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Reduction in nephrotoxicities using short hydration for chemotherapy containing cisplatin: a consecutive analysis of 467 patients with thoracic malignancies

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ABSTRACT

Background Conventional hydration (CH) in chemotherapy containing cisplatin (CDDP) has been recommended to prevent renal toxicity. Although an increasing number of studies have demonstrated the feasibility of short hydration (SH), few large studies have reported the superiority of SH, compared with CH, in terms of nephrotoxicities.

Methods We conducted a consecutive retrospective analysis of 467 patients who had been treated with chemotherapy including CDDP. Statistical analyses were performed to evaluate the risk factors for nephrotoxicities. The following factors were included in the analyses: age, sex, performance status (PS), concomitant thoracic radiotherapy, CDDP dose, magnesium supplementation, baseline creatinine values and method of hydration.

Results The patients' characteristics were as follows: male/female, 323/144 patients; median age (range), 62 (27–69) years; PS 0/1/2/3, 238/217/10/2 patients and SH/CH, 111/356 patients. The proportion of patients requiring a CDDP dose reduction in the SH group was 6.3%, while that in the CH group was 12.9%. Patients who discontinued CDDP because of nephrotoxicities accounted for 0.9% of the patients in the SH group and 2.2% of the patients in the CH group. After CDDP-based chemotherapy, a creatinine increase of more than grade 1 was observed in 14.4% and 33.1% of the patients in the SH and CH groups, respectively. A logistic regression analysis revealed a significantly lower incidence of grade 1 or higher creatinine toxicity after the first cycle of chemotherapy in the SH group (OR, 0.20; 95% CI 0.06 to 0.63; p=0.006).

Conclusions SH resulted in a significantly lower incidence of nephrotoxicity.

Key questions

What is already known about this subject?

- Nephrotoxicity is the main dose-limiting cisplatin-induced adverse event.
- To prevent cisplatin-induced renal toxicity, several strategies including magnesium supplementation and forced diuresis have been reported and introduced to daily practice.

What does this study add?

- We conducted a consecutive retrospective analysis of 467 patients who had been treated with chemotherapy including cisplatin.
- We found that patients with short hydration illuminated a significantly lower frequency and severity of nephrotoxicity than those who with conventional hydration.
- Short hydration not only makes cisplatin use more convenient by minimising the hydration volume and duration, but it also reduces nephrotoxicity, compared with conventional hydration.

How might this impact on clinical practice?

- This study has important implications for practical recommendations regarding optimal hydration methods for the prophylactic management of nephrotoxicity.

INTRODUCTION

Cisplatin (CDDP) continues to play a crucial role in cytotoxic chemotherapy for patients with solid tumours including lung cancer.[1–3] The management of gastrointestinal and renal toxicities has been an important issue concerning the use of CDDP. Based on early phase trials, continuous and high-volume hydration has been recommended to prevent nephrotoxicity in patients who receive CDDP.[4] Novel antiemetics, such as 5-HT_3 receptor and neurokinin-1 (NK-1) receptor antagonist, have dramatically improved the management of gastrointestinal toxicities associated with CDDP, leading to adequate oral intake.[5] Several single-arm prospective trials have shown the safety of short-term and lower volume hydration (short hydration (SH)) using up-to-date antiemetics.[6 7] Recently, a SH regimen has been introduced to daily clinical practice in Japan, and an increasing number of clinical studies have demonstrated the

feasibility of SH. However, only a few large analyses have compared SH with conventional hydration (CH) under up-to-date management involving 5-HT_3 receptor, NK-1 receptor antagonist and dexamethasone. We retrospectively compared the frequency and severity of nephrotoxicity between patients receiving SH and those receiving CH among patients with thoracic malignancies that were treated with CDDP.

