Furosemide versus mannitol in patients who received cisplatin-based chemotherapy using short hydration: study protocol for a randomized controlled trial

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Abstract

Background: Cisplatin (CDDP) is a key drug for various thoracic malignancies. To avoid renal toxicity of CDDP, mannitol is routinely used, but it reportedly causes phlebitis. Furosemide is another widely-used option for diuresis, but to date, it has not been assessed in comparison with mannitol. We therefore undertake a randomized phase II comparative study of furosemide and mannitol in CDDP-based chemotherapy using short hydration. Methods: This study is designed as a two-arm, prospective, randomized, single-center, open-label phase II study. The primary endpoint is set as the proportion of patients who experienced any grade renal dysfunction, defined as elevation in creatinine using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, during the first cycle. Secondary endpoints are: the proportion of patients who experienced ≥ grade 2 renal dysfunction during the first cycle, any grade and ≥ grade 2 renal dysfunction after the completion of forth cycle, and the proportion of patients who had phlebitis. A total of 105 patients will be enrolled in this trial. Discussion: The results of this study will suggest that furosemide can be better choice than mannitol regarding convenience and in reduction of phlebitis. Trial registration: University Hospital Medical Information Network Clinical Trials Registry, ID: UMIN000031910(http://www.umin.ac.jp/ctr/index.htm). Registered on 1 April 2018.

Background

Cisplatin (CDDP) is a key drug for various types of thoracic malignancies, but renal toxicity occurs in about 30% of the patients who receive it [1]. To avoid renal toxicity of CDDP, adequate hydration and diuresis are important [2, 3]. Currently, mannitol is the only drug recommended in National Comprehensive Cancer Network Chemotherapy Order Templates (NCCN Templates®). Although several studies have compared the renal toxicity of mannitol with another drug, furosemide, their studies did not have sufficient power to detect significant difference [4, 5]. One benefit of furosemide is that it can be infused intravenously. Moreover, patients receiving mannitol often experience phlebitis. We therefore undertake a randomized phase II comparative study of furosemide and mannitol in CDDP-based chemotherapy using short hydration.

Methods And Design

Study objectives

We assess the renal toxicity of furosemide compared with mannitol in CDDP-based chemotherapy (≥ 60 mg/m2) using short hydration in chemotherapy-naive patients with thoracic malignancy.

Study setting

This study is designed as a two-arm, prospective, randomized, single-center, open-label phase II study. The protocol scheme is shown in Figure 1. Study duration will be 3 years and 10 months.

Endpoints

Primary endpoint is set as the proportion of patients who experience any grade renal dysfunction, defined as elevation in creatinine using the CTCAE version 4.0 (based on the upper limit of the normal range (ULN) for serum creatinine at each institute), during the first cycle. Secondary endpoints are: the proportion of patients who experience ≥ grade 2 renal dysfunction (based on the ULN for serum creatinine at each institute) during the first cycle, any grade and ≥ grade 2 renal dysfunction (based on the pretreatment baseline creatinine score in each patient) during the first cycle, any grade and ≥ grade 2 renal dysfunction (based on both criteria) after the completion of fourth cycle, and the proportion of patients who had phlebitis.

Sample size

Using mannitol, two previous prospective studies conducted in an academic center reported that proportion of patients who experienced any grade renal dysfunction, defined as elevation in creatinine by CTCAE version 4.0, was 0–9% [6, 7]. Regarding furosemide, another retrospective study, conducted in a municipal hospital, reported that 52.1% of patients have experienced any grade renal dysfunction [8]. Using this information, arm A (reference arm) proportion in the current study is 10.0%. Sample sizes of 51 patients in each arm achieve ≥ 80% power to detect a non-inferiority margin difference between the group proportions (arm B - arm A) of 10.0% using the one-sided binomial test with 0.2 alpha error. Assuming those patients will be censored, a total of 105 patients are required in the present study.

Eligibility Criteria

Inclusion Criteria

Patients are required to fulfill all the following criteria:

1) Histologically or cytologically confirmed thoracic malignancy

2) Aged between 20 and 74 years

3) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1

4) Adequate renal function (including both serum creatinine ≤ 1.2 mg/dL and a creatinine clearance of ≥ 60 mL/min using Cockcroft-Gault equation)

5) Normal cardiac function

6) Written informed consent

Exclusion Criteria

Patients are excluded if they meet any of all the following criteria:

1) Superior Vena Cava syndrome

2) Active mental illness

3) Pregnancy, breast feeding, or possibility of being pregnant

4) Other conditions rendering patients unsuitable for this study

Registration and Randomization

After registration, patients will be randomized in 1:1 ratio, using minimization method that balances the treatment arms considering sex (male vs. female).

