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Hyponatremia timing, incidence, and associated risk factors in patients treated with cisplatin for lung cancer: a retrospective study

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ABSTRACT

The incidence of cisplatin-derived hyponatremia remains unknown, although nausea, vomiting, and renal dysfunction are common adverse events of cisplatin, a platinum-based preparation**.** The factor contributing to hyponatremia is described but not well known. This study aimed to retrospectively investigate the incidence of hyponatremia, timing, and associated risk factors. This study surveyed patients with lung cancer who received cisplatin chemotherapy from August 2013 to July 2019 at Shizuoka Cancer Center. The severity of hyponatremia was evaluated based on Common Terminology Criteria for Adverse Events. A total of 814 patients were included in this study. 682 (83.7%) patients had hyponatremia of any grade: grade 1 (<135–130 mmol/L), grade 3 (<130–120 mmol/L), and grade 4 (<120 mmol/L) hyponatremia were observed in 619 (76.0%), 51 (6.3%), and 12 (1.5%) patients, respectively. Of 63 patients with grade 3–4 hyponatremia, 43 (68.3%) developed it in the first treatment cycle. In multivariate analysis, the short hydration regimen (<3000 mL/day) has a lower incidence of grade 3–4 hyponatremia than a normal (>3000 mL) hydration regimen (OR: 0.35 [0.16-0.80], $p = 0.013$). In addition, if the Na^+ value before the start of administration is < 135mmol/L, the incidence of grade3 and 4 hyponatremia is higher (OR:0.14 [0.07-0.28], $p < 0.001$).

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Hyponatremia due to cisplatin is likely to occur in patients with low Na levels before administration, such as the elderly. Since short hydration might avoid diuretics, hydration methods might need to be reconsidered to prevent hyponatremia.

Keywords: *cancer; cisplatin; hyponatremia; hydration*

INTRODUCTION

The Food and Drug Administration approved the use of cisplatin in 1978 for the treatment of testicular and ovarian cancers, among other indications. It is presently a key drug for many solid cancers such as head and neck and non-small cell lung cancer.[1] In treating lung cancer, relatively high doses of platinum doublet regimens are commonly used as a first-line treatment. In the four-arm cooperative study (FACS) study, nausea/vomiting (severity grade ≥2) and leukopenia (grade ≥3) were reported as side effects of cisplatin, affecting 47–61% and 33–67% of patients, respectively; however, low sodium concentration was not an end point in this study.[2] Antiemetics are used to suppress for control nausea and vomiting, and Granulocyte Colony Stimulating Factor (G-CSF) preparations are used as supportive care for myelosuppression. Cisplatin is prone to nephrotoxicity. It is known that this nephrotoxicity can be reduced by excreting it from the body due to water load.[3] In recent years, a short hydration method has been performed to switch the infusion for renal protection to oral replenishment. Its usefulness, such as reduction of infusion load and renal damage, has been reported.[4] However, a standardized approach to hyponatremia has not been established, so early detection by regular monitoring is important. Similarly, risk factors for hyponatremia remain unclear. Antidiuretic hormone incompatible secretion syndrome (SIADH) and renal salt wasting syndrome have been implicated in developing hyponatremia associated with cisplatin administration.[5,6] However, evidence regarding hyponatremia is inconsistent. The present study aimed to retrospectively examine hyponatremia incidence, timing, and associated risk factors in patients with lung cancer treated with cisplatin for the first time.

METHODS

Patients

This study included lung cancer patients treated with cisplatin between August 2013 and July 2019 at the Shizuoka Cancer Center. Eligible patients received cisplatin for the first time at a dose of 60 mg/m² or above at three-week intervals and whose serum Na^+ concentration at baseline was in the normal range (135–145 mmol/L) or Grade1 hyponatremia (130–134 mmol/L). We excluded patients whose serum Na^+ levels were <130 mmol/L before cisplatin administration.

