

Clinical Study Protocol

Randomized Phase II Study Comparing Mannitol with Furosemide for the Prevention of Renal Toxicity Induced by Cisplatin-based Chemotherapy with Short-term Low-volume Hydration in Advanced Non-small Cell Lung Cancer: The OLCSG1406 Study Protocol

Go Makimoto^a, Eiki Ichihara^{b*}, Katsuyuki Hotta^c, Kiichiro Ninomiya^a,
Isao Oze^d, Daisuke Minami^e, Takashi Ninomiya^b, Toshio Kubo^f,
Kadoaki Ohashi^b, Masahiro Tabata^f, Yoshinobu Maeda^a, and Katsuyuki Kiura^b

^aDepartment of Hematology, Oncology, and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, ^bDepartment of Allergy and Respiratory Medicine, ^cCenter of Innovative Clinical Medicine, ^fCenter for Clinical Oncology, Okayama University Hospital, Okayama 700-8558, Japan, ^dDivision of Epidemiology and Prevention, Aichi Cancer Center, Aichi 464-8681, Japan, ^eDepartment of Respiratory Medicine, Okayama Medical Center, Okayama 701-1192, Japan

Although cisplatin-based chemotherapy shows a survival advantage compared to carboplatin for treating advanced non-small cell lung cancer, high-volume hydration and a long infusion time are necessary to avoid nephrotoxicity, and cisplatin-based chemotherapy has been difficult to administer in outpatient settings. A low-volume hydration method using mannitol or furosemide as forced diuresis was recently introduced, but there are no clear conclusions regarding which agent should be used. We describe our ongoing randomized phase II trial (the OLCSG1406 Study) evaluating the efficacy of forced diuresis. This study will clarify whether mannitol or furosemide is more suitable in cisplatin-based chemotherapy with low-volume hydration.

Key words: cisplatin, mannitol, furosemide, lung cancer, hydration, non-small cell lung cancer

Cisplatin-based chemotherapy shows a survival advantage compared to carboplatin-based chemotherapy for the treatment of advanced non-small cell lung cancer (NSCLC) [1-3]. However, as high-volume hydration and a long infusion time are needed to avoid renal toxicity, cisplatin-based chemotherapy has been difficult to administer in outpatient settings. To address this problem, the U.S. National Comprehensive Cancer Network (NCCN) introduced a low-volume hydration method (short hydration) for cisplatin administration. In addition, we conducted two prospective studies that successfully showed the feasibility of short-term

low-volume orally administered hydration using a total of 2.5 L over a 4.5-h period and 1.7 over a 3-h period [4, 5], enabling the use of cisplatin in an outpatient setting [6].

Nephrotoxicity is among the most important adverse events of cisplatin treatment [7], and mannitol, an osmotic diuretic, is usually used for forced diuresis to reduce cisplatin-induced nephrotoxicity in the short-term hydration method [8]. In an *in vivo* study using dogs, intravenous mannitol infusion and massive hydration were shown to prevent renal toxicity [9]. Furosemide, a loop diuretic, is also used for the prevention of cisplatin-induced renal toxicity [8]. In

Received October 24, 2017; accepted December 20, 2017.

*Corresponding author. Phone: +81-86-235-7227; Fax: +81-86-232-8226
E-mail: ichiha-e@md.okayama-u.ac.jp (E. Ichihara)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

another *in vivo* study, renal function was assessed by the measurement of blood urea nitrogen (BUN), and the estimated glomerular filtration rate (eGFR) was partially protected in rats given furosemide [10].

Some reports comparing the use of mannitol with that of furosemide have been published, but there have been no clear conclusions regarding which agent should be used in cisplatin-based chemotherapy [11,12]. To clarify which diuresis agent (*i.e.*, mannitol or furosemide) is more suitable for cisplatin-based chemotherapy using the short-term hydration method, we have designed a study to evaluate the efficacy of these 2 drugs in patients with advanced NSCLC. We present here the design, methods and protocol of this investigation, which has been named the OLCSG1406 study.

