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# Phase II Study of Short Hydration without Diuretics for Cisplatin-Based Chemotherapy

Tetsuya Wako[1], Ryosuke Arakawa[2], Shinji Nakamichi[3], Masaru Matsumoto[3], Rei Yamaguchi[3], Kaoruko Shimbu[3], Tomoyasu Inoue[3], Takehiro Tozuka[3], Junichi Aoyama[3], Yasuhiro Kato[3], Naomi Onda[3], Akihiko Miyanaga[3], Masahiro Seike[3] and Kaoru Kubota[3]

[1]Department of Pharmacy Services, Nippon Medical School Hospital, Tokyo, Japan
[2]Department of Pharmacology, Nippon Medical School, Tokyo, Japan
[3]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

**Background:** Diuretics are commonly used to reduce renal dysfunction during cisplatin-based chemotherapy; however, reports suggest that renal function is unaffected when diuretics are not administered. This phase II trial evaluated the effectiveness and safety of a short hydration method without diuretics.

**Methods:** Patients were included if they were aged 20-74 years, had a thoracic malignancy for which a cisplatin-based regimen (dose: ≥60 mg/m$^2$) was indicated, and had adequate renal function. All patients received cisplatin-based chemotherapy using a short hydration method without diuretics. The primary endpoint was the proportion of patients without grade 2 or higher elevations in creatinine levels during the first cycle of cisplatin.

**Results:** Forty-six patients were enrolled between June 2019 and April 2022. The patients included 38 men and 8 women with a median age of 64 years (range: 45-74 years). Of these, 13 patients received adjuvant chemotherapy, 19 received chemoradiotherapy, 1 received chemotherapy for post-surgical recurrence, and 13 received chemotherapy for advanced disease. The median number of chemotherapy cycles was 3 (range: 1-4). A total of 93.5% (43/46) of the patients completed cisplatin-based chemotherapy without grade 2 or higher creatinine elevation during the first cycle, and 84.8% (39/46) of participants, including those who discontinued treatment, did not show grade 2 or higher creatinine elevation after all cycles of cisplatin-based chemotherapy.

**Conclusions:** Short hydration without diuretics is safe for patients receiving cisplatin-containing chemotherapy. Randomized trials with or without diuretics in this setting are warranted.

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**Key words:** short hydration, diuretic, cisplatin, thoracic malignancy, renal dysfunction

## Introduction

Cisplatin is an anticancer drug used to treat malignant tumors, including thoracic malignancies[1–5]. Treatments based on driver gene mutations are progressing for some cancers, and the effectiveness of chemotherapy regimens containing cisplatin has been demonstrated, even in patients with gene mutations[6,7]. However, nephrotoxicity and gastrointestinal toxicity are common complications[8–15]. Cisplatin-containing regimens typically involve administering large volumes of fluid to mitigate nephrotoxicity, but the timing of administration, decline in quality of life, and difficulty of outpatient treatment must be considered. Recently, many studies have described the efficacy and safety of short hydration, a commonly used method that reduces the volume and duration of infusion[16,17]. Although there are some differences in the amount of hydration, the method of the present study was based on that described by Horinouchi et al. (2013)[17].

Correspondence to Kaoru Kubota, Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: kkubota@nms.ac.jp
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Forced diuresis is generally performed using diuretics like mannitol or furosemide to reduce nephrotoxicity during cisplatin administration. Mannitol lowers the cisplatin concentration in the kidneys and reduces renal damage[18,19]. A randomized controlled trial comparing mannitol and furosemide in a small patient group reported comparable renal damage[20]. Another study comparing 24-hour creatinine clearance changes before and after cisplatin use among three groups—patients receiving no diuretic (normal saline only), furosemide, and mannitol—found that the no-diuretic and furosemide groups experienced less renal dysfunction than the mannitol group[21]. Thus, although diuretics had demonstrated benefits in animal[22,23] and human studies, renal function may not deteriorate with cisplatin treatment, even in the absence of diuretics. Given the disadvantages of diuretics such as mannitol, which require administration time and can cause vascular pain, it is crucial to investigate the effects on renal function in the absence of diuretics. In addition, furosemide increases the risks of dehydration and electrolyte abnormalities and may induce nephrotoxicity and ototoxicity when combined with cisplatin[24,25]. We therefore examined the effectiveness and safety of a short hydration method without diuretics.

