Oral rehydration solution (OS-1) as a substitute of intravenous hydration after cisplatin administration in patients with lung cancer: a prospective multicenter trial

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ABSTRACT

Background The aim of this trial was to evaluate the safety and efficacy of oral hydration as a substitute for intravenous hydration after cisplatin (CDDP) administration.

Methods The major eligibility criteria included patients with lung cancer, indications for a CDDP-based regimen at a dose of 60 mg/m² or higher, an age of between 20 and 74 years and adequate renal function. Antiemetic prophylaxis consisted of an appropriate dose of palonosetron, aprepitant, dexamethasone and magnesium sulfate (8 mEq). Five hundred millilitres of commercially available oral hydration solution (OS-1: Otsuka Pharmaceutical Factory, Tokushima, Japan) was used as a substitute for intravenous posthydration. The planned sample size was 46 to reject a proportion of 70% under an expectation of 88% with a power of 90% and an alpha error of 5%.

Results Between May and November 2013, 31 men and 15 women with a median (range) age of 65 (33–74) years were enrolled from three institutions. Of these, five received adjuvant chemotherapy, 17 received definitive chemoradiotherapy and 24 received chemotherapy for advanced diseases. The median (range) number of chemotherapy cycles was 4 (1–5). After the first cycle of CDDP administration, none of the patients experienced a creatinine elevation of grade 2 or higher, thereby meeting the primary endpoint. Of the 46 patients, 45 (97.8%, 95% CI 88.2 to 99.9) completed the CDDP-based chemotherapy without grade 2 or higher renal dysfunction.

Conclusion Oral hydration can be used as a safe and convenient substitute for intravenous posthydration for CDDP administration at the standard dose.

Trial registration number UMIN000010201.

INTRODUCTION

Cisplatin is a key drug in the treatment of lung cancer in a wide range of treatment setting.1–3 Conventional long term and large volume hydration is widely performed because of the nephrotoxicity of CDDP, which prevents the optimal use of this platinum agent.5 However, several reports have suggested the absence of any correlation between CDDP nephrotoxicity and the amount of hydration.4 The development of novel antiemetics such as aprepitant and palonosetron has significantly reduced the incidence of nausea and vomiting and has improved oral intake. Furthermore, several strategies including magnesium supplementation and forced diuresis have...
been reported to prevent CDDP nephrotoxicity. We previously conducted a prospective trial examining the feasibility of short-term and lower volume hydration in patients receiving CDDP. In that trial, 97.8% of the participants completed the CDDP-based chemotherapy without experiencing grade 2 or higher elevation in their creatinine (Cr) levels.

OS-1 is a commercially available oral hydration solution containing sodium (50 mEq/L), chloride (50 mEq/L), potassium (20 mEq/L), magnesium sulfate (2 mEq/L), lactate (31 mEq/L) and glucose (18 g/L) with added citrus flavour. OS-1 was developed based on WHO formula of oral rehydration solution. In a rat model, OS-1 exhibited a protective effect against CDDP nephrotoxicity in terms of the serum Cr level, blood urea nitrogen level, Cr clearance and histopathological change in the kidney. To evaluate the feasibility of oral hydration using OS-1, we conducted a first multicenter prospective trial in patients with lung cancer receiving chemotherapy containing CDDP using state-of-the-art protective strategies against renal and gastrointestinal toxicities.

PATIENTS AND METHODS

Patients from two cancer centre hospital and one university hospital provided their written informed consent and participated in this trial. The eligibility criteria were as follows: an age between 20 and 74 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; histologically or cytologically proven lung cancer; candidate for platinum-based chemotherapy or chemoradiotherapy with CDDP (≥60 mg/m²); adequate bone marrow function (white cell count (WCC) ≥3.0×10⁹/L, neutrophil count ≥1.5×10⁹/L, haemoglobin ≥9.0 g/dL and platelet count ≥100×10⁹/L), liver function (total bilirubin ≤1.5 mg/dL and transaminase ≤100 IU/L) and renal function (serum Cr less than or equal to the upper limit of the normal value and Cr clearance ≥60 mL/min) and a peripheral capillary oxygen saturation of 95% or more. Patients were excluded if they had dysphagia caused by recurrent nerve paralysis or large mediastinal masses, uncontrolled malignant pleural or pericardial effusion or concomitant serious illness (such as angina pectoris, myocardial infarction within the previous 6 months, heart failure, infection or other diseases contraindicating chemotherapy or radiotherapy). All the patients provided their written informed consent.