Outcome Evaluation and Data Extraction

Electrolyte levels and renal function were regularly tested before the first and all subsequent treatment cycles. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to evaluate hyponatremia as grades 1, 3, and 4, which corresponded to Na^+ levels of 135–130 mmol/L (the lower end of this rage represented our facility's standard value), <130–120 mmol/L, and <120 mmol/L, respectively. The grade 2 category was not applicable in CTCAE version 4.03. Data on serum Na^+ levels were extracted from medical records for the duration of cisplatin treatment (up to six cycles). Candidate risk factors included sex, age, cancer type, concomitant anticancer drugs such as tegafur/gimeracil/oteracil (S-1), irinotecan (CPT-11), etoposide (ETP), gemcitabine (GEM), vinorelbine (VNR), pemetrexed (PEM), and pemetrexed +

pembrolizumab (PEM + Pembro), hydration volume (first-day volume of 3000 mL or less was defined as the "short" hydration method, whereas higher volumes represented "normal" hydration), and diuretics use (furosemide, mannitol). Figure 1 shows the order of administration and the drugs. Diuretics were used on day1 (the day of cisplatin administration) and added between day2 and day7 at the physician's discretion and a dose determined by the patient's weight gain and urine volume. The timing of hyponatremia onset during the course of cisplatin was noted. The surveyed regimens, including any concomitant anticancer drugs, were summarized in Table 1.

Statistical Analysis

The association between grade 3 and 4 hyponatremia (objective variable) and patient background (explanation variable) was analyzed by logistic regression analysis. As the patient background, gender (male or female), age(≥65years or <65years), hydration method (short hydration or normal hydration), cancer type (SCLC or others), presence or absence of furosemide addition, Na^+ level before the start of administration ($Na^+ \geq 135$ or $Na^+ < 135$), and each combination drug (S-1, CPT-11, ETP, GEM, VNR, PEM, and PEM + Pembro) were selected. Based on the results of univariate analysis, factors with $p \leq 0.2$ were extracted, and multivariate