Methods and Design

Objective. This study was designed to evaluate the efficacies of mannitol and furosemide for forced diuresis in cisplatin-based chemotherapy with short-term hydration for advanced NSCLC.

Study design. The study was designed as a two-arm, prospective, randomized single-center phase II trial. Fig.1 provides an overview of the study design. Written informed consent must be obtained from the patients before any screening or inclusion procedure. This study will be conducted in compliance with the principles of the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Okayama University (approval no. m04009) and was registered with the UMIN Clinical Trials Registry with

the registration number UMIN000015293.

Endpoints. The study's primary endpoint is the rate of patients with serum creatinine elevation, defined as grade 1 or higher by the Common Terminology Criteria for Adverse Events (CTCAE), ver. 4.0, during the first cycle of cisplatin-based chemotherapy. We will record renal toxicity during all of the chemotherapy cycles. Secondary outcome measures are the objective response rate, toxicity, overall survival, and progression-free survival. Regarding the patients' responses to the chemotherapy with either agent, the Response Evaluation Criteria in Solid Tumors (RECIST; ver. 1.1) will be applied.

Eligibility criteria. All patients who meet the main inclusion and exclusion criteria will be invited for screening. The main inclusion and exclusion criteria are listed in Table 1.

Randomization. After the eligibility criteria are confirmed to have been met for a patient, his or her registration is performed by fax or e-mail. The minimization method is employed to assign patients randomly to either the furosemide arm or the mannitol arm, using performance status (0 or 1) and sex as adjustment factors.

Intervention. The treatment schedule is designed as shown in Table 2. Cisplatin will be diluted in 500 ml of normal saline solution and administered over a 1-h period. Magnesium sulfate, the key agent to prevent renal toxicity [13], will be supplemented at 4 mEq both before and after each cisplatin administration. In arm A, furosemide will be infused just after cisplatin administration. In arm B, mannitol will be infused just before cisplatin administration. A total of 1.7 L for hydration will be administered over a 3-h period. Patients will be strongly advised to drink 1.5 L water on day 1 and 1 L on each of days 2 and 3 to avoid dehydration, which may potentially lead to renal failure [14]. This treatment will be repeated every 3 or 4 weeks for 4 to 6 cycles unless disease progression or unacceptable toxicity is observed or the patient refuses further treatment. Maintenance therapy with pemetrexed or bevacizumab is accepted after four cycles of cisplatin. All of the patients will receive the first cycle in an inpatient setting for a precise evaluation of the therapy's safety, and subsequent cycles will be given in an outpatient setting if possible.

This study will be conducted in 2 steps. Step 1 will be performed primarily to evaluate the tolerability of the

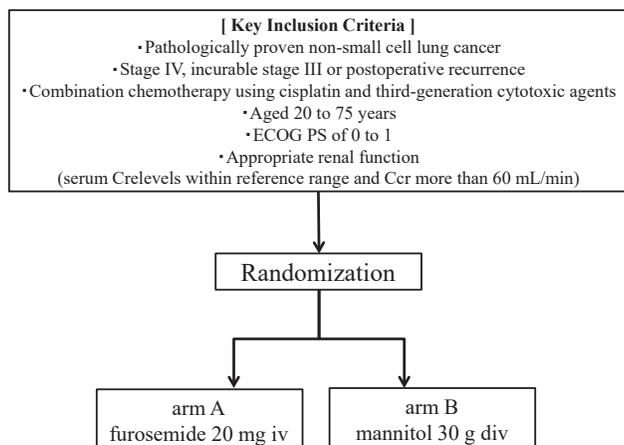


Fig. 1 Overview of the study design.