Treatment

Patients received CDDP-based chemotherapy with a CDDP dose ≥60 mg/m² every 3–4 weeks. As a common antiemetic premedication, palonosetron (0.75 mg) and dexamethasone (9.9 mg) were dissolved in 50 mL of normal saline solution and infused, and oral aprepitant (125 mg on day 1, 80 mg on days 2–3) and dexamethasone (8 mg, days 2–4) were administered before and after chemotherapy. An hour-long infusion of CDDP dissolved in 250 mL of normal saline solution was inserted between the prehydration (potassium chloride (10 mEq) and magnesium sulfate (8 mEq) dissolved in 500 mL of saline-based solution) and the oral posthydration (500 mL of OS-1). Mannitol was infused just before the CDDP administration as an enforced diuresis. The patients received one other cytotoxic agent including pemetrexed (500 mg/m², figure 1), tegafur–gimeracil–oteracil potassium (S-1, 80–120 mg/body, see figure 1 in the online Supplementary file 1), docetaxel (60 mg/m², see figure 2 in the online Supplementary file 2), vinorelbine (20 or 25 mg/m², see figure 3 in the online Supplementary file 3), gemcitabine (1000 mg/m², see figure 4 in the online Supplementary file 4), irinotecan (60 mg/m², see figure 5 in the online Supplementary file 5) or etoposide (100 mg/m², see figure 6 in the online Supplementary file 6) with appropriate premedication in combination with CDDP.

Figure 1 Example of hydration method (cisplatin plus pemetrexed).

Antiemetics (15 min)
- Palonosetron 0.75 mg
- Dexamethasone 9.9 mg
- 0.9% Saline 50 mL

Pemetrexed (10 min)
- Pemetrexed 500 mg/m²
- 0.9% Saline 100 mL

Pre-hydration (1 hour)
- ¼ Saline solution 500 mL
- Potassium chloride 10 mEq
- Magnesium sulfate 8 mEq

Diuresis (30 min)
- 20% Mannitol 200 mL

Cisplatin (1 hour)
- Cisplatin 75 mg/m²
- 0.9% Saline 250 mL

Oral post-hydration
- OS-1® 500 mL
Assessment of toxicities and treatment modification

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), V.4.0, issued in 2009. The CTCAE V.4.0 contains two criteria pertaining to Cr; we adopted the classical upper limit of normal-based method to evaluate Cr elevation as primary analysis endpoint. Additionally, we evaluated change of renal function based on baseline Cr value. Complete blood cell and differential counts and routine chemistry determinants were performed on day 8 of the first cycle and on day 1 of every cycle thereafter. Subsequent cycles of CDDP-based chemotherapy were delayed if any of the following toxicities were noted on day 1: WCC <3.0×10⁹/L, neutrophil count <1.5×10⁹/L, platelet count <100×10⁹/L, serum Cr level >1.4 mg/dL, elevated hepatic transaminase level >100 IU/L or a performance status of two or over. The dose of CDDP was reduced by 25% in all subsequent cycles if the serum Cr level increased to a grade 2 or higher.

Statistical analysis

The primary endpoint was the proportion of patients without renal dysfunction, defined as the proportion of patients without a grade 2 or higher elevation in Cr from the baseline value after the first cycle of CDDP. The sample size was estimated using a Fleming single stage design to test the null hypothesis for a proportion of patients without renal dysfunction of ≤70% versus an alternative hypothesis of a proportion of patients ≥88% at a power of 90%. Under the assumption of a type I error rate of 0.05, with the stated statistical hypothesis, a total of 45 patients were required for the study. It was considered that the study would have fulfilled the primary endpoint if 37 out of a total of 45 patients were able to complete the first cycle CDDP without a grade 2 or higher elevation in Cr. The overall proportion of patients without renal dysfunction and the 95% CI were calculated for the final analysis using data from all the patients who received the study treatment. Secondary endpoints included the number of cycles of chemotherapy, adverse events and the overall response in patients who had measurable lesions according to the Response Evaluation Criteria In Solid Tumours (RECIST) criteria (V.1.1). The STATA V.13 for Windows software package was used for the statistical analyses.

RESULTS

Patient characteristics

Forty-six patients were enrolled between May and December of 2013. The participant’s characteristics were as follows: male/female 31/15; median age (range) 65 (33–74) years and ECOG performance status of 0/1 24/22. Of these, five received adjuvant chemotherapy, 17 received chemoradiotherapy and 24 received chemotherapy for advanced diseases. Most patients had lung adenocarcinoma (n=22), but eight had non-small cell lung cancer (NSCLC) not otherwise specified, six had squamous cell carcinoma, eight small cell carcinoma and two had large cell neuroendocrine carcinoma. The agents that were combined with CDDP were as follows: pemetrexed, n=13; vinorelbine, n=11; S-1, n=10; etoposide,
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n=7; irinotecan, n=3; docetaxel, n=1 and gemcitabine, n=1. The results of the pretreatment renal function tests (median (range)) were as follows: serum Cr 0.7 (0.42–0.99) mg/dL and estimated Cr clearance 89 (57–173) mL/min (table 1).

