Efficacy of a Newly Modified Short Hydration Method for Gemcitabine and Cisplatin Combination Chemotherapy in Patients with Urothelial Carcinoma

Taku Naiki^a Yosuke Sugiyama^b Yoshihiko Tasaki^b Keitaro Iida^a
Toshiki Etani^a Shuzo Hamamoto^a Takashi Nagai^a Satoshi Nozaki^a
Ryosuke Ando^a Noriyasu Kawai^a Takahiro Yasui^a

^aDepartment of Nephro-urology, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan;

^bDepartment of Pharmacy, Nagoya City University Hospital, Nagoya, Japan

Keywords

Short hydration method · Gemcitabine cisplatin · Urothelial carcinoma

Abstract

Introduction: Conventional first-line chemotherapy for patients with metastatic urothelial carcinoma (UC) is gemcitabine and cisplatin (GC). However, cisplatin can cause renal failure, necessitating abundant fluid replacement and hospitalization during treatment. Recent evidence exists for short hydration methods in cisplatin-based chemotherapy.

Objective: This study aims to analyze the efficacy of newly established modified short hydration GC (m-shGC) therapy in patients with UC. **Methods:** From May 2017 to March 2019, 48 patients with UC who received m-shGC therapy were treated with 1,000 mg/m² gemcitabine on days 1, 8, and 15, and 70 mg/m² cisplatin and 2,000 mL fluid replacement on day 1, in each 28-day cycle. We retrospectively evaluated renal function, serum electrolyte abnormalities, and adverse events (AEs) following treatment, and retrospectively com-

pared patients under m-shGC therapy with those under conventional GC (c-GC) therapy from 2015 to 2017. In addition, from April 2019 to August 2019 in a prospective analysis, 15 patients were newly enrolled, and AE profiles and physical activity during m-shGC therapy were quantified using a wearable tracker. **Results:** In a retrospective analysis of 101 patients (53 c-GC and 48 m-shGC), patient characteristics were not statistically significant between the two groups. Myelosuppression, including predominant neutropenia and decreased platelets, fatigue, nausea, and constipation were the main common AEs. However, renal function and serum sodium levels in the m-shGC group remained unchanged. Grade 3–4 AEs were not more severe in the m-shGC compared with the c-GC group. Furthermore, in a prospective analysis using a wearable tracker, the amount of walking by patients on day 1 significantly declined. However, immediate recovery occurred reflecting the short hydration. **Conclusion:** Our m-shGC therapy has an acceptable AE profile compared with conventional therapy, with UC patients showing good physical activity.

© 2020 The Author(s)

Published by S. Karger AG, Basel

Introduction

Urothelial carcinoma (UC) is considered to be a chemosensitive malignancy. A cisplatin-based systemic chemotherapy regimen is regarded as the gold standard for treating patients with advanced or metastatic UC [1–3]. Nowadays, combination chemotherapy with gemcitabine and cisplatin (GC) has become standard treatment for such patients [4–6]. Cisplatin is a widely used anti-tumor agent, being a major component of standard combination chemotherapy for various malignancies. However, with dose-dependent nephrotoxicity and strong emetogenicity, its administration has traditionally required extensive hydration and use of antiemetic agents resulting in a preference for avoiding its use, especially in an outpatient setting. Minimizing hydration without increasing the risk of nephrotoxicity would make the use of cisplatin more convenient. To improve the situation, a reduced hydration protocol includes as much as 2,500 mL on the first day of treatment [7–14]. In addition, the National Comprehensive Cancer Network has been disclosing a short hydration protocol for cisplatin on its website (<http://www.nccn.org>). However, only one report exists on a short hydration protocol for GC chemotherapy in UC by Azuma et al. [15]. In this report, the author describes the safety of a short hydration regimen for renal function in which the treated timing of GC was divided between days 1 and 2. For the purpose of obtaining more convenience in outpatient setting, we newly established a more convenient short hydration GC therapy where the initial injection of GC was performed on the same day on day 1 (modified short hydration GC [m-shGC] therapy). Therefore, in this study, we retrospectively investigated the efficacy of this new regimen with regard to adverse events (AEs), especially in nephrotoxicity, and electrolyte abnormalities. We also prospectively estimated AEs and physical activity in m-shGC-treated patients using a wearable activity tracker.

