

Survey of chemotherapy-induced nausea and vomiting in patients with urothelial carcinoma

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Received April 9, 2021; Accepted July 19, 2021

DOI: 10.3892/mco.2021.2384

Abstract. Chemotherapy-induced nausea and vomiting (CINV) can cause anorexia, weight loss and deterioration of patient quality of life. It is one of the most unpleasant adverse effects of chemotherapy treatment regimens. For the optimal treatment of gastrointestinal symptoms during urothelial carcinoma chemotherapy, the present study investigated the association between gastrointestinal symptoms and therapeutic effects of gemcitabine plus platinum [cisplatin (GC) or carboplatin (GCa)] therapies. The incidence and frequency of nausea/vomiting with GC split therapy (gemcitabine, 1,000 mg/m² on days 1 and 8; split-dose cisplatin, 35 mg/m² on days 1 and 8; 21-day schedule) and GCa therapy [gemcitabine, 750-1,000 mg/m² on days 1, 8 and 15; carboplatin, area under the blood concentration-time curve=5 mg min/ml (Calvert formula) on day 2; 28-day schedule] were lower compared with those of GC therapy (gemcitabine, 1,000 mg/m² on days 1, 8 and 15; single-dose cisplatin 70 mg/m² on day 2; 28-day schedule). However, no differences in therapeutic

outcomes were observed among therapies. GCa therapy, regardless of renal function, and GC split therapy demonstrated significant increases compared with GC therapy in alleviating gastrointestinal symptoms associated with cancer chemotherapy in patients with urothelial carcinoma. Overall, these results suggested that split-dose cisplatin administration or the use of carboplatin instead of cisplatin may be useful in patients who experience CINV without compromising treatment effectiveness.

Introduction

Platinum-based antineoplastic drugs, such as cisplatin, are reported to be effective against several malignant tumors (1); however, they frequently induce nausea and vomiting (2). Chemotherapy-induced nausea and vomiting (CINV) can cause anorexia and weakness (3,4) and is one of the most unpleasant subjective symptoms experienced by patients (5). CINV significantly reduces the quality of life of patients (3) and adversely affects treatment continuation for the underlying disease (6,7). Therefore, measures to alleviate CINV are crucial for the effective and safe administration of cancer chemotherapy.

Several guidelines (2,8-10) have consistently recommended a three-drug combination therapy, consisting of serotonin 5-HT₃ receptor antagonists, selective neurokinin-1 (NK1) receptor antagonists, and corticosteroids as antiemetics for combating anticancer agents with a high emetic risk (≥90%; cisplatin), as well as those with moderate emetic risk (30-90%; carboplatin) (2).

Patients with metastatic or advanced urothelial carcinoma are treated with gemcitabine plus cisplatin (GC) therapy, in which a single dose of cisplatin is administered in combination with gemcitabine as the standard of care (11,12). In contrast, patients with reduced kidney function are prescribed GC split therapy (split-dose of cisplatin) (13,14) or GCa therapy (administration of carboplatin instead of cisplatin) (15,16). To our knowledge, the incidence of CINV and the efficacy of chemotherapy for these alternate treatment regimens compared to

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Abbreviations: AUC, area under the blood concentration-time curve; Ccr, creatinine clearance; CINV, chemotherapy-induced nausea and vomiting; CR, complete response; eGFR, estimated glomerular filtration rate; GC, gemcitabine plus cisplatin; GCa, gemcitabine plus carboplatin; NK1, neurokinin-1; PD, progressive disease; PR, partial response; SD, stable disease

Key words: chemotherapy-induced nausea and vomiting, gemcitabine plus carboplatin therapy, gemcitabine plus single-dose cisplatin therapy, gemcitabine plus split-dose cisplatin therapy, urothelial carcinoma

standard GC therapy in patients with reduced renal function has not been investigated previously.

To elucidate which regimen presented the lowest risk of CINV without compromising effectiveness, in this study, we compared the prevalence of gastrointestinal symptoms, use of antiemetics, therapeutic responses, and survival rates in patients receiving GC therapy, GC split therapy, or GCa therapy for urothelial carcinoma.