PATIENTS AND METHODS

Patients

We conducted a consecutive retrospective analysis of patients with thoracic malignancies who had been treated with chemotherapy or chemoradiotherapy including CDDP at a dose of ≥60 mg/m^2 between December 2009 and December 2013 at the National Cancer Center Hospital, Tokyo, Japan. Patients eligible for inclusion in this study were between the ages of 20 and 69 years. All the patients received aprepitant, a 5-HT_3 blocker, and dexamethasone based on clinical guidelines for the management of gastrointestinal toxicities.[8 9] Horinouchi *et al* conducted a prospective trial examining the safety of SH.[6] After the trial, the hydration regimen shifted away from CH to SH (December 2009 to July 2013 and August 2013 to December 2013, respectively). This retrospective analysis was approved by the institutional review board.

Nephrotoxicity

We assessed nephrotoxicity using three methods: the serum creatinine value, the creatinine clearance (Ccr) and the estimated glomerular filtration rate (eGFR). An abnormal serum creatinine value was defined as higher than the upper limit of the serum creatinine level of 1.1 and 0.8 mg/dL for men and women, respectively. The Ccr was calculated using the Cockcroft-Gault equation, and the eGFR was adjusted for the Japanese population based on the serum creatinine levels. We collected laboratory data before the start of treatment, before the second course of chemotherapy and after the completion of the last chemotherapy treatment.

Treatment

All the cases received aprepitant, a 5-HT_3 blocker, and dexamethasone. As a general antiemetic premedication, palonosetron (0.75 mg) and dexamethasone (9.9 mg) were 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 the start of chemotherapy. Examples of the hydration methods used in our hospital are shown in figure 1. In the CH group, prehydration and posthydration for CDDP consisted of 1000 mL of intravenous fluids each infused over a period of 4 hours. A total volume of 3200–3600 mL of fluid was infused over 12 hours on day 1, and 1000–2000 mL of fluid was infused each day thereafter