Materials and Methods

Patient Enrollment

We enrolled eligible patients with histologically confirmed UC of the urinary bladder or upper urinary tract and who were admitted to Nagoya City University Hospital and four affiliated institutions from May 2015 to August 2019. Patients had previously been surgically treated or had undergone biopsies of their primary lesions, and staging was undertaken by enhanced computed tomography. Patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 2 or lower; an adequate bone marrow reserve (white blood cell count $>3,500/\mu\text{L}$,

platelet count $>100,000/\mu\text{L}$, and hemoglobin $>10\text{ g/dL}$). Other requirements included: reasonable hepatic function (serum bilirubin $\leq 1.5\text{ mg/dL}$), renal function (creatinine clearance $\geq 60\text{ mL/min}$), and an estimated life expectancy of ≥ 12 weeks. Prognostic comorbidity was estimated using the Charlson comorbidity index [16]. Ineligible patients included those with non-malignant systemic diseases such as an active infection that precluded them from receiving therapy, or those with any clinically significant cardiac arrhythmia and/or congestive heart failure. All patients provided written, informed consent prior to this clinical trial. The institutional chemotherapy review boards (ethics committees) of Nagoya City University Hospital and Nagoya City University (#60-17-0105, #60-18-0060) approved this study, which was conducted in accordance with the Declaration of Helsinki (according to the 2004 Tokyo revision).

Treatment Schedule for GC Chemotherapy

The conventional hydration component consisted of pre-hydration with 2,000–1,500 mL over 4–6 h on day 1 with intravenous gemcitabine ($1,000\text{ mg/m}^2$) treatment. This was followed by hydration with 2,000 mL of fluid replacement, with intravenous cisplatin (70 mg/m^2) administered on day 2. Post-hydration with 3,000 mL of fluid replacement was also included, resulting in a total volume of 5,000 mL of fluid replacement. On days 8 and 15, intravenous gemcitabine ($1,000\text{ mg/m}^2$) was performed (conventional GC [c-GC]). In comparison, the m-shGC protocol consisted of 1,900 mL hydration on day 1 as described in Table 1, with both gemcitabine ($1,000\text{ mg/m}^2$) and cisplatin (70 mg/m^2) administered on day 1. Oral hydration using a commercially available oral hydration solution (OS-1; Otsuka Pharmaceutical Factory, Tokushima, Japan) on days 2–5 was routinely recommended. Oral aprepitant at a dose of 125 mg on day 1, and 80 mg on days 2 and 3 was administered. For emesis prophylaxis, intravenous treatment with dexamethasone at a dose of 9.9 mg was administered on days 1–3 for c-GC therapy, whereas it was delivered intravenously at a dose of 9.9 mg on day 1, followed by oral administration at a dose of 8 mg on days 2–4 for the m-shGC protocol. Intravenous gemcitabine ($1,000\text{ mg/m}^2$) was given on days 8 and 15. This cycle was repeated every 28 days. When grade 3 AEs occurred, a 10% dose reduction was performed in the next cycle, and GC treatment was continued until progression.

Treatment Evaluation and Analysis of c-GC and m-shGC Patients in Retrospective Cohorts

From May 2017 to March 2019, 48 patients with UC received m-shGC therapy. We evaluated AEs in patients with UC following all treatment cycles, and compared these to those in patients who received m-shGC and c-GC therapies (53 patients) between 2015 and 2017. Gemcitabine in such first-line regimens was not administered on days 8 and 15 if grade 3 toxicities occurred. The efficacy of the m-shGC chemotherapy regimen was assessed in a retrospective analysis. Antiemetics and analgesics for AEs were given as supportive care to patients in both regimens. The first objective of the evaluation was to compare kidney dysfunction between m-shGC and c-GC groups after two cycles of chemotherapy and the end of first-line GC therapy. In all affiliated institutions, comprehensive information on age, gender, admission status, including whether or not a solitary kidney condition that was induced by the nephroureterectomy or severe hydronephrosis, as well as information about the patients' primary cancer pathology, body mass index,

Table 1. Regimen of modified short hydration gemcitabine and cisplatin chemotherapy