Data collection

Data is collected prospectively for all patients including history, physical examination, laboratory data, all adverse events (Figure 2). Data is collected via datasheets on paper and kept securely. All handling cases are managed by subject identification code or anonymized registration number. The correspondence table of the anonymizing code and names and the consent form containing the names are kept strictly in the separate lockable document storage at Wakayama Medical University Hospital(WMUH).

Interim analysis and monitoring

We plan no interim analysis. In-house monitoring will be performed every 1 year by each data to evaluate and improve study progress and quality.

Treatment

Patients receive CDDP-based chemotherapy (≥ 60 mg/m2). After common antiemetic premedication (aprepitant, palonosetron and dexamethasone) and one other cytotoxic agent, an hour-long infusion of cisplatin dissolved in a 500 mL of normal saline solution is administered between the pre-hydration (potassium chloride and magnesium sulfate dissolved in 500 mL of normal saline solution) and post-hydration (500 mL of maintenance solution). In arm A, patients receive 300 mL of 20% mannitol by intravenous drip infusion just before CDDP, over 30 min. In arm B, patients receive 20 mg of furosemide intravenously an hour before CDDP. CDDP-based chemotherapy is repeated every 3 or 4 weeks for up to four cycles except where there is disease progression, unacceptable toxicity, or patients' refusal. The chemotherapy regimen is shown in Figure 3.

Follow-Up and Assessment

Routine blood tests are evaluated on Day 1 of every cycle and on Day 8 of the first cycle. Phlebitis is assessed by a nurse and another staff physician. All adverse events are defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The study protocol adheres to the SPIRIT statement (Additional file 1).

Statistical Analysis

The primary population for efficacy analysis are the intention-to-treat (ITT) population, defined as all randomized patients. The primary endpoint is the proportion of patients who experienced any grade renal dysfunction. It will be evaluated using risk difference (arm B - arm A) with 80% Confidence intervals (CIs) (one sided). An upper confidence limit below 10% suggest that arm B is non-inferior to arm A. Secondary endpoints are summarized using frequency and percentage with exact 95% CIs using Clopper & Pearson's method for each arm.

Discussion

Diuresis is necessary to avoid renal toxicity by CDDP. Although mannitol is the only drug recommended in NCCN Templates®, furosemide may be a useful option according to previous small studies. These studies were conducted in a prospective manner, but statistical concerns exist. If the current study reaches primary endpoint, it will suggest that furosemide can be better choice than mannitol regarding convenience and in reduction of phlebitis. This study has several limitations. First, It is designed nonblinded. Another limitation is single institutional feature. Despite its limitations, we believe that result of this trial will add useful information to support the utility of furosemide.

Trial Status

Wakayama Medical University Hospital(WMUH) Institutional Review Board approved the final version of the protocol prior to the start of the study (approval number: 2258). It was registered on the University Hospital Medical Information Network Clinical Trials Registry as UMIN000031910(http://www.umin.ac.jp/ctr/index.htm). The trial is open for recruitment from May 2018.

Declarations

Acknowledgements

We deliver our thanks to all the staff for their valuable support in participant recruitment.

Ethics approval and consent to participate

The study is conducted in accordance with the Declaration of Helsinki. WMUH Institutional Review Board approved the final version of the protocol (version 2.0) prior to the start of the study (approval number: 2258). This study was registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN000031910). We will obtain informed consent by written from all participants in the study.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets are generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EM and HA designed the protocol and drafted the manuscript. TS performed the statistical analysis. KW and NY further aided in assessment and revision of the protocol and revised the manuscript. All authors read and approved the final version of the protocol.