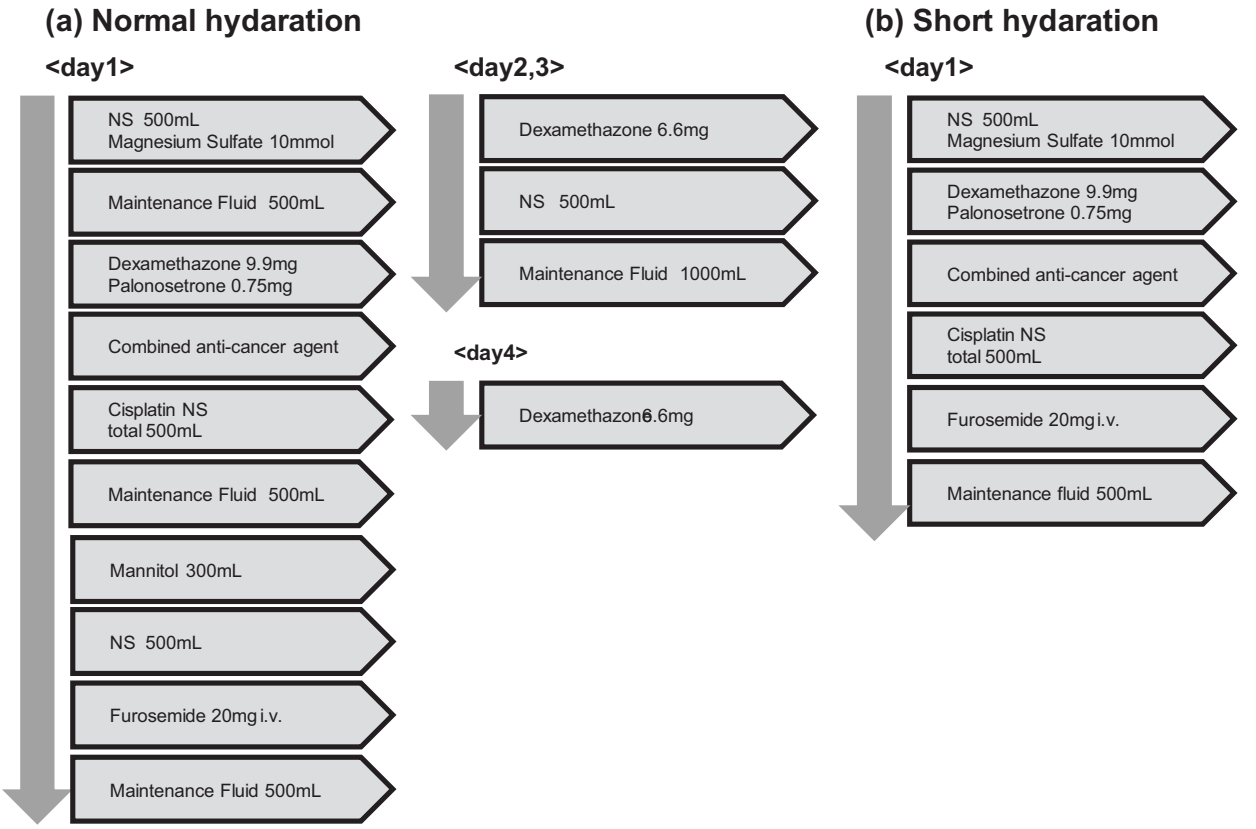

FIGURE 1. The flow of cisplatin containing chemotherapy. (a) Normal hydaration, (b) Short hydaration. NS, normal saline; maintenance fluid (Na^+: 35 mmol/L, K^+: 20 mmol/L , L-Lactate$^-$: 20 mmol/L).

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TABLE 1. Combined anti-cancer drug and fluid volume for each regimen.

Concomitant drug	cisplatin (mg/m²)	Short hydration (day of cisplatin administration)					Normal hydration(day of cisplatin administration)				
		Hydration (mL)*	Na^+ (mmol)	Na^+ (mmol/L)	Furosemide (mg)	Mannitol (mL)	Hydration (mL)*	Na^+ (mmol)	Na^+ (mmol/L)	Furosemide (mg)	Mannitol (mL)
S-1	60	2,075	225	109	20	–	3,375	329	98	20	300
CPT-11	60	2,325	225	97	20	–	3,625	320	88	20	300
ETP	80	2,625	242	92	20	–	3,925	337	86	20	300
GEM	80	–	–	–	–	–	3,600	340	94	20	300
VNR	80	2,225	258	116	20	–	3,975	352	89	20	300
PEM	75	2,125	240	113	20	–	3,505	350	100	20	300
PEM/Pembro	75	2,275	263	116	20	–	–	–	–	–	–

**Excludes anti-cancer drug infusion volume, Standard dose registered in the regimen at our hospital (cisplatin administration date).*
Concomitant drug(mg/m² or mg/Body):
S-1(80mg/m²): Tegafur / Gimeracil / Oteracil potassium, CPT-11(60mg/m²): Irinotecan, ETP(100mg/m²): Etoposide, GEM(1000mg/m²): Gemcitabine, VNR(25mg/m²): Vinorelbine, PEM(500mg/m²): Pemetrexed, Pembro(200mg/Body): Pembrolizumab.

analysis was performed. In all comparisons, a two-sided *p*-value of <5% was considered significant. We used "BellCurve for Excel" ver3.21 published by "Social Survey Research Information Co., Ltd." for statistical analysis.

RESULTS

Of the 3397 patients who received cisplatin during the study period, 814 met the eligibility criteria of the present study (Figure 2).

Patient background and the incidence of hyponatremia are presented in Table 2. A total of 619/814 (84%) cisplatin-treated patients had any grade of hyponatremia. Grade 3 and 4 hyponatremia affected 51/814 (6.3%) and 12/814 (1.5%) patients. There were no missing data. Short and normal hydration regimens were administered to 754/814 (92.6%) and 60/814 (7.4%) patients. Grade 3 and 4 hyponatremia affected 50/754 (6.6%) and 13/60 (21.7%) patients undergoing short and normal hydration, respectively.

