RESEARCH ARTICLE

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Efficacy of Short Hydration for Intermediate to High-Dose Cisplatin-Based Chemotherapy for Outpatients: SHORTCIS Trial

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Abstract

Objective: Supporting data exists concerning short hydration to prevent cisplatin-induced nephrotoxicity. However, only a few studies exist. Further, data remains limited, comprising mostly retrospective data. Therefore, the study would like to evaluate the efficacy of short hydration using a prospective cohort study. **Materials and Methods:** This is a prospective cohort non-randomized controlled study in patients receiving intermediate to high doses of cisplatin. Short hydration was set as the intervention arm, while conventional hydration was set as the controlled arm. The consecutive estimates glomerular filtration rates (eGFR) were compared at baseline, Week 3, Week 6, Week 9, Week 12, and Week 15 for both groups by using multilevel regression analysis with the random-effects model with double adjustment (propensity score and confounding adjustment) was used. The trial was registered with the Thai Registry of Clinical Trials, SHORTCIS ThaiClinicalTrials.org, number TCTR20210128002. **Results:** 30 patients were registered. 14 were assigned to a short hydration group, while 16 were assigned to a conventional hydration group. The levels of consecutive eGFR of the group receiving short hydration were stable (regression coefficients 0.05), while the levels of consecutive eGFR of the group receiving conventional hydration were declined (regression coefficients -1.94). The multilevel regression analysis of consecutive eGFR between conventional group and short hydration group when adjusted for random-effects parameters and double adjustment were significantly different (p-value = 0.001). When analyzing the relationship of received short hydration, it could significantly reduce the risk of nephrotoxicity as well, i.e. acute kidney injury (odds ratio 0.06, 95%CI 0.003, 0.990, p-value 0.049). **Conclusion:** Short hydration was more efficient for preventing nephrotoxicity than conventional hydration protocols in patients receiving intermediate to high doses of cisplatin.

Keywords: Short hydration- chemoprevention- cisplatin-induced nephrotoxicity

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Introduction

Cisplatin is a chemotherapy drug in the group of alkylating agents. It involves anti-cancer activation at all stages of cell division in the cell cycle (cell-cycle nonspecific antineoplastic agents). Therefore, cisplatin is a chemotherapy drug formulated for treating different types of cancer, e.g. lung cancer, gastric cancer, esophageal cancer, head and neck cancer (Bunn, 1989; Aisner and Abrams, 1989; Szturz et al., 2019; Iocca et al., 2018; Li et al., 2017; Wagner et ai., 2017).

Frequent side effects associated with the drug include nausea, vomiting, nephrotoxicity, and neutropenia. Particularly, nephrotoxicity is a common condition when receiving intermediate to high-dose cisplatin over 60 mg/m2 because cisplatin is basically released from the kidneys and can be accumulated in renal proximal tubules, leading to nephrotoxicity, particularly in the dose of over 60 mg/m^2 (Miller et al., 2010; Ozkok and Edelstein, 2014; Higuchi and Yanagawa, 2019). The side effects can be prevented by massive hydration at least 3,000 mL, before and after cisplatin administration (Yao et al., 2007; Horinouchi et al., 2018; Yamada et al., 2011). Most continuous intravenous hydration takes at least 24 hours. Therefore, early admission to hospital is required. Although carboplatin, which is classified as platinum chemotherapy, is the same as cisplatin and does not require hydration, there have been numerous studies showing that cisplatin is still considered standard chemotherapy for many cancers (Lokich and Anderson, 1998; Go and Adjei, 1999; Vogelzang et al., 2003).

A number of studies on hydration for nephrotoxicity prevention in outpatients have revealed that short hydration with lower volume than conventional hydration is safe for patients receiving intermediate to high-dose cisplatin (Horinouchi et al., 2013; Naiki et al., 2020;

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Sakaida et al., 2016; Tanaka et al., 2018; Ouchi et al., 2014). Besides, studies on a systematic review of cisplatin-induced nephrotoxicity prevention have found that hydration is necessary for nephrotoxicity prevention. It was found that using short hydration along with magnesium supplementation, mannitol, and diuretics is the best practice principle for the safe use of cisplatin (Crona et al., 2017).