## Materials and Methods

### Patients

The eligibility criteria were as follows: histologically or cytologically confirmed thoracic malignancy; suitability for platinum-based chemotherapy (including combination therapy with immune checkpoint inhibitors and molecularly targeted therapeutics) or chemoradiotherapy with cisplatin (≥60 mg/m$^2$); no previous treatment with cisplatin; age 20-74 years; Eastern Cooperative Oncology Group (ECOG)[26] performance status of 0 or 1; satisfactory bone marrow function (white blood cell count ≥3.0 × 10$^9$/L, neutrophil count ≥1.5 × 10$^9$/L, hemoglobin ≥9.0 g/dL, and platelet count ≥100 × 10$^9$/L); satisfactory liver function (total bilirubin ≤1.5 mg/dL and transaminase ≤ 100 IU/L); satisfactory renal function (serum creatinine ≤ 1.07 mg/dL for male patients, ≤0.79 mg/dL for female patients, and creatinine clearance ≥60 mL/min); and $SpO_2$ ≥95%.

Patients were excluded if they had dysphagia due to recurrent nerve paralysis, large mediastinal masses, uncontrolled malignant pleural or pericardial effusion, or serious concomitant illnesses (such as angina pectoris, myocardial infarction within the past 6 months, heart failure, infection, or any other condition contraindicating chemotherapy or radiotherapy). Written informed consent was obtained from all patients. This trial was conducted in accordance with the declaration of Helsinki and Ethical Guideline for Clinical Studies of the Ministry of Health, Labor, and Welfare of Japan. This trial was also approved by the Ethics Committee of Nippon Medical School Hospital, Tokyo (approval number: 2018-215) and registered with UMIN (No. UMIN000053657).

### Treatment

Patients received cisplatin-based chemotherapy with a cisplatin dose of ≥60 mg/m$^2$ every 3-4 weeks. Common antiemetic medication included palonosetron (0.75 mg on day 1) and dexamethasone (9.9 mg on day 1) dissolved in 50 mL of normal saline solution and infused, along with oral aprepitant (125 mg on day 1, 80 mg on days 2-3) and dexamethasone (8 mg on days 2-4). Cisplatin was dissolved in 250 mL of normal saline solution and infused over 1 hour. Prehydration with magnesium sulfate (8 mEq) dissolved in 500 mL of 1/4 saline solution and posthydration with 500 mL of 1/4 saline solution were administered before and after cisplatin administration, respectively. Other anticancer agents combined with cisplatin included tegafur-gimeracil-oteracil potassium (S-1, 80-120 mg/body, **Fig. 1**), irinotecan (60 mg/m$^2$), pemetrexed (500 mg/m$^2$), pemetrexed (500 mg/m$^2$) plus pembrolizumab (200 mg/body weight), etoposide (100 mg/m$^2$), or etoposide (100 mg/m$^2$) plus durvalumab (1,500 mg/body).

### Assessment of Toxicities and Treatment Modification

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (2017). In the CTCAE version 5.0, "creatinine increased" is assessed based on the upper limit of the normal range (ULN). For creatinine, the worst value of each cycle was used. Chemotherapy cycles were delayed if the following toxicities were observed on day 1: WBC <3.0 × 10$^9$/L, neutrophil count < 1.5 × 10$^9$/L, platelet count <100 × 10$^9$/L, serum creatinine level >1.4 mg/dL, hepatic transaminase level >100 IU/L, or a performance status of two or higher. The cisplatin dose was reduced by 25% in all subsequent cycles if the serum creatinine level increased to grade 2 or higher (greater than 1.5× ULN). Treatment was discontinued in cases of clear clinical worsening, grade 3 creatinine increase, or at the discretion of the physician.