Drugs	Fluids	Infusion timing, days	Duration, min
	200 mL of sugar electrolyte maintenance transfusion solution	1, 8, 15	300
Dexamethasone 10 mg + 5HT ₃ antagonist	100 mL of 0.9% NaCl solution (normal saline)	1	30
Dexamethasone 6.6 mg + 5HT ₃ antagonist	100 mL of 0.9% NaCl solution (normal saline)	8, 15	30
Gemcitabine	100 mL of 0.9% NaCl solution (normal saline)	1, 8, 15	30
	50 mL of 0.9% NaCl solution (normal saline)	8, 15	5
Potassium chloride 10 mEq + MgSO ₄ 8 mEq	500 mL of hypotonic electrolyte solution (YD SOLITA®-T No.1)	1	60
	200 mL of mannitol	1	30
Cisplatin	300 mL of 0.9% NaCl solution (normal saline)	1	60
Potassium chloride 10 mEq	500 mL of hypotonic electrolyte solution (YD SOLITA®-T No.1)	1	60

Table 2. Patients' characteristics in retrospective cohort

Characteristics	c-GC group (<i>n</i> = 53)	m-shGC group (<i>n</i> = 48)	<i>p</i> value
Median age, years (range)	67 (39–85)	67 (42–85)	ns
Originating organ of urothelial carcinoma, <i>n</i> (%)			
Upper urinary tract	20 (37.7)	16 (33.3)	ns
Bladder	33 (62.3)	32 (66.7)	
Gender, <i>n</i> (%)			
Male	39 (73.6)	41 (85.4)	ns
Female	14 (26.4)	7 (14.6)	
Median CCI scores at the start of chemotherapy (range)	0 (0–2)	1 (0–2)	ns
Patients in solitary kidney condition induced by nephrectomy or severe hydronephrosis, <i>n</i> (%)			
No	37 (69.8)	32 (66.7)	ns
Yes	16 (30.2)	16 (33.3)	
Median serum creatinine levels before chemotherapy (range), mg/dL	0.87 (0.50–1.35)	0.96 (0.38–1.29)	ns
Visceral metastasis, <i>n</i> (%)			
No	36 (67.9)	33 (68.8)	ns
Yes	17 (32.1)	15 (31.2)	
ECOG-PS, <i>n</i> (%)			
0	45 (84.9)	42 (87.5)	ns
1	6 (11.3)	6 (12.5)	
2	2 (3.8)	0 (0)	
RDI, <i>n</i> (%)			
≥90%	29 (54.7)	33 (68.8)	ns
<90%	24 (45.3)	15 (31.2)	
Median total cycle of GC chemotherapy (range), <i>n</i>	3 (2–12)	3 (2–9)	ns

GC, gemcitabine and cisplatin; c-GC, conventional GC therapy; m-shGC, modified short hydration GC therapy; CCI, Charlson comorbidity index; ECOG-PS, Eastern Cooperative Oncology Group performance status; RDI, relative dose intensity; ns, not significant.

Fig. 1. Time course of changes in serum creatinine levels (**a**) and serum sodium levels (**b**) between c-GC and m-shGC groups in retrospective cohorts. Ratio of patients with hyponatremia in each group was shown according to the CTCAE version 4.0. (**c**), and the minimum serum sodium levels during two cycles of GC therapy

(**d**) were plotted. Median $\pm$ SD. c-GC, conventional GC therapy; GC, gemcitabine and cisplatin; m-shGC, modified short hydration GC therapy. *** $p < 0.001$, statistically significant between two groups; ns, not significant compared with pretreatment.

performance status, changes in serum levels of creatinine, sodium, and treatment data were obtained from medical records.

Analysis of m-shGC Patients in Prospective Cohorts

For a prospective cohort study, from April 2019 to August 2019, we newly enrolled 15 patients with UC of the urinary bladder or upper urinary tract who had received m-shGC therapy at our hospital, and estimated the AEs as follows: the first objective was to evaluate kidney dysfunction after two cycles of m-shGC chemotherapy. In addition, we used a Fitbit Charge 2 (Fitbit Inc., San Francisco, CA, USA), which is a wristband type activity tracker with a heart rate monitor derived by algorithms, to estimate energy expenditure and cardio zone time based on physical activity intensity.

Treatment Evaluation

For treatment evaluation, the creatinine clearance was measured prior to each chemotherapy course, and hematological status and serum chemistries were measured twice a week during

treatment and at the end of chemotherapy courses. Radiology was used to assess tumor sizes, and physical examinations were also conducted. The cut-off for the relative dose intensity in first-line chemotherapy was 90% in accordance with a previous report. The National Cancer Institute Common Terminology Criteria for AEs, version 4.0, were used to classify AEs.

