	5,767.61 (± 2,024.88)	.35[c]

NOTE. *P* value from chi-square test.

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; HT, hypertension; IV, intravenous; NG, nasogastric; PEG, percutaneous endoscopic gastrostomy; SD, standard deviation.

[a]*P* value from Fisher's exact test.

[b]*P* value from Mann-Whitney U-test.

[c]*P* value from independent t-test.

Assessments

Twenty-four-hour urine for creatinine, and volume was performed for creatinine clearance measurement at baseline (day 1), 48 hours, 7 days, and 22 days after receiving cisplatin (the end of study analysis). Moreover, the volume of oral fluid/oral nutritional supplement intake and urine output were monitored and recorded daily during hospitalization. If any enrolled patient developed low urine output, < 0.5 mL/kg/h, the protocol was stopped because of safety concerns, and those patients were consequently treated by a nephrologist.

We used Acute Kidney Injury Network (AKIN) criteria (ie, increased serum creatinine level of ≥ 0.3 mg/dL or ≥ 50% within 48 hours or urine output of < 0.5 mL/kg/h for > 6 hours) and 24-hour urine creatinine clearance to define Acute Kidney Injury (AKI) condition as the primary end point.

Furthermore, AEs of special interests such as nausea and vomiting, and electrolyte disturbance were evaluated using the Common Terminology Criteria of Adverse Events system, version 5.0.[8]

Statistical Analysis

On the basis of the result of related studies, IV mannitol was hypothesized to reduce the incidence of cisplatin-induced nephrotoxicity by 30% (Data Supplement). With an α (significance) level of .05 and a power of detection of difference of 90%, assuming a two-tailed approach, the sample size required totaled 45 patients each group. Patients' characteristics were calculated for all variables. Outcomes were compared between groups using chi-square tests for categorical variables. Fisher's exact test and Mann-Whitney U test were used to compare between the two groups for continuous end point. A *P* value of .05 was considered significant. Univariate analysis was conducted to determine which variables were predictive for worsening kidney function. Statistical analysis was performed using STATA V.17.

RESULTS

Patients

A total of 59 patients with solid cancers were screened. Eleven patients (18.6%) were excluded from the study because of patient refusal and worsening GFR at random assignment. Therefore, 48 patients were enrolled in the study between November 2018 and December 2019 (Fig 1). The study enrollment was stopped at 48 patients in December 2019 because of COVID-19 pandemic conditions. Twenty-three of 48 patients (47.9%) received mannitol combined with hydration, and 25 of 48 patients (52.1%) comprised the placebo group. All enrolled patients received complete study treatment. Baseline characteristics were balanced between the two groups (Table 1). The most common primary cancers were head and neck cancer, and esophageal cancer, 66.7%, and 12.5%, respectively. The majority of patients received cisplatin alone, and cisplatin combined with fluorouracil, which were 56.3% and 22.9%, respectively. Thirty-two of 48 patients (66.7%) received concurrent treatment with cisplatin and radiation. The percentage of patients receiving either dose of cisplatin at > 80 mg/m^2 or ≤ 80 mg/m^2 once every three weeks were similar, which were 58.3%, and 41.7%, respectively. The means of total fluid intake including oral fluid intake, oral nutritional support intake, and IV hydration during hospitalization were similar between both groups, which were 6,581.43 $\pm$ 1,208.77 mL in the mannitol group, and 6,115.92 $\pm$ 1,439.15 mL in the placebo group (*P* value = .88). The means of total urine outputs during hospitalization were similar between both groups, which were 5,767.61 $\pm$ 2,024.88 mL in the mannitol group, and 6,007.00 $\pm$ 2,303.44 mL in the placebo group (*P* value = .35). All enrolled patients were followed for 6 months.

Clinical Outcomes

After receiving cisplatin for 48 hours, seven of 23 patients (37.4%) in the mannitol group, and 10 of 25 patients (40%) in the placebo group had increased serum creatinine levels ≥ 0.3 mg/dL meeting AKI criteria by AKIN, which was not a statistically significant difference between the two groups (*P* value = .48; Table 2).

At 7 days after receiving cisplatin, 36.4% in the placebo group and 4.5% in the mannitol group had reduced eGFR to below 60 mL/min/1.73 m^2, which was statistically significance difference between both groups (*P* value = .021; Table 2).