Most previous studies have been retrospective studies or systematic reviews. However, this study aimed to focus on the efficacy of short hydration for nephrotoxicity prevention or acute kidney injury prevention in patients receiving intermediate to high-dose cisplatin-based outpatient chemotherapy regimen. The study was conducted as a prospective cohort, non-randomized controlled study.

Materials and Methods

This is a prospective cohort, non-randomized controlled study. The experimental group received a short course of hydration with magnesium and mannitol supplements before a medium to high dose of cisplatin and treated as outpatients. The control group consisted of patients who received conventional hydration prior to administration of a medium to high- dose of cisplatin, under conventional hydration of the control group, which required hospitalization. The details are described as follows.

Patients: The experiment group received short hydration protocol, used in patients receiving intermediate to high-dose cisplatin for outpatients at the Division of Medical Oncology, Department of Internal Medicine, Buddhasothorn Hospital, between December 2019 and February 2021. The sample size was calculated in the form of one study group by statistical parameters based on anticipated incidence of 60% [8]. The probability of Type I Error was set at the alpha of 0.05, with Type II Error. For the ability to detect the difference between groups when a difference actually exists, power was set at 95%, with the probability of non-response or drop out at 20%. The sample size obtained was 14.

Inclusion criteria

1. Cancer patients treated with intermediate to high dose cisplatin in outpatient
2. Age > 18 years
3. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
4. Adequate renal function [estimates glomerular filtration rate (eGFR)>60 mL/min]

Exclusion criteria

1. Underlying heart disease, poor LV function (LVEF<40%).

2. Hearing impairment

Termination criteria for individual participants

1. Levels of eGFR decline >20% from the baseline after cisplatin administration

Control group received conventional hydration regimen used in cancer patients receiving intermediate to high-dose cisplatin for inpatients, e.g. esophageal cancer, gastric cancer, head and neck cancer, and lung cancer. Data was obtained from Hospital–based Cancer Registry Division of Medical Oncology, Department of Internal Medicine, Buddhasothorn Hospital, between January 2019 and November 2019.

The objective was to evaluate the efficacy of short hydration for nephrotoxicity prevention, i.e. acute kidney injury (AKI). Therefore, the primary outcome of the study was acute kidney injury (AKI). It defined eGFR decline >20% from the baseline after cisplatin administration. Patients with AKI were withdrawn from the study.

The study protocol was approved by the Institutional Review Board of Buddhasothorn Hospital (number BSH-IRB 013/2563). The study was registered in the Thai Registry of Clinical Trials with identification number TCTR20210128002 (Acronym SHORTCIS). All participants signed written informed consent as endorsed by the Ethics Committee.

Hydration methods

Schedule details of the hydration methods for the two groups are shown in Table 1. The conventional hydration protocol consisted of pre-hydration with 3,000 mL over 24 hours on the day before day 1. Intravenous 20%mannitol 65 mL before cisplatin was used, followed by post hydration 1,000 mL plus 20%mannitol 135 mL plus magnesium and potassium supplement. The total amount of hydration was 4-4.5 L, taking over 30 hours. On the other hand, the short hydration protocol consisted of 1,000 mL plus 20%mannitol 200 mL before cisplatin administration, followed by post hydration 500 mL plus potassium supplement. The total amount of hydration was 1.5-2 L, taking 6 hours. Both groups received equal emesis prophylaxis and intravenous treatment with dexamethasone. They were also routinely advised about oral hydration 2-3 L/day during the first 3 days after receiving cisplatin. Both groups received cisplatin every 3 weeks.

Statistical analyses: Data concerning renal function was collected by estimating glomerular filtration rate (eGFR) before receiving cisplatin (baseline before cisplatin) in Week 0. Every 3 weeks, the levels of eGFR were measured each time before receiving cisplatin. In Week 3, Week 6, Week 9, Week 12, and Week 15, patients would be withdrawn from the study if acute kidney injury was found, meaning eGFR declined less than 20%. The variables for both groups were collected, i.e. age, gender, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, cancer type, and underlying diseases (hypertension, gouty arthritis and diabetes mellitus). Confounding was conducted by either indication or contraindication, i.e. age, ECOG performance status, cancer type, and underlying diseases, confounded by prognostic imbalance from non-randomized designs.