Materials and methods

Patients and therapeutic regimens. Patients who were treated with (a) GC therapy, (b) GC split therapy, or (c) GCa therapy (see below and Table I) at the urology ward of Nagoya University Hospital between March 1, 2011, and March 31, 2017, were retrospectively evaluated. For each therapy, the following scenarios were excluded from the analysis: patients who discontinued the use of platinum preparations (cisplatin or carboplatin), cases in which nausea and vomiting during the 10-day observation period could not be clarified, and cases in which the use of opioids rendered it challenging to determine whether nausea and vomiting were induced by chemotherapy.

(a) GC therapy. The GC therapy regimen was administered for 28 days (4-week interval), with cisplatin (70 mg/m²) administered on treatment day 2 and gemcitabine (1,000 mg/m²) administered on treatment days 1, 8, and 15 (Table I). On the day of cisplatin administration, patients were pre-administered serotonin 5-HT₃ receptor antagonists (ramosetron, granisetron, or palonosetron), a corticosteroid (dexamethasone), and a selective NK1 receptor antagonist (aprepitant). Aprepitant was administered on treatment days 2 (125 mg; before cisplatin administration), 3 (80 mg), and 4 (80 mg).

(b) GC split therapy. For GC split therapy, the treatment regimen was administered for 21 days (3-week interval), with cisplatin (35 mg/m²) and gemcitabine (1,000 mg/m²) administered on treatment days 1 and 8 (Table I). On the days of cisplatin administration, patients were pre-administered serotonin 5-HT₃ receptor antagonist and dexamethasone. Aprepitant was administered on treatment days 1 (125 mg; before administration of cisplatin), 2 (80 mg), and 3 (80 mg).

(c) GCa therapy. GCa treatment was performed for 28 days (4-week interval) and consisted of carboplatin [area under the blood concentration-time curve (AUC)=5 mg·min/ml] administered on treatment day 2 and gemcitabine (750-1,000 mg/m²) administered on treatment days 1, 8, and 15 (Table I). On the day of carboplatin administration, patients were pre-administered with a serotonin 5-HT₃ receptor antagonist and dexamethasone.

Assessment. In this study, a 10-day (treatment days 1 to 10) observation period was employed from the start date of each course (GC therapy, GC split therapy, or GCa therapy). The following parameters were investigated: (i) number of days with nausea and vomiting, (ii) prevalence of nausea and vomiting on each treatment day, (iii) administration of a serotonin 5-HT₃ receptor antagonist, (iv) total and additional use of antiemetics (average use count, total dose, and use date of serotonin 5-HT₃ receptor antagonists, aprepitant, dopamine D₂ receptor

antagonists), (v) therapeutic response [complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD)] based on the new response evaluation criteria in solid tumors (RECIST v.1.1) (17), and (vi) the duration of patient survival from the start date of each course of treatment to the date of the final follow-up observation or date of death.

Statistical analysis. Fisher's exact test was used to analyze categorical data related to sex, rate of incidence of nausea and vomiting events on each treatment day, use rate of each serotonin 5-HT₃ receptor antagonist, use rate of additional antiemetics and prevalence of patients with each therapeutic response. The Shapiro-Wilk test was used to determine normality, and Leven's test was used to assess the equality of variances. The Kruskal-Wallis test was used to compare median values of age, estimated glomerular filtration rate (eGFR), creatinine clearance (Ccr) and the number of days with nausea/vomiting per course among three groups, followed by post-hoc testing using the unpaired Mann-Whitney U test, with a Bonferroni-adjusted alpha level. The Cramér-von Mises test was used to assess survival rates. Statistical significance was set at $P < 0.05$. Data analysis, power analysis, and sample size calculations were performed using the R statistical software (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics. In total, 67 patients (48 men and 19 women) were included in this study. There were 43 patients (27 men, 16 women) in the GC therapy group, 9 patients (8 men, 1 woman) in the GC split therapy group, and 15 patients (13 men, 2 women) in the GCa group. There were no statistically significant differences in age or sex among the groups. However, eGFR and Ccr levels were significantly lower in the GC split and GCa therapy groups than in the GC therapy group ($P < 0.01$), and the level of Ccr was also significantly lower in the GCa therapy group than in the GC split therapy group ($P < 0.05$; Table II).