Twelve of 25 patients (48%) in the placebo group developed low eGFR (eGFR $<$ 60 mL/min/1.73 m^2) by 24-hour urine creatinine clearance, and only three of 23 patients (13.6%) in the mannitol group, which differed significantly between the two groups (*P* value = .012). Moreover, a significant difference was found in mean 24-hour urine creatinine clearance between the two groups after receiving cisplatin; the mean 24-hour urine creatinine clearances were 67.4 $\pm$ 30.6 mL/min/1.73 m^2 in the placebo group, and 96.4 $\pm$ 45.5 mL/min/1.73 m^2 in the mannitol group (Fig 2).

Univariate analysis showed that concomitant radiation and high dose of cisplatin ($>$ 80 mg/m^2) were associated with decreased 24-hour urine creatinine clearance ($<$ 60 mL/min/1.73 m^2; Table 3).

Safety

One of 25 patients (4%) in placebo group developed severe infection. Hyponatremia was found for 36% of patients

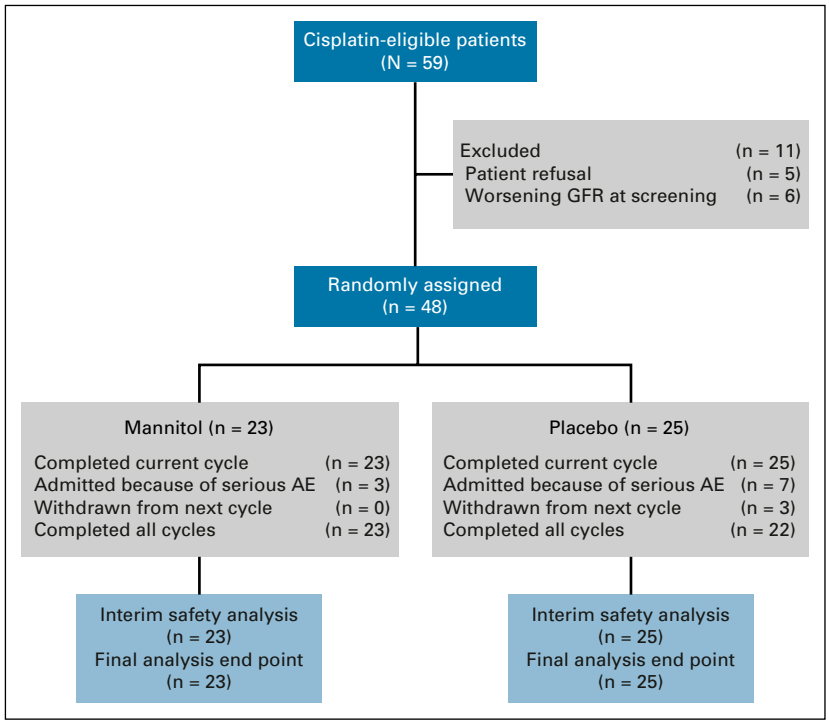

FIG 1. CONSORT diagram. A total of 59 patients with solid cancers were screened. Eleven patients (18.6%) were excluded from the study because of patient refusal and worsening GFR at random assignment. Therefore, 48 patients were enrolled in the study (23 patients in the mannitol arm and 25 patients in the placebo arm). AE, adverse event; GFR, glomerular filtration rate.

TABLE 2. Comparison in Rate of Acute Kidney Injury After Treatment With Cisplatin by Using Serum Creatinine

Outcome of Acute Kidney Injury	Total (n = 48) No. (%)	Placebo (n = 25) No. (%)	Mannitol (n = 23) No. (%)	*P*
Increase in serum creatinine at 48 hours				.489
> 0.3 mg/dL or 1-1.5×	17 (35.4)	10 (40.0)	7 (30.4)	
No	31 (64.6)	15 (60.0)	16 (69.6)	
Increase in serum creatinine at 48 hours				.490[a]
2×	2 (4.2)	2 (8.0)	0 (0)	
No	46 (95.8)	23 (92.0)	23 (100)	
Increase in serum creatinine at day 7				.404
> 0.3 mg/dL or 1-1.5×	36 (75.0)	20 (80.0)	16 (69.6)	
No	12 (25.0)	5 (20.0)	7 (30.4)	
Estimated serum GFR at 48 hours, mL/min/1.73 m^2				1.000[a]
< 60	1 (2.1)	1 (4.0)	0 (0)	
≥ 60	47 (97.9)	24 (96.0)	23 (100)	
Estimated serum GFR at day 7, mL/min/1.73 m^2				.021[a,b]
< 60	9 (20.5)	8 (36.4)	1 (4.5)	
≥ 60	35 (79.5)	14 (63.6)	21 (95.5)	
> 25% decrease in eGFR at 48 hours				.490[a]
Yes	2 (4.2)	2 (8.0)	0 (0)	
No	46 (95.8)	23 (92.0)	23 (100)	
> 25% decrease in the eGFR at day 7				.031[b]
Yes	10 (22.7)	8 (36.4)	2 (9.1)	
No	34 (77.3)	14 (63.6)	20 (90.9)	

NOTE. *P* value from chi-square test.
Abbreviations: eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.
[a]*P* value from Fisher's exact test.
[b]Significant at the .05 level.