### Statistical Analysis

This nonrandomized, single-center, phase II trial primarily measured the proportion of patients without renal dysfunction, defined as the absence of grade 2 or higher

| | Medicine | Dose |
|---|---|---|
| Antiemetics-1 | Aprepitant (oral) | 125 mg (day 1)<br>80 mg (days 2-3) |
| Antiemetics-2 (15 min) | Palonosetron | 0.75 mg |
| | Dexamethasone | 9.9 mg |
| | 0.9% Saline | 50 mL |
| Pre-hydration (1 hour) | 1/4 Saline solution | 500 mL |
| | Magnesium sulfate | 8 mEq |
| Diuresis | none diuretic agent | |
| Cisplatin (1 hour) | Cisplatin | 75 mg/m$^2$ |
| | 0.9% Saline | 250 mL |
| Post-hydration (1 hour) | 1/4 Saline solution | 500 mL |
| Anti-cancer agent | S-1 * | 80-120 mg/body<br>(days 1-14 or 21, per oral) |

* S-1: tegafur-gimeracil-oteracil

Fig. 1 A representative chemotherapy regimen (cisplatin and tegafur-gimeracil-oteracil).

creatinine elevation based on the ULN during the first cycle of cisplatin. Similar to previous studies[9], the sample size was estimated by using a Simon two-stage design, with a minimum acceptable response probability of ≤70% and a maximum unacceptable response probability of ≥88% at a power of 90%. With a type I error of 0.05, 44 patients were required[28]. Successful completion of stage I required 24 patients without renal dysfunction among the first 30 who received the first cycle of cisplatin. The primary endpoint was met if 36 out of 44 patients completed the first cycle without grade 2 or higher creatinine elevation. Secondary endpoints included the number of chemotherapy cycles, adverse events, and overall response rate in patients with measurable lesions according to RECIST criteria (Ver. 1.1)[29]. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

## Results

### Patient Characteristics

Forty-six patients were enrolled between June 2019 and April 2022. The patient demographics were as follows: 38 male patients and 8 female patients, median age 64 years (range: 45-74 years), and an ECOG performance status of 0 or 1 in 22 and 24 patients, respectively. Of these, 13 patients received adjuvant chemotherapy, 19 underwent chemoradiotherapy, 1 received chemotherapy for post-surgical recurrence, and 13 were treated with chemotherapy for advanced disease. Regarding histology, 26 patients had lung adenocarcinoma, 4 had non-small cell lung cancer (NSCLC) not otherwise specified, 7 had squamous cell carcinoma, 6 had small cell carcinoma, 2 had large cell neuroendocrine carcinoma, and 1 had malignant pleural mesothelioma. The following agents were used in combination with cisplatin: tegafur-gimeracil-oteracil potassium (n=27), pemetrexed plus pembrolizumab (n=8), etoposide (n=5), irinotecan (n=4), pemetrexed (n=1), and etoposide plus durvalumab (n=1). Pretreatment renal function (median [range]) was as follows: serum creatinine, 0.73 (0.48-1.04) mg/dL, and estimated creatinine clearance, 84 (63-122) mL/min (**Table 1**).

### Post-Treatment Renal Function and Other Toxicities

Only 2 out of 30 patients experienced grade 2 or higher creatinine elevation at stage I, allowing the study to proceed to stage II. Ultimately, 93.5% (43/46) of patients had no grade 2 or higher creatinine elevations during the first treatment cycle, thus achieving the primary endpoint of the trial. Three patients showed a grade 2 creatinine increase during the first cycle; 2 of these patients received cisplatin plus pemetrexed and pembrolizumab. In both cases, treatment was discontinued after the first cycle for reasons other than renal damage: 1 patient had disease progression due to pericardial effusion, and the other developed drug-induced lung disease. The