Number of days with nausea/vomiting per course. The number of days with nausea/vomiting per course \pm standard deviation in the GC, GC split, and GCa therapy groups is shown in Fig. 1. We found that the number of days with nausea per course was significantly lower in the GC split and GCa therapy groups than in the GC therapy group ($P < 0.01$, $P < 0.05$, respectively; Fig. 1A). Although several patients experienced vomiting during the observation period in the GC and GCa therapy groups, there were no patients with vomiting episodes in the GC split therapy group (Fig. 1B).

Prevalence of nausea and vomiting on each treatment day. The prevalence of nausea on treatment days 4 to 7 was significantly lower in the GC split therapy group than in the GC therapy group (treatment days 4 and 6: $P < 0.01$, treatment days 5 and 7: $P < 0.05$; Fig. 2A). On treatment days 3 and 4, prevalence of nausea/vomiting was significantly lower in the GCa therapy group than in the GC therapy group ($P < 0.01$; Fig. 2A). No differences in the prevalence of vomiting were observed among the treatment groups ($P < 0.05$; Fig. 2B).

Table I. Treatment schedules for GC, GC split and GCa therapy.

Regimen	Emetic risk	Treatment day, administration method													
		1	2	3	4	5	6	7	8	9	10	15			
GC therapy															
Gemcitabine (1,000 mg/m ²)	Low	iv							iv						iv
Cisplatin (70 mg/m ²)	High	(iv)	iv						(iv)						
Serotonin 5-HT ₃ receptor antagonist		iv	iv	iv	iv				iv						iv
Dexamethasone			po	po	po	(po)	(po)								
Aprepitant		(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	
GC split therapy															
Gemcitabine (1,000 mg/m ²)	Low	iv							iv						
Cisplatin (35 mg/m ²)	High	iv							iv						
Serotonin 5-HT ₃ receptor antagonist		iv							iv						
Dexamethasone		iv	iv	iv					iv	iv	iv				iv
Aprepitant		po	po	po	(po)	(po)									
Dopamine D ₂ receptor antagonist		(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)
GCa therapy															
Gemcitabine (750–1,000 mg/m ²)	Low	iv							iv						iv
Carboplatin (AUC=5 mg·min/ml)	Moderate		iv												
Serotonin 5-HT ₃ receptor antagonist		(iv)	iv						(iv)						
Dexamethasone		iv	iv	iv					iv						iv
Aprepitant		(po)	(po)	(po)	(po)	(po)									
Dopamine D ₂ receptor antagonist		(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)	(iv/po)

AUC, area under the blood concentration-time curve; GC, gemcitabine plus cisplatin; GCa, gemcitabine plus carboplatin; iv, intravenous; po, per os; (iv/po), additional use of antiemetics.

AUC, area under the blood concentration-time curve; GC, gemcitabine plus cisplatin; GCa, gemcitabine plus carboplatin; iv, intravenous; po, per os; (iv/po), additional use of antiemetics.

Table II. Patient characteristics.

Characteristic	GC therapy	GC split therapy	GCa therapy
Median age, years (range)	67.0 (36-80)	67.0 (49-76)	73.0 (57-84)
Sex, n (%)			
Men	27 (62.8)	8 (88.9)	13 (86.7)
Women	16 (37.2)	1 (11.1)	2 (13.3)
Number of chemotherapy courses	72	23	19
Median eGFR, ml/min/1.73 m ² (range)	61.8 (36.9-162.5)	38.4 (31.8-50.6) ^a	37.1 (15.8-64.5) ^a
Median Ccr, ml/min (range)	57.6 (31.5-153.8)	46.0 (34.5-62.3) ^a	41.2 (18.1-70.6) ^{a,b}

Ccr, creatinine clearance; eGFR, estimated glomerular filtration rate; GC, gemcitabine plus cisplatin; GCa, gemcitabine plus carboplatin.

^aP<0.01 vs. GC therapy and ^bP<0.05 vs. GC split therapy.