(nine of 25 patients) receiving placebo and for 17.4% of patients (four of 23 patients) receiving mannitol, with no apparent difference between both groups (*P* value = .14). Other AEs of interest such as hypokalemia, nausea, and vomiting were similar between the two treatment groups (Table 4).

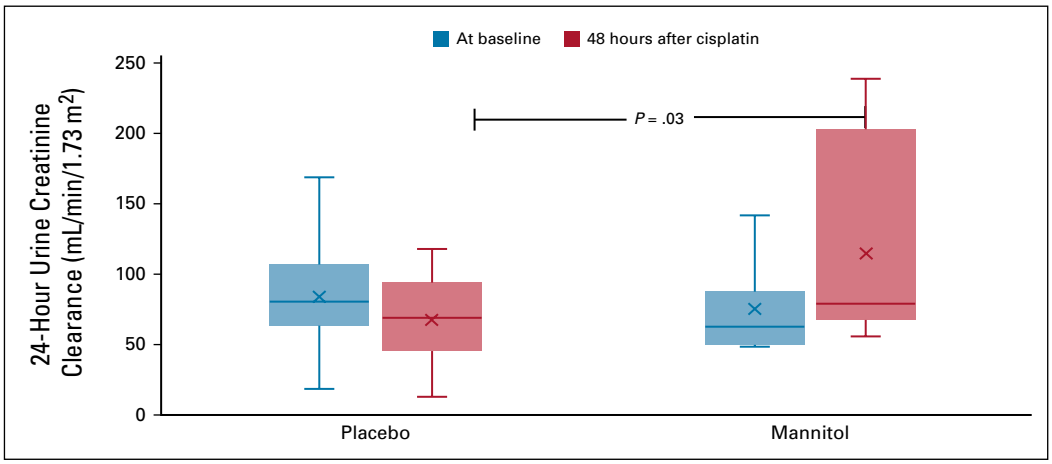

FIG 2. Mean 24-hour urine creatinine clearance (mL/min/1.73 m^2) between the two groups at baseline and after receiving cisplatin. A significant difference was found in mean 24-hour urine creatinine clearance between the two groups after receiving cisplatin; the mean 24-hour urine creatinine clearances were 67.4 ± 30.6 mL/min/1.73 m^2 in the placebo group, and 96.4 ± 45.5 mL/min/1.73 m^2 in the mannitol group (*P* value = .03).

TABLE 3. Associated Factors for Declining of the Mean 24-Hour Urine Creatinine Clearance (< 60 mL/min/1.73 m^2) by Using Univariate Analysis

Variables	Placebo Group (%)	Mannitol Group (%)	*P*
Concomitant radiation	58.0	14.0	.014[a]
No concomitant radiation	8.33	4.76	.53
High-dose cisplatin (> 80 mg/m^2)	60.0	16.7	.028[a]
Cisplatin ≤ 80 mg/m^2	8.83	4.46	.43
BMI < 25 kg/m^2	33.3	19.05	.65
BMI ≥ 25 kg/m^2	8.33	0.0	.50

Abbreviation: BMI, body mass index.
[a]Significant at the .2 level.

DISCUSSION

The incidence of cisplatin-induced nephropathy from our cohort was 35.4%, which was similar to several publications.[2,3,9] There were controversial results from many studies involving mannitol. Three clinical study results showed no benefit for nephrotoxicity prevention and did not support its use.[4,10,11] A study showed no significant increased differences in serum creatinine level between patients with or without mannitol.[10] Moreover, 28% of patients receiving mannitol developed worsening conditions of kidney injury because of overdiuresis effect from mannitol.[10]