Table 1 Eligibility criteria of the OLCSG1406 Study

Inclusion criteria:	
(1)	Age 20-75 years
(2)	Eastern Cooperative Oncology Group (ECOG) performance status 0-1
(3)	Pathologically proven non-small cell lung cancer
(4)	Stage IV, incurable stage III or postoperative recurrence disease
(5)	Combination chemotherapy with cisplatin and third-generation anticancer drug (including triplet therapy using bevacizumab)
(6)	Presence of any measurable or immeasurable lesions (RECIST v1.1)
(7)	No prior systemic cytotoxic chemotherapy except for post-operative adjuvant therapy >6 months prior to registration
(8)	More than 1 week after palliative radiation therapy for metastatic lesions other than extremity bone metastasis
(9)	More than 1 week after the drainage of pleural effusion, cardiac effusion, and ascites
(10)	Adequate organ function as defined by the following: leukocyte count >3,000/ μ L, absolute neutrophil count >1,500/ μ L, platelet count >150,000/ μ L, hemoglobin level >9 g/dL, total bilirubin level <1.5 mg/dL, aspartate aminotransferase and alanine transaminase levels <2.5-fold the institutional upper limit of the normal range (ULN), creatinine within the ULN and creatinine clearance >60 mL/min, arterial oxygen partial pressure >60 mmHg or saturation of pulse oximetry oxygen >90% in room air
Exclusion criteria:	
(1)	Cisplatin level <75 mg/m ² on day 1
(2)	Patients with active co-morbidities, including severe heart disease, cerebrovascular diseases, gastric ulcers, severe infections, uncontrollable diabetes, psychological diseases, and hearing loss
(3)	Active interstitial lung diseases
(4)	Symptomatic brain metastasis
(5)	Uncontrolled third-space fluid retention
(6)	History of other malignancies within the past 3 years
(7)	Pregnant or breast-feeding women
(8)	Regular use of oral diuresis
(9)	Incapable of drinking 1 L per day
(10)	Treatment with the split schedule of the cisplatin or cisplatin-etoposide regimen requiring drip infusion even on days 2 and 3

Table 2 Schedule of short-term low-volume hydration in cisplatin-based chemotherapy on day 1

Chemotherapeutic and Hydration Agents and Their Dosage
Antiemetic premedication: Normal saline solution with palonosetron 0.75 mg, dexamethasone 9.9 mg, magnesium sulfate 4 mEq, 100 mL (15 min)
Cytotoxic agents: Normal saline solution ^a with an anticancer agent that would be combined with cisplatin, 500 mL (1 h)
Diuresis: (Arm B), 20% mannitol, 150 mL (15 min)
Cisplatin: Normal saline solution with cisplatin >75 mg/m ² 500 ^b mL (1 h)
Diuresis: (Arm A), furosemide 20 mg, 2 mL (bolus)
Hydration: 1/4 normal saline solution with magnesium sulfate 4 mEq, KCl 4 mEq, 200 mL (30 min)
Total: 1,700 mL (3 h)

The venous line was maintained using 250 mL of normal saline throughout the infusion. The dose schedules for cisplatin and anticancer agents combined with cisplatin were based on the latest National Comprehensive Cancer Center guidelines. In the case of triplet chemotherapy with bevacizumab, it was diluted in 100 mL of normal saline and administered after the completion of post-hydration.

^a Vinorelbine, pemetrexed, and gemcitabine were diluted in 50, 100, and 100 mL of normal saline (5, 10, and 30 min), respectively. In addition, 250 mL of normal saline solution were administered.

^b A total of 500 mL with cisplatin and normal saline solution.

forced diuresis in short-term hydration chemotherapy. In this step, at least 6 patients will receive treatment in each arm. Step 2 will subsequently be performed if grade 1 or higher serum creatinine elevation is observed in more than 2 patients. All of the adverse events will be defined according to the CTCAE, ver. 4.0. For the evaluation of creatinine toxicity, 2 types of grading systems are available; we will use the one based on the institutional upper limit of the normal range (ULN) for serum creatinine as described [4, 5]. If grade 3 or 4 serum creatinine elevation occurs, the protocol treatment will be stopped and clinically available renal supportive care will be given.