The levels of consecutive eGFR were analyzed and compared at each point in time at the baseline; in week 3, week 6, week 9, week 12, and week 15 of the conventional hydration group and the short hydration group. The levels of eGFR were influenced by treatment effect and time effect. They were repeated measures of correlation data.

Therefore, they were analyzed by multilevel regression analysis with the random-effects model. Prognostic imbalance factors were confounded by indication or contraindication based on a propensity score in the regression model. Statistical analyses were performed using STATA version 16 (StataCorp, TX, USA).

Results

There were 30 patients in the study. 14 were in the short hydration group, while 16 were in the conventional hydration group (Figure 1). Patient characteristics are shown in Table 2. The means of eGFR are compared from the start of treatment by intermediate to high dose cisplatin from the baseline in Cycle 1 (Week 0) to Cycle 6 (Week 15) between the short hydration group and the conventional hydration group (Figure 2).

The level of eGFR was different in each patient from the beginning. The prognostic factors for each patient in each group were also different. The levels of consecutive eGFR in short hydration group and conventional hydration group were affected by both the treatment effect and the time effect. Therefore, repeated measures correlation data must be analyzed by multilevel regression with the random-effects model. It was found that the levels of consecutive eGFR from the baseline and the points of time in Week 3, Week 6, Week 9, Week 12, and Week 15 of the short hydration group were stable (regression coefficients 0.05), while they declined in the conventional hydration group (regression coefficients -1.67), implying a significant difference (p-value = 0.001) (Table 3). The model multilevel regression analysis is displayed in Figure 3.

After adjusting the power of prognostic factors confounded by indication and/or by contraindication, i.e. age, ECOG performance status, cancer type, and