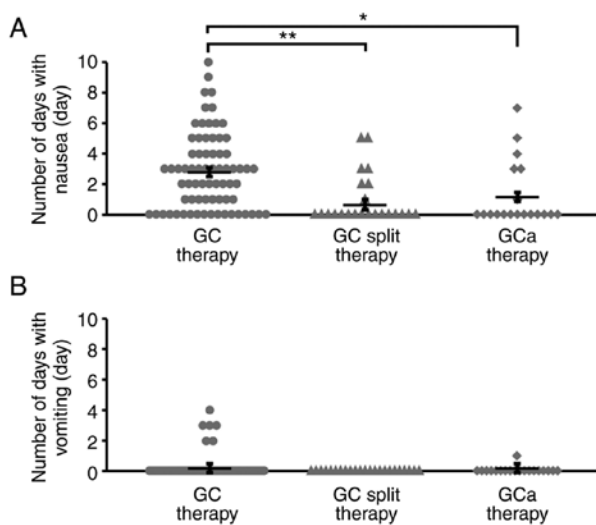


Figure 1. Number of days with nausea/vomiting per course in the GC, GC split and GCa therapy groups. Mean number of days with (A) nausea and (B) vomiting per course is shown as a scatter plot with mean \pm standard error of the mean for the GC therapy group (72 courses), GC split therapy group (23 courses) and GCa therapy group (19 courses). *P<0.05, **P<0.01 vs. GC therapy group. GC, gemcitabine plus cisplatin; GCa, gemcitabine plus carboplatin.

Use rate of each serotonin 5-HT₃ receptor antagonist. The use rates of serotonin 5-HT₃ receptor antagonists (ramosetron, granisetron, or palonosetron) in each therapy group are shown in Fig. 3. A significant difference was observed in the use rate between the GC split therapy and the GC therapy groups (P<0.05; Fig. 3). In particular, a second-generation serotonin 5-HT₃ receptor antagonist (palonosetron) was significantly lower in the GC split therapy group (P<0.05; Fig. 3). No differences were observed between the GCa and GC therapy groups or the GC split therapy group.

Total and additional use of antiemetics. The total and additional use of antiemetics is summarized in Table III. The total dose of antiemetics during the observation period was significantly lower in the GC split therapy group than in the GC and GCa therapy groups (P<0.01). The metoclopramide dose was significantly lower in the GC split therapy group than in the GC therapy group (P<0.05). Aprepitant dose was significantly lower in the GCa therapy group than in the GC and GC split therapy groups (P<0.01).

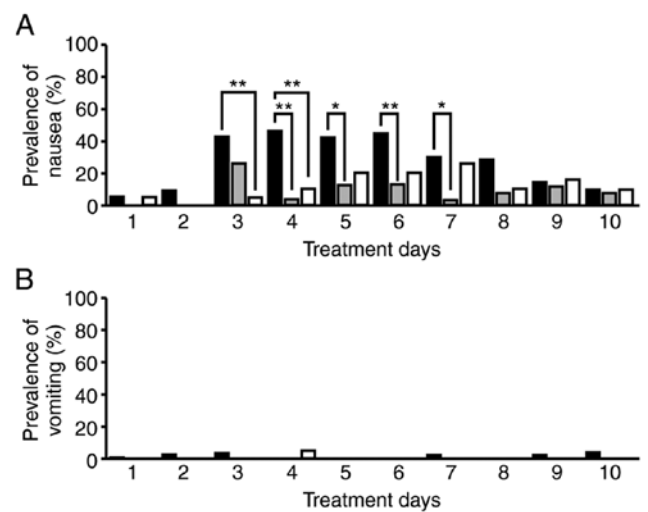


Figure 2. Prevalence of nausea/vomiting on each treatment day in the GC, GC split and GCa therapy groups. Prevalence of (A) nausea and (B) vomiting between treatment days 1-10 is presented for the GC therapy group (black; 72 courses), GC split therapy group (gray; 23 courses) and GCa therapy group (white; 19 courses). *P<0.05, **P<0.01 vs. GC therapy group. GC, gemcitabine plus cisplatin; GCa, gemcitabine plus carboplatin.