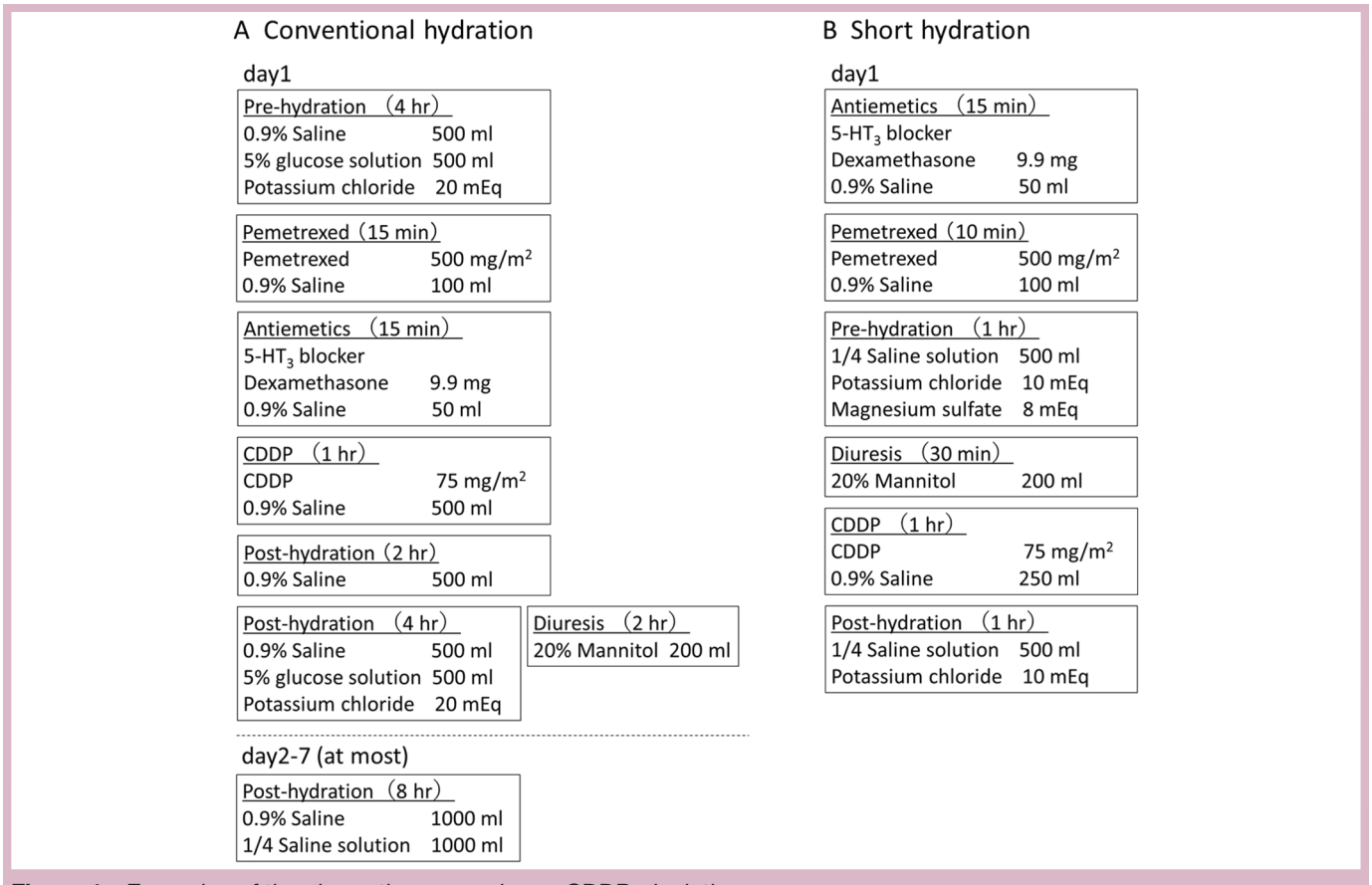

Figure 1 Examples of the chemotherapy regimen. CDDP, cisplatin.

for at least 3 days. In the SH group, patients were given 500 mL of intravenous fluids infused over a period of 1 hour immediately before and after CDDP administration. Hydration was administered only on day 1, with a total of 1550–2050 mL of fluid being infused over a period of 4 hours. Mannitol was used between prehydration and CDDP administration during SH, whereas the diuretic was administered 3 hours after CDDP administration in the CH group. Potassium chloride was supplemented in both methods. Some patients in the CH group were not treated with magnesium sulfate. Both methods were performed in an inpatient setting.

Statistical analyses

A logistic regression analysis was conducted to assess the impact of multiple clinical factors on an abnormal

Table 1 Patient characteristics

	Conventional hydration		Short hydration	
	n=356	% or range	n=111	% or range
Age (years)				
Median (range)	61	27–69	63	33–69
Sex				
Female	108	30.3	36	32.4
Male	248	69.7	75	67.6
Performance status				
0	188	52.8	50	45.1
1	158	44.3	59	53.1
2	8	2.3	2	1.8
3	2	0.6	0	0
Treatment setting				
Advanced disease	152	42.7	58	52.3
Chemoradiotherapy	104	29.2	23	20.7
Adjuvant therapy	66	18.5	21	18.9
Postsurgical recurrence	34	9.6	9	8.1
Treatment regimen				
Cisplatin+Vinorelbine	137	38.4	38	34.2
Cisplatin+Pemetrexed	95	26.7	53	47.8
Cisplatin+Irinotecan	58	16.3	4	3.6
Cisplatin+Etoposide	30	8.4	4	3.6
Cisplatin+Docetaxel	26	7.3	7	6.3
Cisplatin+Gemcitabine	8	2.3	5	4.5
Cisplatin+Amrubicin	2	0.6	0	0
Histology				
Adenocarcinoma	204	57.5	83	74.8
Squamous cell carcinoma	42	11.8	16	14.4
NSCLC	14	3.9	4	3.6
Small cell carcinoma	73	20.6	5	4.5
LCNEC	14	3.9	3	2.7
MPM	8	2.3	0	0
Comorbidities				
Hypertension	98	27.5	25	22.5
Diabetes mellitus	20	5.6	2	1.8
Cardiac disease	17	4.8	0	0
Pulmonary disease	43	12.1	13	11.7
Magnesium supplementation	295	82.9	110	99.0

LCNEC, large-cell neuroendocrine carcinoma; MPM, malignant pleural mesothelioma NSCLC, non-small cell lung cancer.