Grade 3 and 4 hyponatremia developed after the first, second, third, and fourth rounds of treatment in 43/63 (68.3%), 13/63 (20.6%), 6/6 (39.5%),

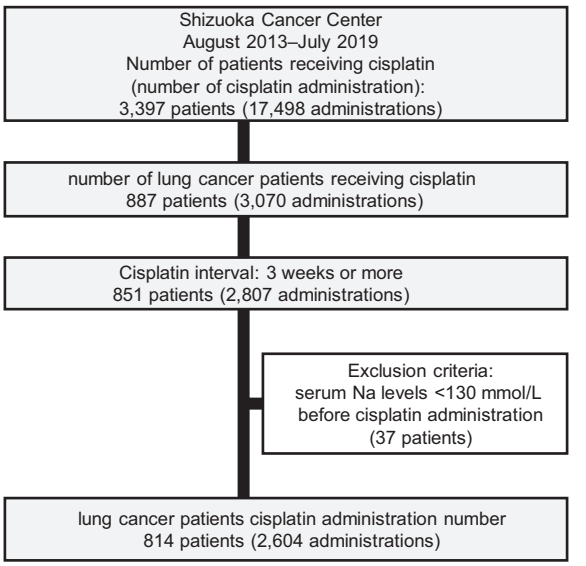

FIGURE 2. Flow diagram of patient selection.

TABLE 2. Patient background / hyponatremia incidence

		Number	Hyponatremia	
			Grade 1	Grade 3/4
Patient	Total	814	619 (76%)	63 (7.7%)
Sex	Male	572	441 (77%)	43 (7.5%)
	Female	242	178 (74%)	20 (8.3%)
Cancer type	SCLC	155	120 (77%)	13 (8.4%)
	others	659	499 (76%)	50 (7.6%)
Combined anti-cancer agent	S-1	88	74 (84%)	5 (5.7%)
	CPT-11	42	34 (81%)	5 (12%)
	ETP	113	86 (76%)	8 (7.1%)
	GEM	9	4 (44%)	4 (44%)
	VNR	205	163 (80%)	15 (7.3%)
	PEM	333	242 (73%)	25 (7.5%)
	PEM/Pembro	24	16 (67%)	1 (4.2%)
Hydration	Short	754	579 (77%)	50 (6.6%)
	Normal	60	40 (67%)	13 (22%)
Na^{+}[*1] (mmol/L)	≥135	760	581(76%)	47(6.2%)
	<135	54	38(70%)	16(30%)
Furosemide[*2]	yes	37	27 (73%)	6 (16%)
	no	777	592 (76%)	57 (7.3%)

*[*1]Initial serum Na (mmol/L), [*2]Administration after day 2.*
Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to evaluate hyponatremia. SCLC: small cell lung cancer, others : non-small cell lung cancer and Malignant pleural mesothelioma, hydration volume (first-day volume of 3000 mL or less was defined as the "short" hydration method, whereas higher volumes represented "normal" hydration), S-1: Tegafur / Gimeracil / Oteracil potassium, CPT-11: Irinotecan, ETP: Etoposide, GEM: Gemcitabine, VNR: Vinorelbine, PEM: Pemetrexed, Pembro: Pembrolizumab

and 1/63 (1.6%) patients, respectively. No case of initial onset was observed after the fifth round of treatment. The median treatment cycle was 4 cycles (1–6 cycles).

Factors associated with hyponatremia grades 3 and 4 obtained by logistic regression analysis are presented in Table 3.

Elderly patients (≤65 years) tended to have a higher incidence of hyponatremia (OR:1.65 [0.94-2.91] , $p = 0.082$) .

The incidence of grade 3 and 4 hyponatremia in the normal hydration group was significantly higher than that in the short hydration group (OR:0.35 [0.16-0.80], $p = 0.013$).

Additional intravenous infusions of furosemide on the second or later day of treatment were administered to 28/754 (3.7%) and 9/60 (15%) patients receiving the short and normal hydration regimens, respectively. Additional intravenous infusions of furosemide tended to increase the incidence of grade 3 and 4 hyponatremia (OR:1.88 [0.69-5.15] , $p = 0.220$) . A total of 51 doses of furosemide were administered to 37 patients. The mean dose (±SE) of furosemide was 17.1mg (± 4.6).