Table 1 Patient characteristics

| | n = 46 |
|---|---|
| Age (years) | |
| Median | 64 |
| Range | 45-74 |
| Sex | |
| Male | 38 |
| Female | 8 |
| Performance status | |
| 0 | 22 |
| 1 | 24 |
| Treatment setting, n (%) | |
| Adjuvant therapy | 13 (28.3) |
| Chemoradiotherapy | 19 (41.3) |
| Postoperative recurrence | 1 (2.2) |
| Advanced disease | 13 (28.3) |
| Histology, n (%) | |
| Adenocarcinoma | 26 (56.5) |
| Squamous cell carcinoma | 7 (15.2) |
| NSCLC* | 4 (8.7) |
| Small cell carcinoma | 6 (13.0) |
| Large cell neuroendocrine carcinoma | 2 (4.3) |
| Malignant pleural mesothelioma | 1 (2.2) |
| Treatment regimen, n (%) | |
| CDDP+S-1 | 27 (58.7) |
| Pembrolizumab+CDDP+PEM | 8 (17.4) |
| CDDP+ETP | 5 (10.9) |
| CDDP+CPT | 4 (8.7) |
| CDDP+PEM | 1 (2.2) |
| Durvalumab+CDDP+ETP | 1 (2.2) |
| Comorbidities, n (%) | |
| Hypertension | 18 (39.1) |
| Diabetes mellitus | 8 (17.4) |
| Pulmonary disease | 5 (10.9) |
| Cardiac disease | 12 (26.1) |
| Serum creatinine (mg/dL) | |
| Median | 0.73 |
| Range | 0.48-1.04 |
| Estimated creatinine clearance (mL/min) ** | |
| Median | 84 |
| Range | 63-122 |
| Calculated eGFR (mL/min 1.73 m$^2$) *** | |
| Median | 77 |
| Range | 58-116 |

*Non-small cell lung cancer, not otherwise specified.
**Creatinine clearance calculated using the Cockcroft-Gault equation.
***Estimated glomerular filtration rate calculated using Japanese equations.
CDDP, cisplatin; S-1, tegafur-gimeracil-oteracil potassium; PEM, pemetrexed; ETP, etoposide; CPT, irinotecan

remaining patient received cisplatin plus etoposide and discontinued the second cycle because of acute kidney injury. Post-treatment renal function test results (median [range]) were serum creatinine, 0.88 (0.57-2.27) mg/dL, and estimated glomerular filtration rate, 71 (25-131) mL/min (**Table 2**, **Fig. 2**). The proportion of patients without grade 2 or higher creatinine elevation after all treatment cycles (including discontinued cases) was 84.8%. The profiles of toxicities other than renal dysfunction are summarized in **Table 3**.

**Treatment Delivery and Efficacy**

Twenty-seven patients (58.7%) received cisplatin combined with S-1, the most common treatment regimen. Thirty-six patients (78.3%) completed 2-4 planned cycles of cisplatin-containing chemotherapy. The reasons for early termination of chemotherapy were as follows: 2 patients (4.3%) discontinued treatment because of acute kidney injury, 5 patients (10.9%) because of side effects other than renal dysfunction (myelosuppression, drug eruption, hyponatremia, drug-induced lung disease, nausea/anorexia), and 3 patients (6.5%) because of disease progression (pericardial effusion, leptomeningeal carcinomatosis, brain infarction). Thirteen patients received intravenous hydration, and 6 patients required a dose reduction of cisplatin, mainly because of gastrointestinal toxicities (**Table 4**). The objective response rate was 69.7% among patients who received chemoradiotherapy, had a postoperative recurrence, and had advanced NSCLC with measurable lesions according to the RECIST criteria (V.1.1, **Table 5**).

## Discussion

In this prospective trial of short hydration without diuretics, 93.5% (43/46) of patients did not show grade 2 or higher creatinine levels during the first treatment cycle. Additionally, 84.8% (39/46) of the patients, including those who discontinued treatment, did not show grade 2 or higher creatinine elevation after all cycles of cisplatin-based chemotherapy. Cisplatin nephrotoxicity primarily affects the proximal tubules, especially the S3 segment situated in the outer stripe of the outer medulla[30]. The pathophysiological mechanism for renal injury is not fully understood; however, high-volume hydration and hyperdiuresis are usually employed to prevent cisplatin nephrotoxicity[18,19]. These strategies aim to lower the cisplatin concentration and shorten the duration of direct cisplatin exposure. Tiseo et al.[31] retrospectively examined patients receiving magnesium supplementation and forced diuresis with short hydration and found that this method could be adapted to outpatient settings. Currently, the National Comprehensive Cancer Network provides chemotherapy order templates recommending the short hydration method for many cancers, including lung