Table 2 Sequential evaluations of renal function

	Conventional hydration			Short hydration		
	Before treatment	After first cycle	After last cycle	Before treatment	After first cycle	After last cycle
Creatinine elevation* (n, %)						
Grade 0	344 (96.6)	308 (86.5)	238 (66.9)	107 (96.4)	107 (96.4)	95 (85.6)
Grade 1	12 (3.4)	45 (12.6)	103 (28.9)	4 (3.6)	4 (3.6)	16 (14.4)
Grade 2*	0 (0)	3 (0.9)	15 (4.2)	0 (0)	0 (0)	0 (0)
Serum creatinine (mg/dL)						
Median	0.7	0.76	0.80	0.7	0.75	0.79
Range	0.37–1.3	0.37–2.5	0.37–2.5	0.4–1.1	0.4–1.3	0.4–1.6
Ccr† (mL/min)						
Median	92.4	83.6	73.2	93.1	87.2	82.1
Range	44.2–253.7	30.3–240.6	27.0–216.9	49.4–173.2	42.9–153.2	38.1–176.1
eGFR‡ (mL/min/1.73 m^2)						
Median	85.0	76.0	65.3	80.8	77.5	73.7
Range	43.4–198.3	22.2–167.4	22.2–167.4	53.0–126.1	44.1–141.7	36.9–141.7

*Maximum grade of creatinine elevation according to the National Cancer Institute Common Toxicity Criteria (CTCAE), V.4.0.
†Calculated creatinine clearance using the Cockcroft-Gault equation, mL/min.
‡eGFR using the Japanese equations for estimating the glomerular filtration rate from the serum Cr level, mL/min/1.73 m^2.
Ccr, creatinine clearance; eGFR, estimated glomerular filtration rate.

creatinine value after the first cycle of CDDP. The predictive factors included were as follows: age, sex, Eastern Cooperative Oncology Group performance status (PS), concomitant thoracic radiotherapy, CDDP dose, magnesium supplementation, baseline serum creatinine level and the method of hydration. A p value of <0.05 was regarded as being statistically significant. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method. Tumour response analyses were conducted for patients with stage IIIB and IV (recurrence or metastatic) non-small cell lung cancer (NSCLC) using the Response Evaluation Criteria in Solid Tumors (RECIST), V.1.0. We assessed PFS and OS in patients with stage IIIB or IV NSCLC without an *EGFR* mutation or *ALK* rearrangement. The PFS period was defined as the date from the start of CDDP administration until disease progression or death. The OS period was defined as the interval between the date of the first administration of CDDP and death or the date of the last follow-up for patients who were alive at the end of the study period. Living patients without an event were censored as of the date of the most recent visit. All the statistical analyses were conducted using STATA V.15.

RESULTS

Patient characteristics

A total of 467 patients were analysed in this study: 356 patients in the CH group and 111 patients in the SH group. The median age was 62 years (range, 27–69 years). The patients' characteristics are shown in table 1. There were no differences in the proportions of sex, age and PS between the two groups. CDDP was administered with vinorelbine, pemetrexed, irinotecan, etoposide, docetaxel, gemcitabine or amrubicin. The proportions of adenocarcinoma (74.8% vs 57.5%), pemetrexed administration (47.8% vs 26.7%) and magnesium supplementation (99% vs 82.9%) were higher in the SH group.