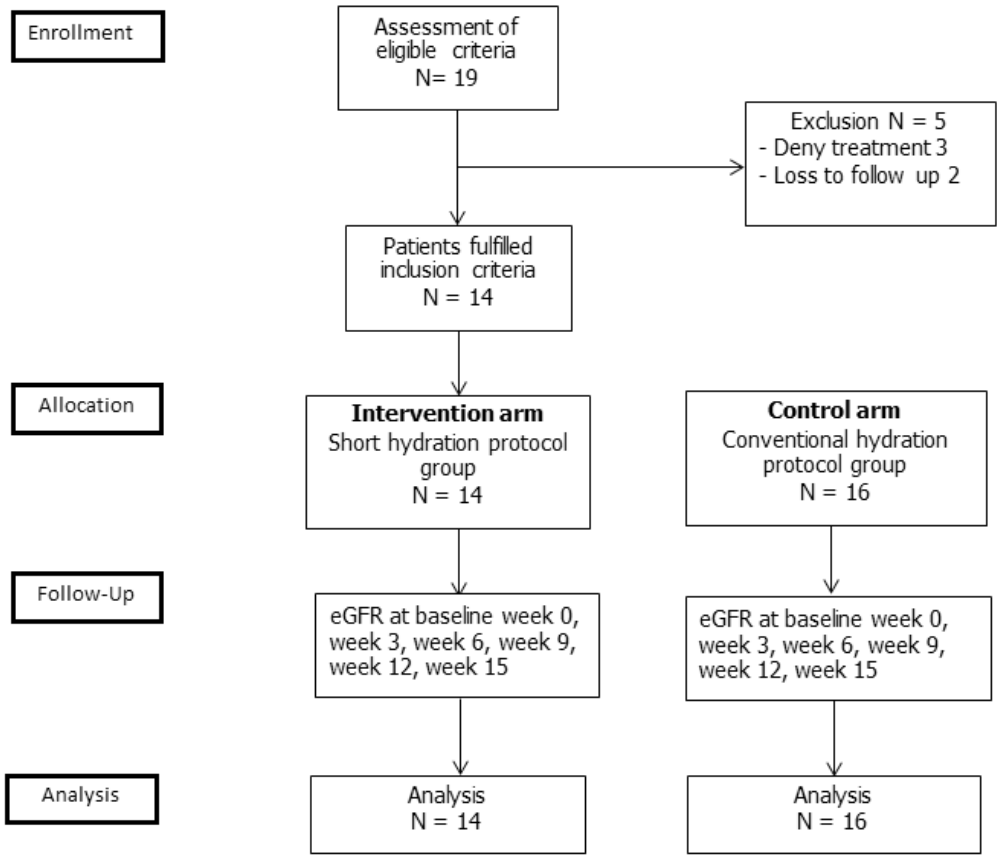

Figure 1. The CONSORT Flow Diagram

Table 1. Protocols for Conventional and Short Hydration

Schedule Conventional hydration protocol	Infusion time	Schedule Short hydration protocol	Infusion time
NSS 1000 mL IV infusion in 8 hours x 3 bottles	24 hours	NSS 1000 mL + KCL 10 mEq + 50% MgSO4 2 mL + IV infusion 500 mL/hour X 1 bottle	2 hours
Dexamethasone 20 mg +Ondansetron 16 mg in NSS 100 mL	30 minutes	Dexamethasone 20 mg +Ondansetron 16 mg in NSS 100 mL	30 minutes
20% mannitol 65 mL	10 minutes	20% mannitol 200 mL	30 minutes
Cisplatin in NSS 200 mL	1 hour	Lasix (40) 1 tab per oral	
20% mannitol 135 mL+ D5NS 1000 mL+10%MgSO4 10 mL +KCL 20 mEq	6 hours	Cisplatin in NSS 250 mL	2 hours
		NSS 500 mL + KCL 10 mEq	1 hour

Table 2. Patient Characteristics of Conventional Hydration Group and Short Hydration Group

Characteristics	Conventional hydration N=16	Short hydration N= 14	p-value
Age (year)			
Mean (± SD)	57.31 (± 9.96)	59.14 (±10.85)	0.634
Gender, N (%)			
Male	16 (100.00)	10 (71.43)	0.037*
BMI			
Mean (± SD)	21.72 (±4.78)	23.36 (±4.07)	0.323
ECOG performance status, N (%)			
0	3 (18.75)	4 (28.57)	0.194
1	9 (56.25)	10 (71.43)	
2	4 (25.00)	0 (0.00)	
Cancer type, N (%)			
Lung cancer	10 (62.50)	14 (100.00)	0.032*
Head and neck	4 (25.00)	0 (0.00)	
Upper GI tract	2 (12.50)	0 (0.00)	
Underlying, N (%)			
Yes	3 (18.75)	8 (57.14)	0.030*
Diabetes mellitus	3	0	
Hypertension	0	7	
Gouty arthritis	0	1	
Combined agent, N (%)			
Gemcitabine	1 (6.25)	14 (100.00)	<0.001*
Etoposide	9 (56.25)	0 (0.00)	
Fluorouracil	6 (37.50)	0 (0.00)	

*Statistically significant p-values

underlying diseases by propensity score and adjustment of confounding factors (double adjustment), i.e. gender and BMI in the equation of multilevel regression analysis with the random-effects model, it was found that the levels of consecutive eGFR from the baseline and the points of time in Week 3, Week 6, Week 9, Week 12, and Week 15 of the short hydration group were stable (regression coefficients 0.05), while they declined in the conventional hydration group (regression coefficients -1.94), implying a significant difference (p-value = 0.001) (Table 4.). The model of multilevel regression analysis with random-effects with double adjustment (propensity score and confounding variables) of repeated measures correlation data (consecutive eGFR) is displayed in the form of a relationship model in Figure 4.