Table 2 Renal function after cisplatin administration

| | | n = 46 |
|---|---|---|
| After first cycle | | |
| Maximum grade of creatinine elevation, n (%) | | |
| | Normal | 34 (73.9) |
| | Grade 1 | 9 (19.6) |
| | Grade 2 | 3 (6.5) |
| Serum creatinine (mg/dL) | | |
| | Median | 0.88 |
| | Range | 0.57-2.27 |
| Estimated creatinine clearance (mL/min) * | | |
| | Median | 71 |
| | Range | 25-131 |
| Calculated eGFR (mL/min 1.73 $m^2$) ** | | |
| | Median | 69 |
| | Range | 23-106 |
| After all cycles | | |
| Maximum grade of creatinine elevation, n (%) | | |
| | Normal | 29 (63.0) |
| | Grade 1 | 10 (21.7) |
| | Grade 2 | 6 (13.0) |
| | Grade 3 | 1 (2.2) |
| Serum creatinine (mg/dL) | | |
| | Median | 0.96 |
| | Range | 0.57-3.32 |
| Estimated creatinine clearance (mL/min) * | | |
| | Median | 70 |
| | Range | 20-141 |
| Calculated eGFR (mL/min 1.73 $m^2$) ** | | |
| | Median | 62 |
| | Range | 16-104 |

* Creatinine clearance calculated using the Cockcroft-Gault equation.
** Estimated glomerular filtration rate calculated using Japanese equations.

cancer, to improve the safety of drugs and biologics in cancer care. In Japan, numerous reports have demonstrated the effectiveness and safety of this short hydration method, which is now commonly used[16,17].

Although short hydration periods reduce the burden on patients, opinions vary on the necessity and type of diuretic administration. To examine the need for diuretics, we conducted a study on cisplatin chemotherapy without diuretics. Our initial goal was for 44 patients to complete their first cycle of cisplatin without experiencing a grade 2 or higher increase in creatinine levels, which was achieved by 36 out of 44 patients. These results suggest that short cisplatin hydration without diuretics is safe.

However, 2 other studies conducted in Japan using short hydration methods with diuretics reported that 97.8% of patients did not experience a grade 2 or higher increase in creatinine levels after all cycles, which was higher than in our study[16,17]. One possible reason is the choice of regimen. Four out of 7 patients who experienced a grade 2 or higher increase in creatinine levels after all cycles were treated with cisplatin plus pemetrexed and pembrolizumab. The KEYNOTE-189 study, which investigated the efficacy and safety of adding pembrolizumab to cisplatin plus pemetrexed or carboplatin plus pemetrexed in patients with previously untreated metastatic non-squamous lung cancer without driver mutations, reported that the incidence of acute kidney injury was higher in the pembrolizumab plus chemotherapy group than in the chemotherapy alone group (5.2% vs. 0.5%)[32]. When patients treated with immune checkpoint inhibitors were excluded, the proportions of patients without a grade 2 or higher increase in creatinine levels during the first cycle and all cycles were 97.3% (36/37) and 91.9% (34/37), respectively.