Nephrotoxicity

The changes in the serum creatinine, Ccr and eGFR values in each group are summarised in table 2. Figure 2 shows dot plots describing the renal function of all the patients at pretreatment and after the first and last cycles. The serum creatinine levels before chemotherapy were not significantly different between the two groups. After the first cycle, the proportion of patients with a creatinine increase of more than grade 1 was 3.6% in the SH group, compared with 13.5% in the CH group. After the last cycle, the proportions of patients with a creatinine increase of more than grade 1 were 14.4% and 33.1% in the SH and CH groups, respectively. After the first cycle, the incidence of a creatinine elevation of more than grade 2 was 0% in the SH group, compared with 0.9% in the CH group. After the last cycle, the incidence of a creatinine elevation of more than grade 2 was 0% in the SH group, compared with 4.2% in the CH group. A lower rate of nephrotoxicity in the SH group was also observed when the Ccr and eGFR levels were compared between the two groups. A logistic regression analysis revealed a significantly lower incidence of grade 1 or higher abnormal creatinine levels after the first cycle of CDDP-based chemotherapy in the SH group (OR, 0.19; 95% CI 0.06 to 0.61; p=0.006) (table 3).

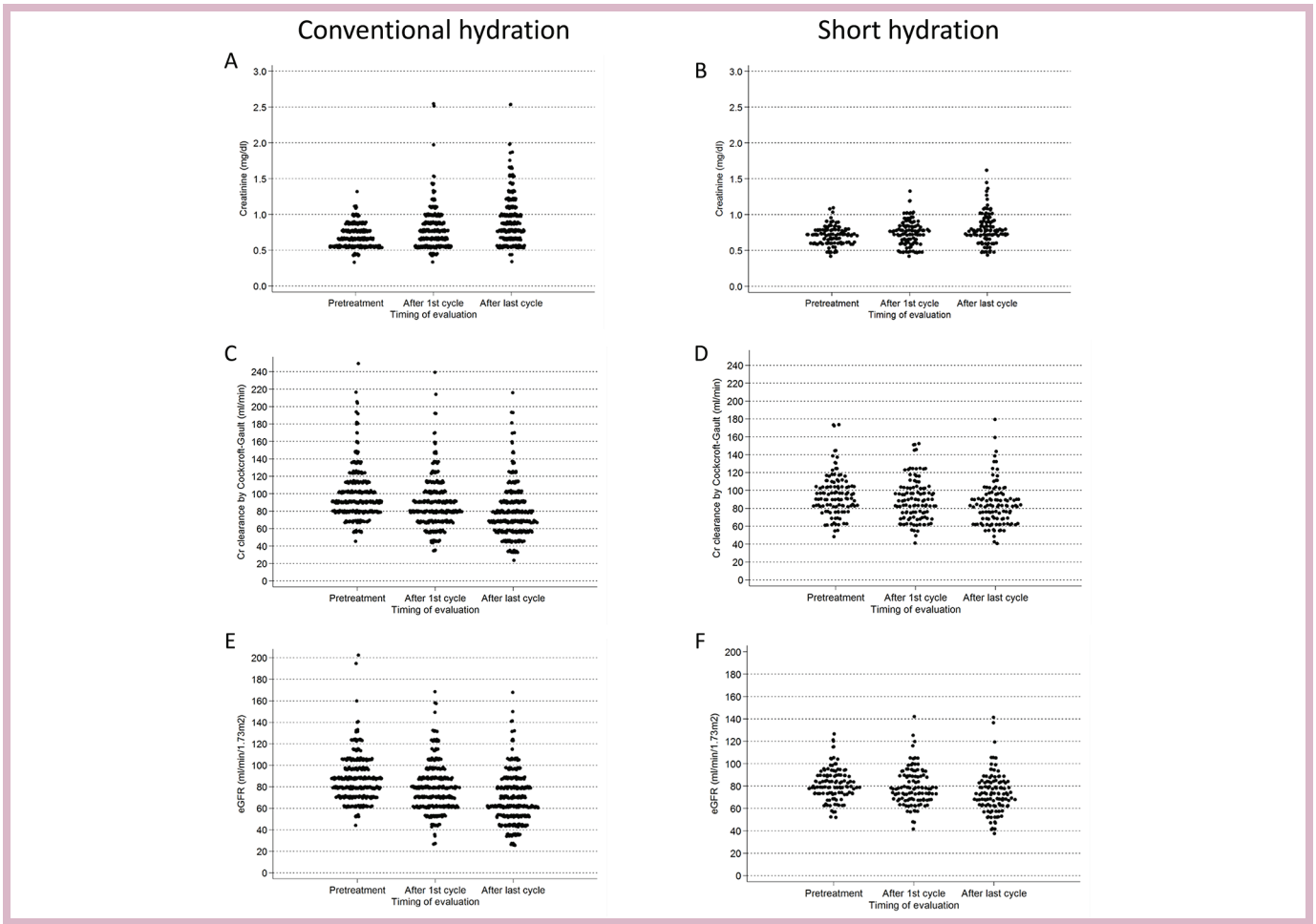

Figure 2 Dot plots comparing changes in renal function at pretreatment and after the first and last cycles in both hydration groups. (A) Serum creatinine level in the CH group. (B) Serum creatinine level in the SH group. (C) Ccr in the CH group. (D) Ccr in the SH group. (E) eGFR in the CH group. (F) eGFR in the SH group. Ccr, creatinine clearance; CH, conventional hydration; eGFR, estimated glomerular filtration rate; SH, short hydration.

Treatment delivery