Among patients with a baseline (before cisplatin administration) serum Na^{+} concentration of 135-145 mmol/L, the incidence of grade 3 and 4 hyponatremia after treatment initiation was 6.2%

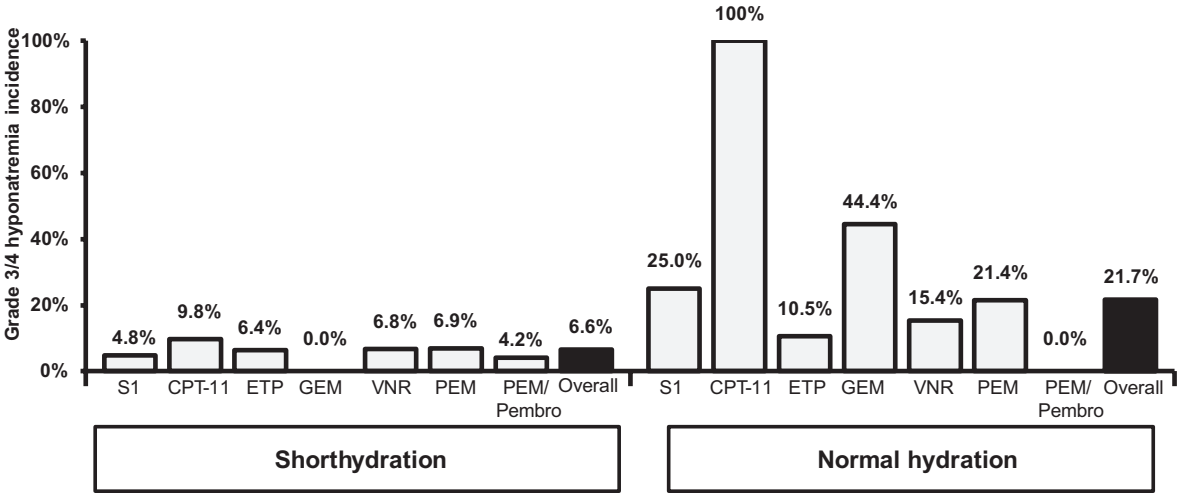

FIGURE 3. Grade 3/4 hyponatremia incidence per hydration type. % value represents the frequency of hyponatremia grades 3/4 for each hydration/combination of anticancer drugs.
S-1. Tegafur/Gimeracil/Oteracil potassium, CPT-11: Irinotecan, ETP: Etoposide, GEM: Gemcitabine, VNR: Vinorelbine, PEM: Pemetrexed, Pembro: Pembrolizumab.

TABLE 3. Comparison of patient background and incidence of Gr3/4 hyponatremia.

		Univariate analysis			Multivariate analysis		
		OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
≧65 years (vs. ＜65 years)		1.65	0.97-2.83	0.067	1.65	0.94-2.91	0.082
Male(vs. female)		0.90	0.52-1.57	0.716	–	–	–
Short hydration (vs. normal hydration)		0.26	0.13-0.51	< 0.001	0.35	0.16-0.80	0.013
SCLC (vs. others)		1.12	0.59-2.10	0.738	–	–	–
Furosemide[*1]		2.44	0.98-6.10	0.056	1.88	0.69-5.15	0.220
Na^+≧135 (vs. Na^+＜135)		0.16	0.08-0.30	< 0.001	0.14	0.07-0.28	< 0.001
Concomitant drug	S-1	0.69	0.27-1.78	0.447	–	–	–
	PEM	0.95	0.56-1.60	0.837	–	–	–
	GEM	10.12	2.65-38.7	< 0.001	3.45	0.71-16.7	0.124
	CPT-11	1.66	0.63-4.40	0.305	–	–	–
	VNR	0.92	0.51-1.67	0.794	–	–	–
	PEM/Pembro	0.51	0.07-3.84	0.514	–	–	–
	ETP	0.89	0.41-1.93	0.777	–	–	–