Preventing cisplatin-induced nephrotoxicity with mannitol combined with hydration observed in our study was in line with values from one study. Al-Sarraf et al[1] conducted a phase II randomized, controlled study among patients with refractory advanced melanoma, treated with cisplatin 100 mg/m^2 once every 3 weeks. Patients with mannitol (n = 34) exhibited lower incidence of nephrotoxicity after the first cycle of cisplatin compared with patients with hydration alone (n = 33), of which the percentages were 15% and 30%, respectively. However, this study did not report statistically significant values.[1] Although our study results were not demonstrated a significant difference in the incidence of AKI by AKIN criteria at 48 hours after receiving cisplatin between the two groups, a significant difference was found between the two groups in terms of kidney function impairment (eGFR below 60 mL/min/1.73 m^2) using 24-hour urine creatinine clearance measurement (13.6% in the mannitol group *v* 48% in the placebo group, *P* value = .012). Furthermore, our result demonstrated a nephroprotective effect at 7 days after receiving cisplatin.

TABLE 4. Comparison in Rate of Acute Adverse Drug Reaction

Adverse Events	Total (n = 48) No. (%)	Placebo (n = 25) No. (%)	Mannitol (n = 23) No. (%)	*P*
Hyponatremia, mEq/L				.147
< 135	13 (27.1)	9 (36.0)	4 (17.4)	
≥ 135	35 (72.9)	16 (64.0)	19 (82.6)	
Hypokalemia, mEq/L				1.000[a]
< 3.5	5 (10.4)	3 (12.0)	2 (8.7)	
≥ 3.5	43 (89.6)	22 (88.0)	21 (91.3)	
Nausea grade				.668[a]
≥ 2	6 (12.5)	4 (16.0)	2 (8.7)	
< 2	42 (87.5)	21 (84.0)	21 (91.3)	
Vomiting grade				1.000[a]
≥ 2	4 (8.3)	2 (8.0)	2 (8.7)	
< 2	44 (91.7)	23 (92.0)	21 (91.3)	

NOTE. *P* value from chi-square test.
[a]*P* value from Fisher's exact test.

Our results were similar to related studies.[4,6] For example, a retrospective study among patients with squamous cell carcinoma of the head and neck receiving concurrent chemoradiation of 100 mg/m^2 of cisplatin and mannitol plus hydration demonstrated 84% lower risk for increasing grade 3 serum creatinine.[6] From a systematic review, mannitol was considered among patients receiving cisplatin more than 100 mg/m^2.[5] This corresponded with our subgroup analysis; patients receiving concurrent radiation and patients receiving cisplatin > 80 mg/m^2 showed the greatest nephroprotective effect from mannitol combined with hydration.

Several relevant studies have generally used serum creatinine, and calculated serum eGFR to clarify the definition of nephrotoxicity.[5] Two of 24 studies from a systematic review used urine creatinine clearance for measurement.[5,12,13] Regarding several limitations to measure kidney function, our study considered using both serum creatinine and 24-hour urine creatinine clearance to measure the primary end point. Serum creatinine is a convenient measurement, but many confounding factors could have affected the accuracy of kidney function such as muscle mass and dietary protein intake. The 24-hour urine creatinine clearance is widely used to assess GFR. However, the accuracy of urine collection involves a challenge interpreting the results.

We performed the following steps of standard approach for IV hydration with isotonic solution to ensure equivalency in hydration and alleviate confounding factors. Therefore, our study protocol is applicable to general clinical practice. However, neurokinin-1 receptor antagonist and second-generation 5-hydroxytryptamine-3 receptor antagonist[14] were not included in the protocol regarding reimbursement issues. For safety concerns, any enrolled patient who developed low urine output (< 0.5 mL/kg/h) was defined at AKI end point by AKIN criteria rather than potential bias.

Our study emphasized the common clinical practice using mannitol with hydration to reduce cisplatin nephrotoxicity. This study was prematurely stopped because of slow recruitment regarding COVID-19 pandemic conditions. In fact, the statistical power of study depends on clinical relevant difference (effect size) and sample size. If the effect size is large, it is possible to detect an effect in smaller sample size. Our study obtained significant results with the relatively small sample size, and suggests that the effect size reported above are large. Moreover, the relatively small

sample size may not have exhibited the power to expose such a particularly small effect on additional variables with tumor groups. Furthermore, the data of subsequent cycles of cisplatin and cisplatin induced kidney injury on next cycles were not collected. Furthermore, the definition of nephrotoxicity varied across related studies. Therefore, a larger study is required to confirm the results and to explore an appropriate measurement method for cisplatin-induced nephrotoxicity.

In conclusion, mannitol combined with hydration significantly prevented acute kidney impairment. Furthermore, mannitol should be particularly considered among patients receiving cisplatin > 80 mg/m^2, or patients receiving concomitant radiation. However, IV hydration with isotonic solution and avoidance of coadministration with nephrotoxic agents constitute the mainstay of treatment.