The median number of treatment cycles was four (range, one to six cycles) in both treatment groups (online supplementary table S1). The proportion of patients requiring a dose reduction of CDDP in the CH group was 12.9%, while that in the SH group was 6.3%. The proportion of CDDP discontinuation because of nephrotoxicity was 2.2% in the CH group and 0.9% in the SH group. The proportion of patients who received intravenous hydration because of renal toxicity was 6.7% in the CH group and 1.8% in the SH group. Patients with advanced and postsurgical recurrent NSCLC who received second-line treatment accounted for 74.7% of the patients in the CH group and 82.0% of the patients in the SH group. The percentage of patients who received maintenance pemetrexed treatment after CDDP and pemetrexed was 55.6% in the CH group and 58.7% in the SH group. The mean hospital stay for a course of chemotherapy including CDDP and pemetrexed was 10.3 days for the CH group and 6.8 days for the SH group. The SH group had a shorter period of hospitalisation.

Response and survival

The treatment efficacies in patients with advanced NCLC (n=153) are shown in the online supplementary table S2. The overall response rate (ORR) was 37.5% in the SH group and 34.0% in the CH group. No significant difference was seen between the two groups. The Kaplan-Meier curves for PFS and OS are shown in figure 3. Among the patients with stage IIIB or IV NSCLC without an *EGFR* mutation or *ALK* rearrangement (n=88), a total of 27 patients in the SH group and 61 in the CH group were included in the survival analysis. The median PFS was 5.2 and 6.2 months (HR, 0.98; 95% CI 0.59 to 1.63) and the median OS was 16.1 and 19.0 months (HR, 1.00; 95% CI 0.58 to 1.73) for the SH and CH groups, respectively. No significant difference in survival was seen between the two groups.

DISCUSSION

This retrospective study evaluated the effectiveness of SH for CDDP-based chemotherapy compared with CH in patients aged ≤70 years. We found that patients treated

Table 3 Evaluation of predictors of an abnormal creatinine value* after the first cycle of cisplatin-based chemotherapy (logistic regression analysis)