The use rates of additional antiemetics in the GC, GC split, and GCa therapy groups were 70.8% (51/72 courses), 39.1% (9/23 courses), and 78.9% (15/19 courses), respectively. The use rate was significantly lower in the GC split therapy group than in the GC and GCa therapy groups (P<0.05). Considering the dose of additional antiemetics during the observation period, aprepitant dose was significantly lower in the GC split therapy group than in the GC therapy group (P<0.01), whereas it was significantly higher in the GCa therapy group than in the GC and GC split therapy groups (P<0.01; Table III).

Therapeutic response and survival rates. No differences were observed in the proportion of each therapeutic response in the GC therapy group [CR: 0% (0/34 patients), PR: 8.8% (3/34 patients), SD: 50.0% (17/34), PD: 41.2% (14/34 patients)], GC split therapy group [CR: 0% (0/4 patients), PR: 25.0% (1/4 patients), SD: 75.0% (3/4 patients), PD: 0.0% (0/4 patients)], and GCa therapy group [CR: 0% (0/6 patients), PR: 16.7% (1/6 patients), SD: 66.7% (4/6 patients), PD: 16.7%

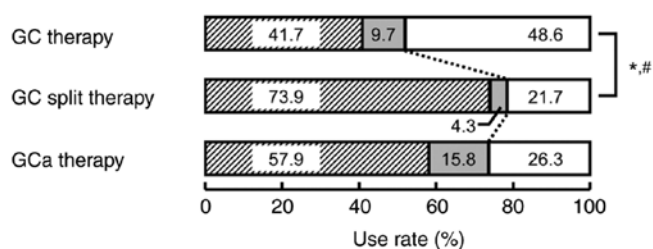


Figure 3. Use rate of each serotonin 5-HT₃ receptor antagonist in the GC, GC split and the GCa therapy groups. Use rates of ramosetron (diagonal lines), granisetron (gray), and palonosetron (white) are shown for the GC therapy group (72 courses), GC split therapy group (23 courses) and GCa therapy group (19 courses). * $P < 0.05$, comparison of the rate of each serotonin 5-HT₃ receptor antagonist; # $P < 0.05$, comparison of the rate between the first-generation (ramosetron and granisetron) and the second-generation [serotonin 5-HT₃ receptor antagonist (palonosetron)] vs. GC therapy group. GC, gemcitabine plus cisplatin; GCa, gemcitabine plus carboplatin.

(1/6 patients)] ($P > 0.05$). No differences in the duration of survival or survival rates were observed among the treatment groups ($P > 0.05$; Fig. 4).

Power analysis and sample size calculation. This study had a power of 0.42-0.59 to detect a medium effect (18) and could not obtain the estimated sample size ($n = 53$ -108).

Discussion

This study compared the prevalence of gastrointestinal symptoms, use of antiemetics, therapeutic responses, and survival rates in patients receiving GC therapy, GC split therapy, or GCa therapy for urothelial carcinoma. Although CINV in the acute phase (within the first 24 h after chemotherapy) was well-controlled in all therapy groups, patients receiving GC therapy showed a higher incidence of vomiting in the delayed phase (>24 h after chemotherapy) than the other groups. In the GC split therapy group, there were no vomiting episodes, and the number of days with nausea per course and the prevalence of nausea on treatment days 4 to 7 were significantly lower than those observed in the GC therapy group. This suggests that low-dose cisplatin administration can suppress the emergence of delayed nausea. In the GCa therapy group, the number of days with nausea per course was significantly lower, and the prevalence of nausea on treatment days 3 and 4 was significantly lower than that observed in the GC therapy group. These results can be explained by the fact that carboplatin is a platinum-based antineoplastic drug with moderate emetic risk (2).