Statistics

Differences in categorical parameters were assessed using Fisher's exact test, or Friedman, Kruskal-Wallis, or χ^2 tests, whichever was appropriate. A value of $p < 0.05$ was considered statistically significant. In prospective analysis, the number of enrolled patients was small because of the high cost of the wearable tracker. Therefore, to minimize the risk of a type I error, the threshold p value for significance was calculated, after correction for multiple comparisons using the Bonferroni method, by dividing 0.05 by the total number of comparisons (=10), yielding $p = 0.005$. All data were analyzed using EZR software (Saitama Medical Center, Jichi Medical University, Yakushiji, Japan).

Table 3. Comparison as to adverse events in retrospective cohort between c-GC and m-shGC therapy groups (in hematological adverse events, the incidence rate of grade 3–4 events were statistically compared between the two groups; in non-hematological adverse events, the total incidence rate of events was statistically compared between the two groups)

Adverse events	c-GC group (n = 53)		m-shGC group (n = 48)		p value
	patients, n (%)	grade 3–4 patients, n (%)	patients, n (%)	grade 3–4 patients, n (%)	
Hematological					
Decreased WBC	39 (73.6)	24 (45.3)	40 (83.3)	14 (29.2)	ns
Neutropenia	46 (86.8)	30 (56.6)	40 (83.3)	15 (31.3)	*
Decreased platelets	46 (86.8)	19 (35.8)	36 (75.0)	7 (14.6)	ns
Anemia	28 (52.8)	8 (15.1)	17 (35.4)	0 (0)	**
Non-hematological					
Rash	2 (3.8)	0 (0)	1 (2.1)	0 (0)	ns
Fatigue	15 (28.3)	0 (0)	14 (29.2)	0 (0)	ns
Elevated AST/ALT	4 (7.5)	0 (0)	4 (8.3)	0 (0)	ns
Constipation	20 (37.7)	0 (0)	26 (54.2)	0 (0)	*
Nausea	34 (64.2)	0 (0)	8 (16.7)	0 (0)	***
Alopecia	3 (5.7)	0 (0)	8 (16.7)	0 (0)	ns

GC, gemcitabine and cisplatin; c-GC, conventional GC therapy; m-shGC, modified short hydration gemcitabine and cisplatin; WBC, white blood cells; AST, aspartate transaminase; ALT, alanine aminotransferase; ns, not significant. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ indicates a significant difference.

Results

Effect of m-shGC Therapy on Renal Function and Serum Sodium Levels in a Retrospective Analysis

A total of 101 patients were enrolled in this retrospective analysis, with 53 patients in the c-GC group and 48 patients in the m-shGC group. As shown in Table 2, patients' characteristics were not statistically significant between the two groups. The median total cycle for GC chemotherapy was indifferent between the two groups (median cycles [range]: 3 [2–12] vs. 3 [2–9] in c-GC vs. m-shGC groups). Nephrotoxicity in m-shGC therapy, as represented by serum creatinine levels, remained unchanged after two cycles and the end of chemotherapy compared with pretreatment, similar to c-GC therapy (Fig. 1a). In addition, serum sodium levels in m-shGC therapy were also unchanged after two cycles and the end of chemotherapy compared with pretreatment as also found for c-GC therapy (Fig. 1b). The incidence of severe hyponatremia was higher in c-GC group than m-shGC group (Fig. 1c; $p < 0.001$), and minimum sodium levels during two cycles of GC therapy were significantly better in m-shGC than in c-GC therapy (Fig. 1d; $p < 0.001$). As shown in Table 3, Grade 3–4 hematological AEs in the m-shGC group were not more severe, and the incidence of non-hematological AEs was also not more severe, com-

pared with the c-GC group, except for a high incidence of constipation. Deaths related to treatment were not noted.

Effect of m-shGC Therapy on Renal Function, Serum Sodium Levels, and Activity of Patients in a Prospective Analysis

In a prospective cohort, the characteristics of m-shGC patients are shown in Table 4. As a result, nephrotoxicity after treatment with m-shGC, as represented by serum creatinine levels, remained unchanged as found in a retrospective study (Fig. 2a). Serum sodium levels after treatment were also unchanged compared with pretreatment levels (Fig. 2b). Furthermore, in the analyses using a wearable tracker, the amount of walking significantly improved on days 2–5 compared with that on day 1; calorie consumption remained unchanged on days 1–10 (Fig. 2c, d). These results revealed that the effect of m-shGC chemotherapy on activity was tolerable.