When analyzing the relationship between acute kidney

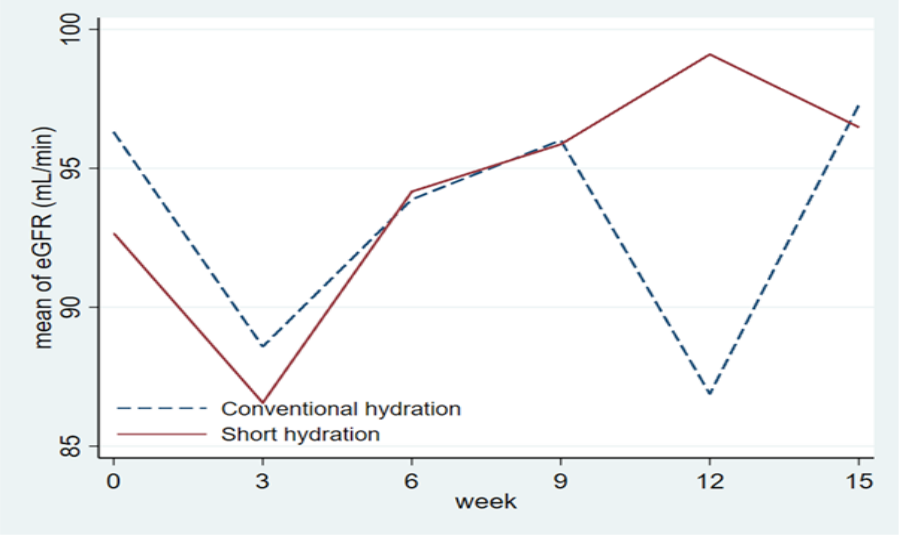

Figure 2. Comparison of the Changing Means of eGFR between the Conventional Hydration Protocol Group (dash line) and the short hydration protocol group (solid line) from the start of treatment using the chemotherapy drug, Cycle 1 (Week 0) to Cycle 6 (Week 15).

Table 3. Multilevel Regression Analysis with the Random-Effects Model for Repeated Measures Correlation Data

eGFR	coefficient	95% Confidence Interval	p-value
Short hydration	-6.05	-21.732, 9.638	0.45
Adjusted interaction of week			
Conventional hydration	-1.67	-2.426, -0.921	<0.001
Short hydration	0.05	-0.663, 0.758	0.896
Random-effects Parameters			
patient: Independent	Estimate	95% Confidence Interval	
var (week)	1.16	0.203, 6.695	
var (_cons)	439	254.861, 756.176	
var (Residual)	68.68	46.907, 100.565	
eGFR between conventional group and short hydration group when adjusted for random-effects parameters		chi2 = 10.62 , p-value = 0.001*	

*Statistically significant p-values

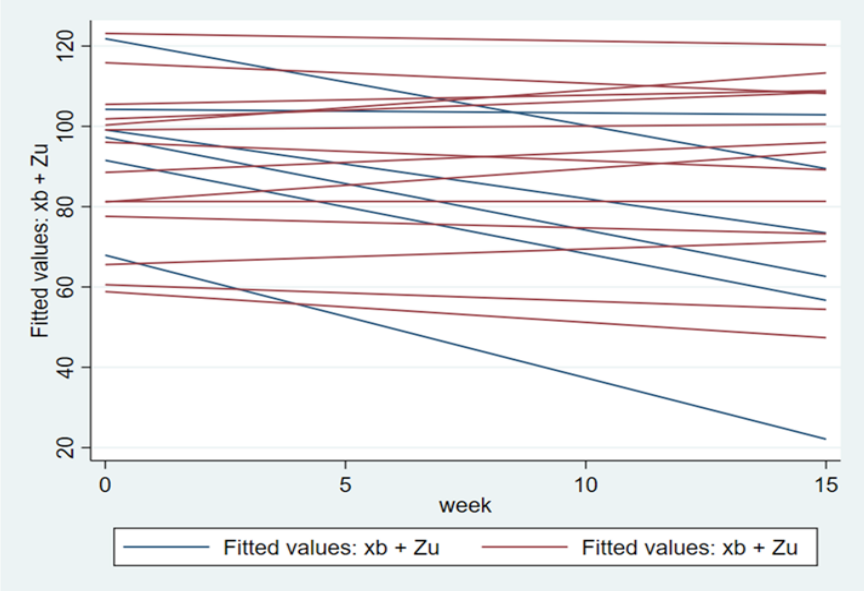

Figure 3. Model of Multilevel Regression Analysis with Random-Effects for Repeated Measures Correlation Data (consecutive eGFR) between short hydration group (red line) and conventional hydration group (blue line)