Follow-up. All of the randomized patients will be followed-up for at least 1 year after the study's patient accrual is completed. General physical findings, laboratory data (including renal function), tumor markers (carcinoembryonic antigen [CEA], cytokeratin 19 fragment [CYFRA], sialyl LeX-i antigen [SLX], squamous

cell carcinoma-related antigen [SCC]), and chest X-ray results will be obtained monthly during the first year and every 3 months after the first year until the patients complete or stop cisplatin-based chemotherapy, or until disease progression. Enhanced chest and abdominal computed tomography or brain magnetic resonance imaging will be evaluated as necessary.

Statistical consideration. This study will evaluate the feasibility of the two forced diuresis methods in cisplatin-based chemotherapy with short-term hydration for advanced NSCLC. The primary endpoint is the rate of patients without an elevation in serum creatinine levels, defined as grade 1 or higher during the first cycle, according to CTCAE, ver. 4.0.

In previous studies of mannitol, 15-27% of the patients developed grade 1 or higher creatinine toxicity [4,15,16]. In studies of furosemide, 18-52% of the patients developed grade 1 or higher creatinine toxicity [8,17]. Thus, we estimated that the probability of grade 1 or higher creatinine toxicity was 35% with furosemide and 20% with mannitol. The target sample size to select the arm with the lower probability of renal toxicity, with an accuracy of 90%, is 30 cases in each arm according to Simon's selection theory. With an assumed 10% dropout rate, 66 patients are needed in total.

Overall survival will be defined as the interval between the date of enrollment in this study and death or the last follow-up visit. Progression-free survival will be defined as the interval between the date of enrollment in this study and progressive disease (RECIST PD) or death. The survival distribution will be estimated using the Kaplan-Meier method. All of the statistical analyses will be conducted using STATA/SE ver. 14.0 software (College Station, TX, USA).

Discussion

To date, cisplatin-based chemotherapy is the standard therapy for advanced NSCLC. We reported the safety of short-term low-volume hydration [5], but few prospective randomized studies regarding the appropriate forced diuresis have been conducted. Mannitol, an osmotic diuretic, has been used worldwide for forced diuresis, but it has the potential side effect of vascular pain, which impairs patients' quality of life. This study will clarify whether the use of mannitol or that of furosemide is more feasible for forced diuresis in moder-

ate-dose cisplatin-based chemotherapy with short-term hydration. We hope this study will provide novel data that can assure a more feasible method of moderate-dose cisplatin-based chemotherapy with short-term hydration for advanced NSCLC.

Acknowledgments. This study will be conducted with support from the Center for Innovative Clinical Medicine, Okayama University Hospital. We thank the study coordinator and all of the other investigators at Okayama University Hospital who made this study possible: Masamoto Nakanishi, Hirohisa Kano, Hiromi Watanabe, Yusuke Hata, Kazuya Nishii, Naohiro Oda, and Yousuke Toyota.