Post-treatment renal function and other toxicities

The proportion of patients without a grade 2 or higher Cr elevation after the first cycle of study treatment was 97.8% (95% CI 88.5 to 99.9). Therefore, this trial successfully met the primary endpoint. One patient experienced a grade 2 elevation in Cr (maximum value, 1.97 mg/dL) after the administration of CDDP plus S-1. The patient experienced grade 3 diarrhoea because of chemotherapy and exhibited a prompt improvement in the Cr level to 1.11 mg/dL after the resolution of the diarrhoea.

Cr, creatinine; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal value.

Subgroup analysis based on cisplatin dosage (60 mg/m² or 75–80 mg/m²) showed higher incidence (60.6% vs 38.5%) of grade 1 post-cisplatin Cr elevation in comparison with baseline Cr value in patients with higher dose cisplatin.

Treatment delivery and efficacy

Twenty patients received CDDP combined with pemetrexed as the most frequent regimen. The majority of patients (39 patients, 85%) completed the preplanned 3–5 cycles of CDDP-based chemotherapy. The reasons for the early termination of chemotherapy in the remaining patients are summarised in table 3. Subgroup analysis based on cisplatin dosage (60 mg/m² or 75–80 mg/m²).

| Table 2 | Renal function after the first cycle of cisplatin administration |
|-----------------|------------------|
| **Cr elevation by CTCAE** | % or range |
| Without G2 or more elevation by ULN Cr | n=46 |
| Normal | 45 97.8 |
| G1 | 1 2.2 |
| G2* Cr Elevation | 1 2.2 |
| Without G2 or more elevation by baseline Cr | n=46 |
| Normal | 45 97.8 |
| G1 | 20 43.5 |
| G2* Cr elevation | 1 2.2 |
| Serum Cr value |  |
| Median (mg/dL, range) | 0.69 0.44–1.31 |
| Estimated Cr clearance (mL/min, median) | 84 53–155 |
| Calculated eGFR (mL/min, median) | 79 42–114 |

*The patient who experienced a G2 elevation in Cr (maximum value, 1.97 mg/dL) experienced G3 chemotherapy-induced diarrhoea and exhibited a prompt improvement in the Cr level to 1.11 mg/dL after the resolution of the diarrhoea.

Cr, creatinine; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal value.

| Table 3 | Adverse events other than renal toxicities according to Common Terminology Criteria for Adverse Events V.4 |
|-----------------|------------------|
| **n=46** | **G1 (%)** | **G2 (%)** | **G3 (%)** | **Total (%)** |
| Fever | 10 (22) | 0 | 0 | 10 (22) |
| Fatigue | 14 (30) | 3 (7) | 0 | 17 (37) |
| Body weight loss | 6 (13) | 0 | 0 | 6 (13) |
| Anorexia | 18 (39) | 12 (26) | 2 (4) | 32 (70) |
| Nausea | 17 (37) | 12 (26) | 1 (2) | 30 (65) |
| Vomiting | 5 (11) | 1 (2) | 0 | 6 (13) |
| Constipation | 23 (50) | 1 (2) | 0 | 24 (52) |
| Diarrhoea | 5 (11) | 1 (2) | 2 (4) | 8 (17) |
| Stomatitis | 2 (4) | 0 | 0 | 2 (4) |
| Febrile neutropaenia | 0 | 0 | 3 (7) | 3 (7) |
| Alopecia | 6 (13) | 4 (9) | 0 | 10 (22) |

No G4 or severe adverse events were observed.
patients were as follows: seven (16%) developed progressive disease and one (2%) patient refused to continue treatment because of gastrointestinal toxicities. During the study treatment, seven patients received intravenous hydration and six patients required a dose reduction of CDDP mainly because of gastrointestinal toxicities except for one patient with a grade 2 elevation of Cr (table 4). The objective response was 45.0% (95% CI 24.4 to 67.8) among patients with postsurgical recurrences and advanced NSCLC who had measurable lesions according to the RECIST criteria (V.1.1, table 5).