	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)						
<62	1			1		
≥62	1.43	0.79 to 2.57	0.234	1.70	0.89 to 3.26	0.109
Sex						
Female	1			1		
Male	1.00	0.54 to 1.87	0.991	1.27	0.61 to 2.63	0.528
Performance status						
0–1	1			1		
2–3	0.72	0.09 to 5.69	0.756	1.04	0.12 to 8.78	0.968
Chemoradiotherapy						
No	1			1		
Yes	2.34	1.30 to 4.23	0.005	2.50	1.26 to 4.96	0.009
Dose of cisplatin (mg/m^2)						
60	1			1		
75 or 80	1.95	0.68 to 5.61	0.216	2.03	0.60 to 6.87	0.255
Magnesium supplementation						
No	1			1		
Yes	1.91	0.93 to 3.96	0.080	1.63	0.73 to 3.65	0.230
Baseline creatinine value						
Normal	1			1		
Abnormal*	16.2	5.62 to 46.9	<0.001	30.5	8.87 to 104	<0.001
Method of hydration						
Conventional hydration	1			1		
Short hydration	0.24	0.08 to 0.68	0.007	0.19	0.06 to 0.61	0.006

*Creatinine value higher than the upper limit of the creatinine value.

with SH had a significantly lower frequency and severity of nephrotoxicity than those treated with CH. To our knowledge, our sample size is the largest retrospective analysis to compare two types of hydration methods.

CDDP-induced nephrotoxicity has been attributed to the accumulation of CDDP in renal tubules and associated tubular cell necrosis, particularly in the proximal tubules in the outer renal medulla in the S3 segment.[10] Moreover, a reduction in Ccr after CDDP administration is correlated with the peak plasma level of platinum.[11] Therefore, saline hydration and forced diuresis using mannitol or furosemide are crucial for preventing nephrotoxicity, and hydration for >24hours after the introduction of CDDP has been conventionally performed. However, CDDP exhibits unique pharmacokinetics in that the plasma concentration of protein-unbound platinum reaches its peak just after intravenous administration and is cleared to below a measurable level within the first 2hours following CDDP administration.[12] Furthermore, Stewart *et al* assessed the effects of various factors on elevated serum creatinine levels in 425 patients treated with CDDP and suggested that the amount of hydration had no effect on the incidence of renal dysfunction.[13] These features and reports suggest the significance of rapid and short-term hydration for the prevention of nephrotoxicity, with long-term and high-volume hydration possibly being unnecessary. Additionally, the importance of magnesium supplementation for the prevention of CDDP nephrotoxicity has also been highlighted. Hypomagnesaemia causes dehydration and the upregulation of rat organic cation transporter 2, which plays a role in urinary excretion and the uptake of CDDP in the proximal tubules,[14] thereby increasing the renal accumulation of CDDP.[15]

In 2007, Tiseo *et al* conducted a retrospective study showing the feasibility of SH in CDDP-based chemotherapy using magnesium supplementation and forced diuresis for the treatment of lung cancer and mesothelioma.[16] Three different single-arm prospective trials also concluded that SH is safe and feasible.[17–19] Several other retrospective analyses have compared SH with CH. An analysis of 143 patients reported by Sakaida *et al* showed that the incidence of an elevated serum creatinine level of more than equal to grade 1 was 3.8% in an SH group and 21.0% in a CH group. In