References

1. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M and Tanimoto M: Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* (2004) 22: 3852-3859.
2. Hotta K and Matsuo K: Long-standing debate on cisplatin-versus carboplatin-based chemotherapy in the treatment of advanced non-small cell lung cancer. *J Thorac Oncol* (2007) 2: 96.
3. Hotta K, Fujiwara Y, Matsuo K, Suzuki T, Kiura K, Tabata M, Takigawa N, Ueoka H and Tanimoto M: Recent improvement in the survival of patients with advanced nonsmall cell lung cancer enrolled in phase III trials of first-line, systemic chemotherapy. *Cancer* (2007) 109: 939-948.
4. Hotta K, Takigawa N, Hisamoto-Sato A, Ichihara E, Kudo K, Uchida K, Yanase-Nakamura K, Tanaka H, Kato Y, Tabata M, Tanimoto M and Kiura K: Reappraisal of short-term low-volume hydration in cisplatin-based chemotherapy: results of a prospective feasibility study in advanced lung cancer in the Okayama Lung Cancer Study Group Trial 1002. *Jpn J Clin Oncol* (2013) 43: 1115-1123.
5. Ninomiya K, Hotta K, Hisamoto-Sato A, Ichihara E, Gotoda H, Morichika D, Tamura T, Kayatani H, Minami D, Kubo T, Tabata M, Tanimoto M and Kiura K: Short-term low-volume hydration in cisplatin-based chemotherapy for patients with lung cancer: the second prospective feasibility study in the Okayama Lung Cancer Study Group Trial 1201. *Int J Clin Oncol* (2016) 21: 81-87.
6. Hotta K, Ninomiya K, Takigawa N, Tanimoto M and Kiura K: Reappraisal of short-term low-volume hydration in cisplatin-based chemotherapy; hoping for it as a public domain. *Jpn J Clin Oncol* (2015) 45: 603-604.
7. Stewart DJ, Dulberg CS, Mikhael NZ, Redmond MD, Montpetit VA and Goel R: Association of cisplatin nephrotoxicity with patient characteristics and cisplatin administration methods. *Cancer Chemother Pharmacol* (1997) 40: 293-308.
8. Tiseo M, Martelli O, Mancuso A, Sormani MP, Bruzzi P, Di Salvia R, De Marinis F and Ardizzone A: Short hydration regimen and nephrotoxicity of intermediate to high-dose cisplatin-based chemotherapy for outpatient treatment in lung cancer and mesothelioma. *Tumori* (2007) 93: 138-144.
9. Cvitkovic E, Spaulding J, Bethune V, Martin J and Whitmore WF: Improvement of cis-dichlorodiammineplatinum (NSC 119875): therapeutic index in an animal model. *Cancer* (1977) 39: 1357-1361.
10. Pera MF, Jr., Zook BC and Harder HC: Effects of mannitol or furosemide diuresis on the nephrotoxicity and physiological dispo-

- sition of cis-dichlorodiammineplatinum(II) in rats. *Cancer Res* (1979) 39: 1269–1278.
11. Ostrow S, Egorin MJ, Hahn D, Markus S, Aisner J, Chang P, LeRoy A, Bachur NR and Wiernik PH: High-dose cisplatin therapy using mannitol versus furosemide diuresis: comparative pharmacokinetics and toxicity. *Cancer Treat Rep* (1981) 65: 73–78.
 12. Santoso JT, Lucci JA, 3rd, Coleman RL, Schafer I and Hannigan EV: Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. *Cancer Chemother Pharmacol* (2003) 52: 13–18.
 13. Bodnar L, Wcislo G, Gasowska-Bodnar A, Synowiec A, Szarlej-Wcislo K and Szczylik C: Renal protection with magnesium subcarbonate and magnesium sulphate in patients with epithelial ovarian cancer after cisplatin and paclitaxel chemotherapy: a randomised phase II study. *Eur J Cancer* (2008) 44: 2608–2614.
 14. Furukawa N, Kawaguchi R and Kobayashi H: Use of high-dose cisplatin with aprepitant in an outpatient setting. *Eur J Cancer Care (Engl)* (2012) 21: 436–441.
 15. Horinouchi H, Kubota K, Itani H, Taniyama TK, Nakamichi S, Wakui H, Kanda S, Nokihara H, Yamamoto N, Sekine I and Tamura T: Short hydration in chemotherapy containing cisplatin ($\geq 75 \text{ mg/m}^2$) for patients with lung cancer: a prospective study. *Jpn J Clin Oncol* (2013) 43: 1105–1109.
 16. Hata A, Katakami N, Masuda Y, Kaji R, Fujita S, Iwamori S, Horai A, Takatori K, Ose T, Kitajima N, Mifune Y and Fukae M: [Cisplatin administration for outpatients with short hydration of less than four hours]. *Gan To Kagaku Ryoho* (2012) 39: 1385–1388.
 17. Korogi Y, Yoshioka H, Kunimasa K, Nishiyama A, Iwasaku M, Tsubouchi K, Konishi S, Fukuda Y, Ito A and Ishida T: Retrospective analysis of short-hydration cisplatin-based chemotherapy. *Nihon Kogyaku Gakkai Zasshi* (2013) 2: 730–736.