A second-generation serotonin 5-HT₃ receptor antagonist, palonosetron, is effective against both the acute and delayed phases of CINV (19). Among the serotonin 5-HT₃ receptor antagonists used in this survey, the use rate of palonosetron in the GC split and GCa therapy groups was lower than that in the GC therapy group. This could be attributed to the fewer number of days with nausea per course, as well as the lower prevalence of nausea on each treatment day in both the GC split and GCa therapy groups than in the GC therapy group. Therefore, our findings suggest that both GC split therapy and GCa therapy can reduce the prevalence of acute and delayed CINV, regardless of palonosetron administration. The GC

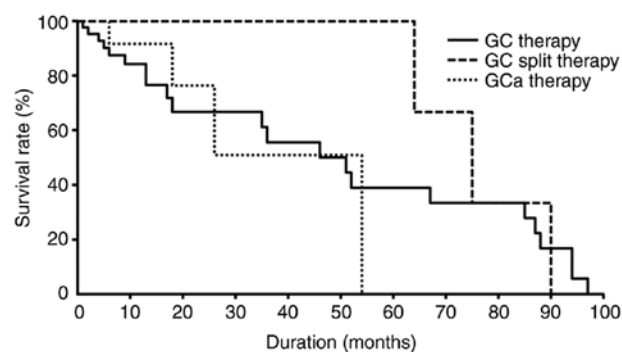


Figure 4. Survival curves for the GC, GC split and GCa therapy groups. Survival rates and duration of survival are shown for the GC therapy group (43 patients), GC split therapy group (9 patients) and GCa therapy group (15 patients). GC, gemcitabine plus cisplatin; GCa, gemcitabine plus carboplatin.

split therapy group presented a significantly lower administration rate and aprepitant dose of additional antiemetics than the GC therapy and GCa therapy groups. This could be attributed to several factors. First, GC split therapy has a lower risk of CINV than GC or GCa therapy. Second, all patients receiving GC therapy and GC split therapy, who were administered cisplatin (a high emetic risk drug), were also administered a three-drug combination antiemetic therapy according to the treatment schedules. Third, patients receiving GCa therapy, using carboplatin, were additionally administered aprepitant, which was not listed in the treatment schedule. When we compared the need for antiemetic use during the observation period, the aprepitant dose was significantly lower in the GCa therapy group than in the GC and GC split therapy groups. Moreover, the frequency of additional use of serotonin 5-HT₃ receptor antagonist was lower in aprepitant users (16.7%) than in non-users (61.5%). GCa therapy can reduce both early and late CINV with the minimum requirement of aprepitant use, and aprepitant use may result in additional antiemetic effects. Furthermore, although the treatment duration for the GC split therapy was shorter (21 days) than that for a single course of GC therapy (28 days), CINV events were adequately controlled with the three-drug antiemetic therapy. Therefore, if the dose of cisplatin administered per course was the same, split-dose treatments may be more effective in mitigating CINV onset than single-dose treatments.

Cisplatin-based treatment regimens are used as first-line therapies for metastatic or advanced urothelial carcinoma; however, the use of cisplatin has been associated with renal dysfunction, deterioration of the general condition, and medical complications in 40-50% of patients (20). Carboplatin or split-dose administration of cisplatin is employed as an alternative platinum formulation in patients presenting with these adverse events (13-16). In this study, we found that eGFR and Ccr levels were significantly lower in patients receiving GC split therapy and GCa therapy than in those receiving GC therapy, suggesting that GC split therapy and GCa therapy can be prioritized in patients with reduced kidney function. It has been suggested that adverse events are less common in regimens that use carboplatin instead of cisplatin (21), although the therapeutic efficacy of cisplatin is significantly inferior to that of carboplatin (22). However, only a few reports have presented direct comparisons between GC, GC split, and GCa therapies (16,23).

Table III. Antiemetics.

A, Total use of antiemetics (included in regimen and additional use).