Discussion

In this study, a newly established short hydration regimen using cisplatin was shown to be tolerated with regard to renal function and serum sodium levels in patients with UC. Serum creatinine levels did not worsen

Table 4. Patients' characteristics of a prospective cohort in m-shGC therapy

Characteristics	Prospective m-shGC patients (<i>n</i> = 15)
Median age (range), years	73 (61–84)
Originating organ of urothelial carcinoma, <i>n</i> (%)	
Upper urinary tract	5 (33.3)
Bladder	10 (66.7)
Gender, <i>n</i> (%)	
Male	11 (73.3)
Female	4 (26.7)
Median CCI scores at the start of chemotherapy (range)	0 (0–2)
Visceral metastasis, <i>n</i> (%)	
No	13 (86.7)
Yes	2 (13.3)
Patients in solitary kidney condition induced by nephrectomy or severe hydronephrosis, <i>n</i> (%)	
No	10 (66.7)
Yes	5 (33.3)
ECOG-PS, <i>n</i> (%)	
0	10 (66.7)
1	5 (33.3)
2	0 (0)
RDI, <i>n</i> (%)	
≥90%	15 (100)
<90%	0 (0)
Median total cycle of m-shGC chemotherapy (range), <i>n</i>	3 (3–12)

GC, gemcitabine and cisplatin; m-shGC, modified short hydration GC therapy; CCI, Charlson comorbidity index; ECOG-PS, Eastern Cooperative Oncology Group performance status; RDI, relative dose intensity.

with this modified short hydration regimen of cisplatin-based chemotherapy in both retrospective and prospective analyses. Several previous reports have described the safety of the short hydration method for patients with lung or bile duct cancers. However, to date, only a few limited reports have described its use in patients with UC [15].

Patients with UC have two major characteristics: first, patients tend to be older in this cohort compared with other malignancies, and second, they often have impaired renal function due to advanced age, prior treated remedies because of comorbidities, prior nephrectomy and/or disease-related hydronephrosis. Azuma et al. [15] describes the safety of a short hydration regimen for renal function in 61 patients with UC in which the treated timing of GC were divided between days 1 and 2, which differs from our regimen. In c-GC therapy for UC, only one

article has reported that the initial injection of GC was performed on the same day; no report has described a short hydration method. In this article, using the treatment outlined in Table 1, we are the first to report on the safety for renal function of using a less burdensome method of GC therapy on an outpatient basis. Further investigation as to its efficacy on long-term follow-up is currently being performed. Therefore, it is hoped that we can report on the results of this trial in due course.

Of AEs, electrolyte abnormalities are common regardless of the primary cancer site. Hyponatremia induced by chemotherapy (HIC) is one of the most frequently encountered AEs in clinical practice [17, 18]. Previously, we explored the prognostic value of HIC on survival time by analyzing our pooled cumulative data, and reported that severe HIC in the first treatment cycle affected survival time [19]. In addition, univariate and multivariate analyses revealed that cisplatin-containing regimens and large amounts of hydration were significant prognostic risk factors for severe HIC. Reflecting on these consequences, because of the reduced hydration involved, serum sodium levels in patients on the m-shGC therapy of this study remained unchanged during chemotherapy. Minimum sodium levels during two cycles were significantly better in patients under m-shGC rather than c-GC therapy. In addition, the results of the prospective analysis also reinforced the consequences. Patients undergoing cisplatin-based chemotherapy tend to have electrolyte abnormalities such that frequent monitoring of serum electrolyte levels are necessary. This partly explains the difficulties of performing c-GC therapy on an outpatient basis.

It is well known that elderly patients, as often observed in UC, may be less tolerant of chemotherapy because of the likelihood of having comorbidities as well as decreased organ and hematological functions. Therefore, special attention needs to be paid to the occurrence of AEs [20–22]. A reduction in hydration may cause dehydration and induce nausea and vomiting because of a dysfunctional central nervous system. However, the incidence of nausea was significantly higher in c-GC than in m-shGC therapy, even though differences did not exist in the use of antiemetic drugs among patients of the two groups. The mechanism responsible for the reduction in digestive tract symptoms in patients with m-shGC therapy was not unclear; however, with regard to AEs, this new modified GC regimen may be tolerable, including with regard to hematological AEs.