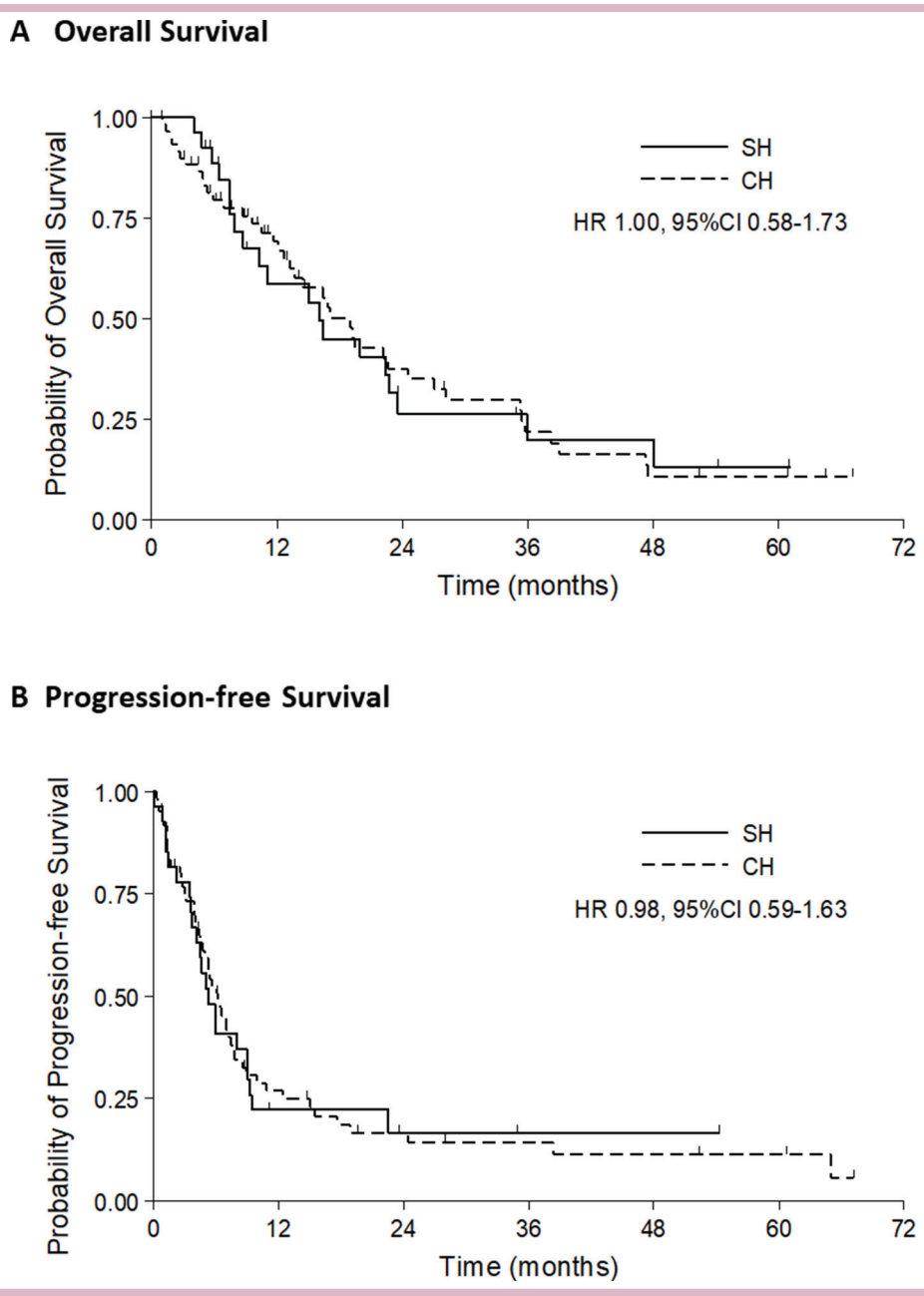

Figure 3 Kaplan-Meier estimates of progression-free survival and overall survival. CH, conventional hydration; SH, short hydration.

their study, the administration of mannitol as a diuretic and magnesium supplementation were only performed in the SH group.[20] In the presently reported study, 467 patients divided into two groups received the same antiemetics and mannitol treatment, and most of the patients also received magnesium supplementation. Nevertheless, a significant difference in the incidence of renal toxicity was observed between the two methods of hydration.

In terms of treatment efficacy, the response and survival rates in this study were consistent with previously reported data.[3] The ORR, PFS and OS were not significantly different between the SH and CH groups. We found that the treatment efficacy was maintained even when the SH method was used.

The present study had some limitations. Because it was a retrospective and non-randomised analysis, there were some imbalances in clinical factors, such as histology and the administration of other anticancer drugs in combination with CDDP. However, to minimise potential biases in patient selection, patients in both groups were enrolled consecutively irrespective of their medical background (eg, renal function) or treatment (eg, dose of CDDP).

CONCLUSION

Short hydration resulted in a significantly lower incidence of nephrotoxicity than CH. To reduce nephrotoxicity in cisplatin-containing regimens, SH should be recommended.

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