AFFILIATIONS

[1]Division of Medical Oncology, Department of Medicine, Phramongkutklao Hospital, College of Medicine, Bangkok, Thailand
[2]Division of Nephrology, Department of Medicine, Phramongkutklao Hospital, College of Medicine, Bangkok, Thailand

CORRESPONDING AUTHOR

Naiyarat Prasongsook, MD, MS, Clinical Research Center, Phramongkutklao Hospital, 315, Rachwithi Rd, Phayathai, Rachathewi, Bangkok, Thailand 10400; Twitter: @NaiyaratPR; e-mail: naiyarat_p@yahoo.co.th/.

SUPPORT

Supported by the Office of Research Development, Phramongkutklao College of Medicine, Phramongkutklao Hospital, Bangkok, Thailand.

DATA SHARING STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

AUTHOR CONTRIBUTIONS

Conception and design: Panot Sainamthip, Naiyarat Prasongsook
Financial support: Naiyarat Prasongsook
Administrative support: Naiyarat Prasongsook
Provision of study materials or patients: Siriwimon Saichaemchan, Naiyarat Prasongsook
Collection and assembly of data: Panot Sainamthip, Siriwimon Saichaemchan, Naiyarat Prasongsook
Data analysis and interpretation: Panot Sainamthip, Bancha Satirapoj, Naiyarat Prasongsook
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Panot Sainamthip
Stock and Other Ownership Interests: Ladprao General Hospital

Naiyarat Prasongsook
Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim, Roche, Novartis, Bristol Myers Squibb/Celgene
Travel, Accommodations, Expenses: AstraZeneca, Roche

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors are grateful to the Office of Research Development, Division of Nephrology, Division of Medical Oncology, Department of Internal Medicine, and PMK Cancer Center, Phramongkutklao Hospital, for supporting this study.

REFERENCES

1. Al-Sarraf M, Fletcher W, Oishi N, et al: Cisplatin hydration with and without mannitol diuresis in refractory disseminated malignant melanoma: A southwest oncology group study. Cancer Treat Rep 66:31-35, 1982
2. Madias NE, Harrington JT: Platinum nephrotoxicity. Am J Med 65:307-314, 1978
3. Manohar S, Leung N: Cisplatin nephrotoxicity: A review of the literature. J Nephrol 31:15-25, 2018
4. Morgan KP, Snavely ACWind LS, et al: Rates of renal toxicity in cancer patients receiving cisplatin with and without mannitol. Ann Pharmacother 48:863-869, 2014
5. Crona DJ, Faso A, Nishijima TF, et al: A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. Oncologist 22:609-619, 2017
6. McKibbin T, Cheng LL, Kim S, 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 24:1789-1793, 2016
7. Cvitkovic E, Spaulding J, Bethune V, et al: Improvement of cis-dichlorodiammineplatinum (NSC 119875): Therapeutic index in an animal model. Cancer 39:1357-1361, 1977
8. National Institutes of Health, National Cancer Institutes: Common Terminology Criteria for Adverse Events (CTCAE) Version 5. US Department of Health and Human Service. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
9. Latcha S, Jaimes EA, Patil S, et al: Long-term renal outcomes after cisplatin treatment. Clin J Am Soc Nephrol 11:1173-1179, 2016
10. Ostrow S, Egorin MJ, Hahn D, et al: High-dose cisplatin therapy using mannitol versus furosemide diuresis: Comparative pharmacokinetics and toxicity. Cancer Treat Rep 65:73-78, 1981
11. Santoso JT, Lucci JA, Coleman RL, et al: Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: A randomized trial. Cancer Chemother Pharmacol 52:13-18, 2003

12. Somlo G, Doroshow JH, Lev-Ran A, et al: Effect of low-dose prophylactic dopamine on high-dose cisplatin-induced electrolyte wasting, ototoxicity, and epidermal growth factor excretion: A randomized, placebo-controlled, double-blind trial. J Clin Oncol 13:1231-1237, 1995
13. Yamamoto Y, Watanabe K, Tsukiyama I, et al: Nephroprotective effects of hydration with magnesium in patients with cervical cancer receiving cisplatin. Anticancer Res 35:2199-2204, 2015
14. Vimolchalao V, Sakdejayont S, Wongchanapai P, et al: The efficacy and safety of the addition of olanzapine to ondansetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Int J Clin Oncol 25:396-402, 2019