In addition to estimating quality of life (QOL), we evaluated daily activity during m-shGC therapy cycles us-

Fig. 2. Time course of changes in serum creatinine (a) and serum sodium (b) levels in a prospective cohort of the m-shGC group. Time course of changes in the amount of walking (c) and calorie consumption (d) obtained and calculated by a wearable activity

tracker in this cohort. Median $\pm$ SD. GC, gemcitabine and cisplatin, m-shGC, modified short hydration GC therapy. * $p < 0.05$, statistically significant compared with day 1; ns, not significant compared with pretreatment or day 1.

ing a wearable activity tracker, a Fitbit Charge 2. Several recent studies exist on the assessment of exercise capacity using wearable trackers in patients with coronary syndrome, cancers, and other diseases [23–26]. However, reports do not exist on the evaluation of activities using trackers in patients with cancer during chemotherapy. As a result of their use, we found that the amount of walking by patients significantly improved on days 2–6 compared to day 1 because of the absence of hydration and cisplatin treatment following day 2. Furthermore, the calorie consumption remained unchanged from days 1 to 10, which may have led to the maintenance of QOL in patients. So far, reports describe an improvement in QOL with a short hydration regimen [15]; however, no study has estimated the daily activities of patients during chemotherapy using wearable trackers. It is therefore important to further our

investigations on how we can use and validate such physical data obtained in this manner. Our trials may even lead to the development of monitoring methods for GC therapy on an outpatient basis, and an improvement of the QOL of patients with UC, even in the elderly or those with impaired renal function.

There were several limitations in this present study. These included the typical shortcomings associated with both retrospective and prospective analyses, such as selection bias and using a relatively small sample size. However, it is believed that such limitations would not have adversely affected our ability to capture an acceptable AE profile and good activity in our short hydration therapy compared to conventional therapy. Further investigations will be needed to confirm our data in an interventional large-sized prospective study.

Conclusions

In conclusion, in patients with UC, our newly established m-shGC therapy shows an acceptable AE profile compared to conventional therapy, and may be used on an outpatient basis with the help of wearable activity trackers.

Statement of Ethics

Written informed consent was obtained from all patients. This study was approved by the ethics committee of Nagoya City University Hospital and Nagoya City University. Each author certifies that all investigations were conducted in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors wish to declare that they have no conflicts of interest.

References

- 1 Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, et al. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol*. 1997; 15(7):2564–9.
- 2 Sternberg CN, de Mulder P, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer*. 2006;42(1):50–4.
- 3 Kuroda M, Kotake T, Akaza H, Hinotsu S, Kakizoe T. Efficacy of dose-intensified MEC (methotrexate, epirubicin and cisplatin) chemotherapy for advanced urothelial carcinoma: a prospective randomized trial comparing MEC and M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). Japanese Urothelial Cancer Research Group. *Jpn J Clin Oncol*. 1998;28(8):497–501.
- 4 von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol*. 2000; 18(17):3068–77.
- 5 Kaufman D, Raghavan D, Carducci M, Levine EG, Murphy B, Aisner J, et al. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. *J Clin Oncol*. 2000;18(9):1921–7.
- 6 von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol*. 2005;23(21):4602–8.
- 7 Tiseo M, Martelli O, Mancuso A, Sormani MP, Bruzzi P, Di Salvia R, et al. Short hydration regimen and nephrotoxicity of intermediate to high-dose cisplatin-based chemotherapy for outpatient treatment in lung cancer and mesothelioma. *Tumori*. 2007;93(2): 138–44.
- 8 Horinouchi H, Kubota K, Itani H, Taniyama TK, Nakamichi S, Wakui H, et al. Short hydration in chemotherapy containing cisplatin (≥ 75 mg/m²) for patients with lung cancer: a prospective study. *Jpn J Clin Oncol*. 2013; 43(11):1105–9.
- 9 Ouchi A, Asano M, Aono K, Watanabe T, Kato T. Comparison of short and continuous hydration regimen in chemotherapy containing intermediate- to high-dose Cisplatin. *J Oncol*. 2014;2014:767652.
- 10 Lavolé A, Danel S, Baudrin L, Gounant V, Ruppert AM, Epaul C, et al. Routine administration of a single dose of cisplatin ≥ 75 mg/m² after short hydration in an outpatient lung-cancer clinic. *Bull Cancer*. 2012;99(4): E43–8.
- 11 Sato J, Morikawa N, Nitani H, Nagashima H, Nihei S, Yamauti K, et al. Feasibility study of short hydration using oral rehydration solution in cisplatin including chemotherapy of lung cancer. *J Pharm Health Care Sci*. 2016;2: 6.
- 12 Ashrafi F, Ebrahimi Z, Nematbakhsh M. Effect of short hydration on cisplatin-induced nephrotoxicity in cancer patients: a retrospective study. *Int J Hematol Oncol Stem Cell Res*. 2017;11(4):262–7.
- 13 Sakaida E, Iwasawa S, Kurimoto R, Ebata T, Imai C, Oku T, et al. Safety of a short hydration method for cisplatin administration in comparison with a conventional method—a retrospective study. *Jpn J Clin Oncol*. 2016; 46(4):370–7.
- 14 Ninomiya K, Hotta K, Hisamoto-Sato A, Ichihara E, Gotoda H, Morichika D, et al. 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(1):81–7.
- 15 Azuma T, Matayoshi Y, Sato Y, Sato Y, Nagase Y, Oshi M. The safety and effect of chemotherapy with short hydration for urothelial cancer on patients' quality of life. *Jpn J Clin Oncol*. 2016;46(10):958–63.
- 16 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40(5):373–83.