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Figures

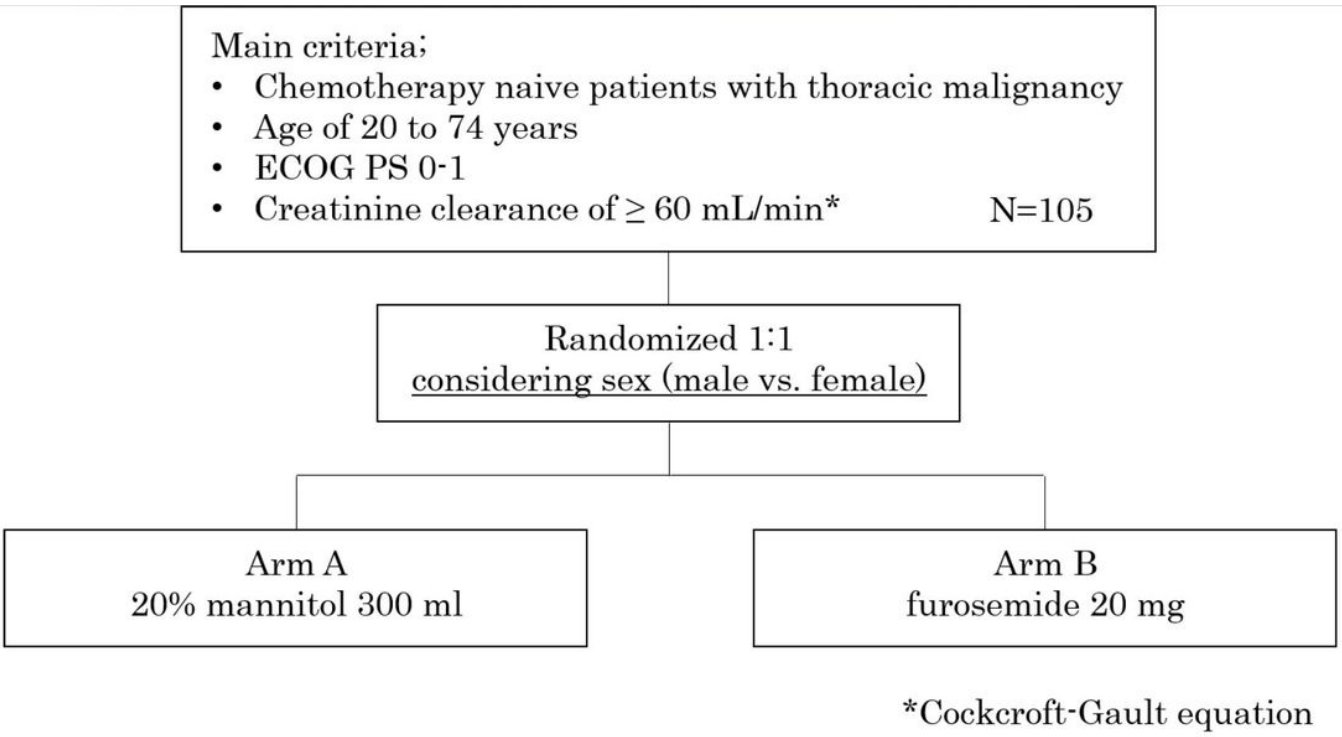

Figure 1

The protocol scheme

	STUDY PERIOD														
	Enrolment	Allocation	Post-allocation												close-out
			1							2		3		4		
TIMEPOINT	-14days	0	1d (start)	1d (end)	2d	3d	4d	5d	8d	1d (start)	1d (end)	1d (start)	1d (end)	1d (start)	1d (end)	within 30days(after protocol off)
ENROLMENT:																
Eligibility screen	X															
Informed consent	X															
Allocation		X														
INTERVENTIONS:																
[Arm A]			←	→						←	→	←	→	←	→	
[Arm B]			←	→						←	→	←	→	←	→	
ASSESSMENTS:																
Hight	X															
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X		X						X	X		X		X		
Blood test	X		X						X	X		X		X		X
phlebitis				X	X	X	X	X	X		X		X		X	

Figure 2

Standard Protocol Items: Recommendations for Interventional Trials(SPIRIT) Figure

Arm A (mannitol)	Arm B (furosemide)
Antiemetic-1 (30 min) Aprepitant 150 mg Normal saline solution 250 ml	Antiemetic-1 (30 min) Aprepitant 150 mg Normal saline solution 250 ml
Antiemetic-2 (5 min) Palonosetron 0.75mg/50 ml Dexamethasone 9.9 mg	Antiemetic-2 (5 min) Palonosetron 0.75 mg/50 ml Dexamethasone 9.9 mg
Another cytotoxic agent	Another cytotoxic agent
Pre-hydration (1 hour) Normal saline solution 500 ml Potassium chloride 10 mEq Magnesium sulfate 10 mEq	Diuresis (intravenously) Furosemide 20 mg
Diuresis (30 min) 20% mannitol 300 ml	Pre-hydration (1 hour) Normal saline solution 500 ml Potassium chloride 10 mEq Magnesium sulfate 10 mEq
CDDP (1 hour) CDDP + normal saline solution total 500 ml	CDDP (1 hour) CDDP + normal saline solution total 500 ml
Post-hydration (1 hour) Maintenance solution 500 ml	Post-hydration (1 hour) Maintenance solution 500 ml

Figure 3

Treatment

Supplementary Files

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- supplement1.doc