*[*1]Administration after day 2, OR: odds ratio; CI: confidence interval; i.v.: intravenous; SCLC: small cell lung cancer, others: non-small cell lung cancer and Malignant pleural mesothelioma, S-1: Tegafur/Gimeracil / Oteracil potassium, CPT-11: Irinotecan, ETP: Etoposide, GEM: Gemcitabine, VNR: Vinorelbine, PEM: Pemetrexed, Pembro: Pembrolizumab.*

(47/760); however, for patients with a baseline serum Na^+ concentration of 130-134 mmol/L, the corresponding value was 30% (16/54). A baseline (before cisplatin administration) serum Na^+ concentration was associated with the incidence of grade 3 and 4 hyponatremia (OR:0.14 [0.07-0.28] , $p < 0.001$).

About concomitant anticancer drugs, the incidence of grade 3 and 4 hyponatremia was 44% (4/9) in patients treated with GEM. (Figure 3) The administration of GEM tended to increase the incidence of grade 3 and 4 hyponatremia (OR:3.45 [0.71-16.7], $p = 0.124$).

DISCUSSION

In this study, the overall incidence of grade 3 and 4 hyponatremia was 7.8%. Concurrently, the incidence was higher among patients receiving the normal hydration than those receiving the short hydration regimen. The short hydration does not involve continuous infusion, and the burden on the patient is reduced compared to normal hydration, which involves a large amount of fluid replacement.[7] Previous studies have shown no differences between these methods in the associated risk of renal damage.[8,9] Nevertheless, no previous study has reported the differences in hyponatremia incidence between these two regimens. Previous studies involving normal hydration reported the incidence of hyponatremia due to cisplatin as 20.3% and 13.5%.[10,11] Meanwhile, Hotta et al. reported the incidence of grade 3 and 4 hyponatremia associated with short hydration as 9%.[12] The difference in the hydration method used may account for these discrepancies, indicating the potential benefits of using short hydration to prevent hyponatremia.

Of patients who developed grade 3 and 4 hyponatremia, 31.7% experienced its onset after the second course of chemotherapy. Previous reports have limited the low Na^+ expression status at the first dose to eliminate the effects of cumulative doses.[10,13] In this study, patients developed hyponatremia at different stages throughout the treatment, but no previous studies have addressed the timing of hyponatremia.

Grade 1 hyponatremia is rarely clinically relevant and does not require cisplatin discontinuation. In the present study, patients with a baseline serum Na^+ concentration of <135 mmol/L were at an increased risk of grade 3 and 4 hyponatremia. This finding is consistent with that of a previous study, which showed that a baseline serum Na^+ level of <135 mmol/L was associated with hyponatremia following cisplatin administration.[13] Cancer patients are prone to fluid retention, including ascites and edema; diuretics may be used for such patients.[14] Patients with hyponatremia who present with few subjective symptoms are at a high risk of falls and light-headedness.[15] Careful observation of such patients after treatment administration is required.

In the present study, diuretics may have affected the reported estimates. Furosemide and mannitol were shown to reduce the urine levels of cisplatin; in fact, National Comprehensive Cancer Network guidelines recommend the use of mannitol.[16,17] At our facility, furosemide was incorporated as a diuretic on the day of cisplatin administration in both short and normal regimens. In addition, mannitol was incorporated into the normal hydration regimen on the same day; the strong diuretic effects of both furosemide and mannitol may have induced hyponatremia. From the second day onward, furosemide was added at the attending physician's discretion, based on the change in urine volume and weight relative to baseline values.

In this study, despite the lack of a statistically significant difference, the incidence of hyponatremia tended to be high following the addition of furosemide after the second day of treatment. Furosemide is classified as a loop diuretic whose mechanism of action is consistent with this result as it acts on the proximal tubule and promotes the excretion of Na^+. The low incidence of hyponatremia in the short hydration group may be due to the low rate of fluid retention, including edema, in this

study. Hyponatremia has been reported to co-occur with fluid retention, likely due to systemic edema.[18] Although factors such as oral rehydration, weight gain, and incidence of edema were not investigated in the present study, the rate of additional furosemide administration after day two was low in the short hydration group. Thus, the risk of weight gain associated with edema was low in short hydration groups.