Table 4. Multilevel Regression Analysis with the Random-Effects Model for Repeated Measures Correlated Data with Double Adjustment (Propensity Score and Confounding Variables)

eGFR	coefficient	95% Confidence Interval	p-value
Short hydration	-7.83	-27.551, 11.891	0.436
Adjusted interaction of week			
Conventional hydration	-1.94	-2.982, -0.902	<0.001
Short hydration	0.05	-0.516, 0.620	0.858
Propensity score	3.67	-128.474, 135.810	0.957
Gender	14.82	-6.892, 36.538	0.181
BMI	-1.15	-3.520, 1.217	0.341
Random-effects Parameters			
patient: Independent	Estimate	95% Confidence Interval	
var (week)	0.73	0.123, 4.381	
var (_cons)	313.49	161.536, 608.396	
var (Residual)	45.96	30.187, 69.965	
eGFR between conventional group and short hydration group when adjusted for random-effects parameters and double adjustment model		chi2 = 10.87, p-value = 0.001*	

*Statistically significant p-values

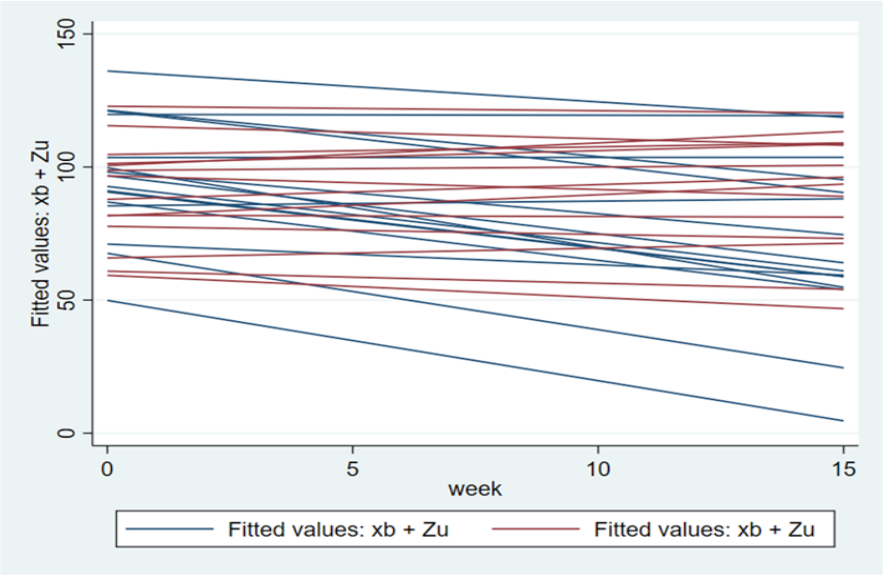

Figure 4. Model of Multilevel Regression Analysis with Random-Effects with Double adjustment (propensity score and confounding variables) for repeated measures correlation data (consecutive eGFR) between short hydration group (red line) and conventional hydration group (blue line)

Table 5. Logistic Regression Analysis with Double adjustment Method

Acute kidney Injury	Odds Ratio	95% Confidence Interval	p-value
Short hydration	0.06	0.003, 0.990	0.049*
Propensity score	0.0003	6.42e-15, 1.63e+07	0.523
Gender	1 (omitted)		
BMI	0.9	0.622, 1.294	0.562

*Statistically significant p-values

injury (nephrotoxicity) and short hydration protocol, the confounding factors were adjusted by double adjustment. It was found that receiving short hydration before intermediate to high dose cisplatin administration could significantly reduce the risk of acute kidney injury (odds ratio 0.06, 95%CI 0.003, 0.990, p-value 0.049).