Funding Sources

This work was supported in part by a Grant-Aid from the Aichi Cancer Research Foundation in 2019.

Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. Details regarding authorship, conflicts of interest, and ethics approval are given in the accompanying Author Submission Requirement Form. The contribution of each author to the manuscript is sufficient enough for each to take public responsibility for appropriate portions of the content. Taku Naiki made critical revisions of the manuscript. Toshiki Etani, Takashi Nagai, Satoshi Nozaki, Ryosuke Ando, Shuzo Hamamoto, Noriyasu Kawai, and Yoshihiko Tasaki carried out the acquisition of data and coordinated and helped to draft the manuscript. Yosuke Sugiyama and Keitaro Iida conducted statistical analyses concerning this study. Takahiro Yasui supervised the manuscript. All authors read and approved the final manuscript.

- 17 Thompson C, Hoorn EJ. Hyponatraemia: an overview of frequency, clinical presentation and complications. *Best Pract Res Clin Endocrinol Metab.* 2012;26(Suppl 1):S1–6.
- 18 Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transpl.* 2014; 29(Suppl 2):i1–31.
- 19 Sugiyama Y, Naiki T, Tasaki Y, Kondo Y, Kataoka T, Etani T, et al. Prognostic significance of hyponatremia induced by systemic chemotherapy in a hospital-based propensity score-matched analysis. *Int J Clin Oncol.* 2019.
- 20 Sawhney R, Sehl M, Naeim A. Physiologic aspects of aging: impact on cancer management and decision making, part I. *Cancer J.* 2005; 11(6):449–60.
- 21 Sehl M, Sawhney R, Naeim A. Physiologic aspects of aging: impact on cancer management and decision making, part II. *Cancer J.* 2005; 11(6):461–73.
- 22 Jan AS, Dolan DE, Lombardi K, Gupta S. Tolerability of gemcitabine plus cisplatin for treatment of urothelial cancer in the elderly population. *Clin Genitourin Cancer.* 2016; 14(3):e257–63.
- 23 Hartman SJ, Natarajan L, Palmer BW, Parker B, Patterson RE, Sears DD. Impact of increasing physical activity on cognitive functioning in breast cancer survivors: rationale and study design of Memory & Motion. *Contemp Clin Trials.* 2015;45(Pt B):371–6.
- 24 Leth S, Hansen J, Nielsen OW, Dinesen B. Evaluation of commercial self-monitoring devices for clinical purposes: results from the future patient trial, phase I. *Sensors (Basel).* 2017;17(1).
- 25 Nogic J, Thein PM, Cameron J, Mirzaee S, Ihsdayhid A, Nasir A. The utility of personal activity trackers (Fitbit Charge 2) on exercise capacity in patients post acute coronary syndrome [UP-STEP ACS Trial]: a randomised controlled trial protocol. *BMC Cardiovasc Disord.* 2017;17(1):303.
- 26 Strain T, Wijndaele K, Brage S. Physical activity surveillance through smartphone apps and wearable trackers: examining the UK potential for nationally representative sampling. *JMIR Mhealth Uhealth.* 2019;7(1):e11898.