There was no significant difference between GEM and grades 3 and 4 hyponatremia in multiple analyses, but there was a tendency for hyponatremia to occur. The incidence of grade 3 and 4 renal dysfunctions in patients undergoing GEM combination therapy was reported as 4.8%, which is higher than the incidence of renal dysfunction in patients undergoing cisplatin alone (2.0%).[19] In contrast, the CAPPA-2 trial, which compared GEM combination therapy with GEM alone, reported no cases of severe renal dysfunction.[20] In the present study, renal dysfunction was not observed among four patients with grade 3 and 4 hyponatremia in the GEM combination group (data not shown). SIADH is generally considered to cause hyponatremia regardless of renal function status; it may have been the cause of hyponatremia in this study. Although the onset of SIADH due to treatment with GEM alone has not been reported, there have been cases of severe hyponatremia in patients with bladder cancer undergoing GEM + cisplatin therapy.[21] In the present study, the short administration time and low infusion volume of GEM therapy may have affected the onset of hyponatremia; however, the exact mechanism remains unclear. Moreover, in the present study, all nine patients undergoing GEM therapy received normal hydration, which may have affected the findings. Future studies should investigate the impact of GEM combination therapy on serum Na^+ levels in patients receiving short hydration.

Only one patient who received CPT-11 underwent normal hydration. Since severe hyponatremia occurred in the patient, the incidence is calculated to be high in Figure 3. Due to the small number of cases, the relationship between CPT-11 and hyponatremia needs further investigation in the future.

This study has some limitations. First, previous reports have shown that SIADH, alongside renal dysfunction, may cause hyponatremia.[6] In the present study, urinary Na^+ concentration, urinary osmolality, and plasma vasopressin concentration, which are required for the diagnosis of SIADH, were not investigated; thus, the impact of SIADH on the present findings cannot be assessed.[22] Second, hyponatremia may occur due to diarrhea or vomiting, which are the side effects of treatment with cisplatin. However, antiemetic therapy with NK1 receptor antagonists, palonosetron, steroids, and olanzapine is unlikely to cause frequent vomiting. Third, patients instructed about the importance of fluid intake may have been drinking excessively; the differences in electrolyte content of various drinks may have affected the present findings. Finally, this study was a retrospective observational study that involved a small number of patients treated at a single center. The frequency of occurrence and the validity of its sample size calculation have not been evaluated. Future studies that involve large samples and account for the diagnosis of SIADH are required.

CONCLUSION

The results suggest that using the short hydration method may have a lower incidence of hyponatremia than conventional large-scale, long-term hydration. In addition, if the Na^+ value before the start of administration is <135 mmol/L, hyponatremia is likely to become serious. Therefore, it may be useful to measure the serum Na+ level before using the short hydration method. If it is low, correct the electrolyte in advance using an oral rehydration solution. However, it is necessary to investigate in more detail in the future whether this fact is universal due to the composition of the short hydration used this time. There are few reports on the onset

of hyponatremia during cisplatin administration from the perspective of hydration and diuretics. Therefore, this research will help to reconsider the hydration method in the future.

ETHICAL APPROVAL

This study was conducted with the approval of the Ethics Review Committee of Shizuoka Cancer Center (review approval number: J2019-89-2019-1-3).

FUNDING

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CONFLICT OF INTEREST

The Authors declare no conflict of interest.

INFORMED CONSENT

Informed consent was obtained in the form of opt-out on our hospital website.

AUTHORSHIP CONTRIBUTIONS

Conception, design, comment, and approval: all authors. Data collection: Sumiaki Ogawa, Tatsuya Sakakibara. Data analysis: Sumiaki Ogawa, Rei Tanaka. Supervise: Junya Sato, Rei Tanaka, Michihiro Shino.

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