**DISCUSSION**

In this first multicenter prospective trial evaluating OS-1 as an adequate substitute for conventional intravenous posthydration, we demonstrated that oral hydration was successfully conducted without resulting in a grade 2 or higher Cr elevation in 97.8% of the trial participants. By combining short-term and lower volume hydration with oral posthydration, CDDP-based chemotherapy could be administered in less than 3 hours of intravenous infusion. Oral posthydration did not appear to have significant effect on either the treatment delivery (median four cycles) or the response (45% (95% CI 24.4 to 67.8) in patients with NSCLC with target lesions).

| Number of chemotherapy cycles (number, %) | n=46 | Percentage |
|------------------------------------------|------|------------|
| 1 cycle                                  | 3 7  |            |
| 2 cycles                                 | 4 9  |            |
| 3 cycles                                 | 6 13 |            |
| 4 cycles                                 | 32 69|            |
| 5 cycles                                 | 1 2  |            |

**Additional intravenous hydration**

| Number of patients | 7 15 |
|-------------------|------|
| Total number of days (median, range) | 2 1–19 |

*Intravenous hydration on days other than those on which cisplatin was administered.

The pathophysiological mechanism for renal injury is not fully understood; however, high-volume hydration and forced diuresis are usually employed to prevent CDDP-related nephrotoxicity. Basic and clinical research suggest that both mannitol and furosemide are equally effective for the prevention of renal dysfunction. These strategies are intended to lower the concentration and to shorten the period of direct CDDP exposure. Hypomagnesaemia has also been considered as a cause of renal dysfunction and as a target of intervention. Magnesium is associated with the active transport mechanism in the tubular cells of the kidney. Söbro et al suggested that hypomagnesaemia during CDDP administration may lead to an elevated concentration of CDDP in tubular cells, thereby damaging the proximal tubules and resulting in subsequent renal dysfunction. Several studies, including a randomised trial, have demonstrated a favourable effect to prevent renal dysfunction during CDDP-based chemotherapies.

Based on these findings, the National Comprehensive Cancer Network (NCCN) has provided chemotherapy order templates to improve the safe use of drugs and biologics in cancer care. The CDDP template of the NCCN recommends hyperdiuresis using mannitol and magnesium supplementation, which were included in the protocol treatment for the current trial. Several trials have been conducted to evaluate the efficacy and safety of short-term low-volume hydration using contemporary antiemetics and magnesium supplementation. Hotta et al reported that 0% (evaluation based on upper limit of the normal range) and 4% (evaluation based on baseline Cr value in each patient) of the participants in their series experienced grade 2 or greater Cr elevation and concluded that short-term low-volume hydration was feasible in a phase II (OLCSG1002) trial. Horinouchi et al demonstrated that 43 out of 46 participants (97.8%) completed chemotherapy containing CDDP (75 mg/m² or over) without experiencing grade 2 or greater elevation in creatinine in a phase II trial.

Oral rehydration solution has been widely used as an effective method of fluid resuscitation in many medical situations, especially for patients with acute infectious diarrhoea. In several clinical trial, oral hydration was evaluated as an appropriate substitute for intravenous hydration to prevent drug-induced nephrotoxicities. The composition of OS-1 is based on common oral rehydration solution formula recommended by WHO. Dana et al reported a small randomised trial comparing the oral and intravenous hydration in patients receiving CDDP-based chemotherapies. The participants (65 patients) were randomised into three arms of prehydration before CDDP: a control arm (conventional intravenous administration of 3000 mL of normal saline hydration followed by hyperdiuresis with mannitol), oral hydration with mannitol (3000 mL of oral fluids followed by mannitol) and oral hydration with furosemide (3000 mL of oral fluid followed by furosemide). As a result, the participants experienced a similar frequency of kidney dysfunction when
evaluated using the blood urea value, and the authors concluded that oral hydration was feasible for patients receiving CDPD.\(^5\) In the present trial, we demonstrated that oral posthydration using OS-1 could shorten the time required for intravenous hydration by about 1 hour without increasing renal or other toxicities. A 1-hour time savings would benefit both patients and medical staff and would free up equipment required for drug administration, especially in outpatient settings. Substitution of post-cisplatin hydration by oral hydration could be widely adapted using other oral rehydration solution which have similar composition as OS-1.

In this multicenter phase II trial, we confirmed the safety of oral posthydration with regard to renal function in almost all (98%) of the participants who received CDDP-based chemotherapy. Oral hydration can be used as a safe and convenient substitute for intravenous posthydration for cisplatin administration at the standard dose.

Contributors All authors contributed this study equally.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was conducted with the approval of the Institutional Review Board at each site.

Provenance and peer review Not commissioned; externally peer reviewed.

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