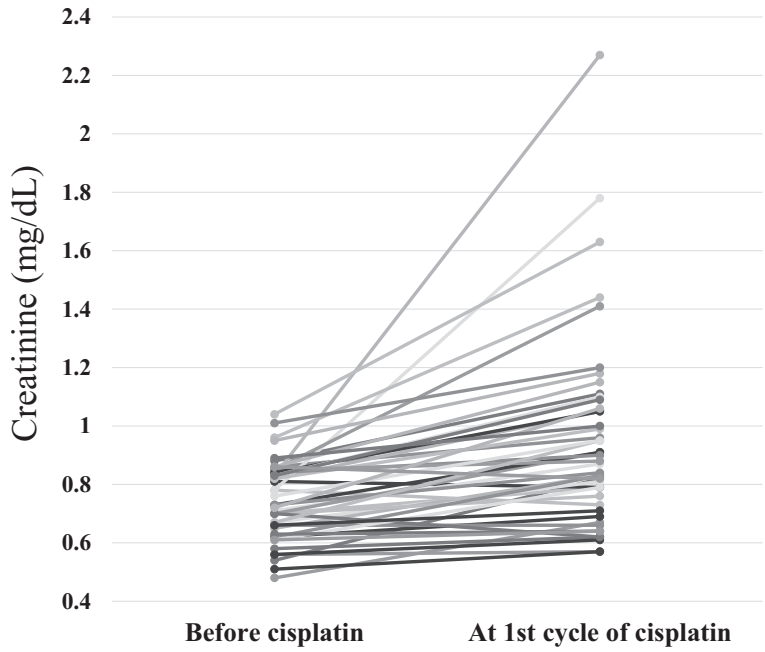


Fig. 2 Change in creatinine values in the participants.

Table 3 Adverse events other than renal toxicities

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 3/4 |
|---|---|---|---|---|---|
| Number of patients, n (%) | | | | | |
| Fever | 8 (17) | 0 | 0 | 0 | 0 |
| Fatigue | 10 (22) | 2 (4) | 0 | 0 | 0 |
| Body weight loss | 0 | 0 | 0 | 0 | 0 |
| Anorexia | 15 (33) | 9 (20) | 0 | 0 | 0 |
| Constipation | 17 (37) | 6 (13) | 1 (2) | 0 | 1 (2) |
| Diarrhea | 6 (13) | 3 (7) | 2 (4) | 0 | 2 (4) |
| Stomatitis | 5 (11) | 0 | 0 | 0 | 0 |
| Nausea | 16 (35) | 7 (15) | 0 | 0 | 0 |
| Vomiting | 0 | 0 | 0 | 0 | 0 |
| Febrile neutropenia | 0 | 0 | 3 (7) | 0 | 3 (7) |
| Alopecia | 6 (13) | 3 (7) | 0 | 0 | 0 |

Table 4 Treatment summary

| | n = 46 | Percentage or range |
|---|---|---|
| Number of chemotherapy cycles, n (%) | | |
| 1 | 6 | 13 |
| 2 | 17 | 37 |
| 3 | 3 | 6.5 |
| 4 | 20 | 43.5 |
| Additional intravenous hydration* | | |
| Number of patients | 13 | 28.3 |
| Total number of days (median, range) | 5 | 2-15 |
| Dose reduction of cisplatin (number) | 6 | |

*Intravenous hydration on days other than cisplatin administration.

Table 5 Anti-Tumor Response

| | n = 33 | Percentage |
|---|---|---|
| Objective response* | 23 | 69.7 |
| Complete response | 6 | 18.2 |
| Partial response | 17 | 51.5 |
| Stable disease | 5 | 15.2 |
| Progressive disease | 2 | 6.1 |
| Not evaluable | 3 | 9.1 |

*Responses were evaluated in patients who received chemoradiotherapy, experienced postoperative recurrence, or had advanced disease with target lesions.

## Limitations

This study has limitations. It was performed at a single center, the sample size was small, cisplatin dosing differed, and there was a single treatment arm. Future studies should enroll a larger number of patients and include multiple arms to identify which patients and regimens require diuretics, such as those in combination with immune checkpoint inhibitors.

## Conclusion

In summary, our results suggest that a short hydration method without diuretics is safe for regimens containing cisplatin. Randomized trials comparing regimens with and without diuretics in this setting are thus warranted.

**Data availability:** The datasets generated and/or analyzed in this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Conceptualization: TW, RA, KK; Methodology: TW, RA, KK; Formal analysis and investigation: TW, KK; Writing—original draft preparation: TW; Writing—review and editing: RA, KK; Resources: SN, MM, RY, KS, TI, TT, JA, YK, NO, AM, MS; Supervision: KK. All authors have read and approved the final version of the manuscript.

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