Discussion

According to the study of Crona (2017), it was found to support short-duration, low-volume, and outpatient hydration regimens for nephrotoxicity prevention in patients receiving intermediate to high doses of cisplatin. The amount of short hydration was 2-4 L, with duration of hydration for 2-6 hours. When cisplatin 50 mg/m^2 and over was provided, potassium and magnesium supplement should be provided as well. After receiving more than 100 mg/m2 of cisplatin, mannitol was also recommended. However, care must be taken because mannitol could cause diuresis, possibly resulting in dehydration and nephrotoxicity (Crona et al., 2017). There have been numerous previous studies on the role of mannitol in nephrotoxicity prevention among patients receiving cisplatin. In fact, it has been available and used widely. Although the role of mannitol as a nephroprotective agent remains unclear, it does not increase the incidence of nephrotoxicity at all (Corbin and Bossaer, 2017; Santoso et al., 2003; Morgan et al., 2012; Ruggiero et al., 2016). Previous studies had also shown that hydration was mostly necessary. However, the short hydration protocols still differed in terms of the amount of fluid hydration, the duration of hydration, or even with or without the administration of mannitol. They were different in each study and the conclusions were unclear.

In this study, patients in the short hydration protocol group received a total of 1.5-2 L of fluid hydration for 6 hours. The received amounts were rather less than the report of systematic review by Crona (2017). Also, all patients in this study received short hydration protocol with potassium and magnesium supplement, along with mannitol. This was in accordance with theories stating that cisplatin-induced nephrotoxicity arises from the accumulation of cisplatin in renal tubules and associated tubular cell necrosis, particularly in the proximal tubules in the outer renal medulla in the S3 segment (Ban et al., 1994). As for nephrotoxicity, it was found to relate to the peak plasma level of platinum after receiving cisplatin (Reece et al., 1987). Receiving hydration and forced diuresis using mannitol or furosemide could prevent this condition. Moreover, there is data supporting the notion that receiving magnesium supplement is one of the most necessary factors to prevent cisplatin induced nephrotoxicity (Casanova et al., 2020; Hamroun et al., 2019). That is because hypomagnesemia causes dehydration and the upregulation of rat organic cation transporter 2, which plays a role in urinary excretion and

the uptake of cisplatin in the proximal tubules. Therefore, it results in renal accumulation of cisplatin that can ultimately lead to nephrotoxicity.

According to the results of this study, it was found that the levels of consecutive eGFR in the short hydration group were stable (regression coefficients 0.05), while they declined in the conventional hydration group (regression coefficients -1.94), implying a significant difference (p-value = 0.001). When analyzing the relationship of receiving short hydration protocol, it could significantly reduce the risk of nephrotoxicity, i.e. acute kidney injury (odds ratio 0.06, 95%CI 0.003, 0.990, p-value 0.049). This implied the efficacy of short hydration to prevent intermediate to high dose cisplatin induced nephrotoxicity.

Despite previous data supporting the efficacy of short hydration protocol to prevent cisplatin-induced nephrotoxicity, most studies were retrospective or systematic reviews. This study was more prominent than previous prospective studies in view of selecting patients based on real-life practice. Decision making on such selection depended on many factors, e.g. age, underlying diseases, and cancer type. For cancer type, it affected the consideration to select a combination drug and cisplatin. Combination drug would be another factor for considering whether to treat patients as outpatients or inpatients. Applying a short hydration protocol would be useful for both outpatient chemotherapy regimen and inpatient chemotherapy regimen. This can help reduce admission durations for patients receiving chemotherapy drugs in hospitals.

Regarding the limitations, this study was non-randomized controlled, with confounding factors affecting prognostic imbalance at first. Despite double adjustment for confounding control, both by propensity score and confounding adjustment, randomized controlled studies are still required in order to confirm the efficacy and safety of short hydration in the future.

In conclusion, short hydration was more efficient to prevent nephrotoxicity, i.e. acute kidney injury, than a conventional hydration protocol in patients receiving intermediate to high doses of cisplatin.

Author Contribution Statement

Chaichana Chantharakhit: Designed the study, collected data, analyzed data, and edited the final version. Nantapa Sujaritvanichpong: Collected data and reviewed the paper. Both authors read and approved the final version.

Acknowledgments

The study protocol was approved by the Institutional Review Board of Buddhasothorn Hospital (number BSH-IRB 013/2563). The study was registered in the Thai Registry of Clinical Trials with identification number TCTR20210128002. This research did not receive a specific grant from any funding agency in the public, commercial, or not-for-profit sectors. As such, there is no funding statement to declare.

Conflicts of interest

The authors affirm that there are no relevant financial or non-financial competing interests to report or conflicts of interest to declare.

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