Antiemetics	Regimen	N ^a	Mean count \pm SD (range)	Mean dose, mg/course \pm SD (range)
Granisetron	GC	7	1.14 \pm 0.38 (1-2)	2.00 \pm 1.00 (1-3)
	GC split	1	1.00 \pm 0.00 (1)	3.00 \pm 0.00 (3)
	GCa	3	1.00 \pm 0.00 (1)	3.00 \pm 0.00 (3)
Palonosetron	GC	35	1.00 \pm 0.00 (1)	0.75 \pm 0.00 (0.75)
	GC split	5	1.00 \pm 0.00 (1)	0.75 \pm 0.00 (0.75)
	GCa	5	1.00 \pm 0.00 (1)	0.75 \pm 0.00 (0.75)
Ramosetron	GC	30	2.23 \pm 0.94 (1-3)	0.67 \pm 0.28 (0.3-0.9)
	GC split	17	1.00 \pm 0.00 (1)	0.30 \pm 0.00 (0.3) ^d
	GCa	11	2.55 \pm 0.82 (1-3)	0.74 \pm 0.28 (0.3-0.9) ^e
Domperidone	GC	72	0.15 \pm 0.82 (0-6)	3.61 \pm 22.35 (0-180)
Metoclopramide	GC	72	4.04 \pm 8.96 (0-31)	20.97 \pm 45.48 (0-160)
	GC split	23	0.06 \pm 0.24 (0-1)	0.29 \pm 1.21 (0-5) ^c
	GCa	19	2.16 \pm 4.89 (0-15)	11.05 \pm 24.47 (0-75)
Aprepitant	GC	72	3.57 \pm 0.90 (3-5)	330.56 \pm 72.09 (285-445)
	GC split	23	3.35 \pm 0.49 (3-4)	313.24 \pm 39.41 (285-365)
	GCa	19	0.95 \pm 1.43 (0-3)	90.00 \pm 136.11 (0-285) ^{d,e}

B, Additional use of antiemetics (not included in regimen).

Antiemetics	Regimen	N ^b	Mean count \pm SD (range)	Mean dose, mg/course \pm SD (range)	Day administered (N)
Granisetron	GC	1	1.00 \pm 0.00 (1)	1.00 \pm 0.00 (1)	Day 1 (1)
Ramosetron	GC	20	1.85 \pm 0.37 (1-2)	0.56 \pm 0.11 (0.3-0.6)	Day 1 (20), day 8 (17)
	GCa	9	1.89 \pm 0.33 (1-2)	0.57 \pm 0.10 (0.3-0.6)	Day 1 (9), day 8 (8)
Domperidone	GC	3	3.67 \pm 2.08 (2-6)	86.67 \pm 83.27 (20-180)	Day 3 (1), day 4 (2), day 5 (3), day 6 (2), day 7 (1)
Metoclopramide	GC	29	10.03 \pm 11.88 (1-30)	52.07 \pm 59.72 (5-150)	Day 1 (7), day 2 (8), day 3 (12), day 4 (13), day 5 (15), day 6 (16), day 7 (15), day 8 (15), day 9 (10), day 10 (9)
	GC split	1	1.00 \pm 0.00 (1)	5.00 \pm 0.00 (5)	Day 9 (1)
	GCa	4	10.25 \pm 5.74 (2-15)	52.50 \pm 26.30 (15-75)	Day 3 (1), day 4 (1), day 5 (2), day 6 (3), day 7 (3), day 8 (2), day 9 (3), day 10 (2)
Aprepitant	GC	21	1.95 \pm 0.22 (1-2)	156.19 \pm 17.46 (80-160)	Day 5 (21), day 6 (20)
	GC split	9	1.00 \pm 0.00 (1)	80.00 \pm 0.00 (80) ^d	Day 4 (9)
	GCa	6	3.00 \pm 0.00 (3)	285.00 \pm 0.00 (285) ^{d,e}	Day 2 (6), day 3 (6), day 4 (6)

SD, standard deviation; N, the number of courses; GC, gemcitabine plus cisplatin; GCa, gemcitabine plus carboplatin; date, treatment day during observation period (from day 1-10). ^aNumber of serotonin 5-HT₃ receptor antagonists (granisetron, palonosetron and ramosetron) indicates courses of each serotonin 5-HT₃ receptor antagonist users receiving each chemotherapy. The number of dopamine D₂ receptor antagonists (domperidone and metoclopramide) and neurokinin-1 receptor antagonist (aprepitant) indicates all courses receiving each chemotherapy. ^bAdditional user of each antiemetics. ^cP<0.05, ^dP<0.01 vs GC therapy and ^eP<0.01 vs GC split therapy.

Results from our preliminary survey indicated that there were no significant differences in the therapeutic effects and survival rates among the three groups. Therefore, the selection of GC

split therapy or GCa therapy, instead of GC therapy, may reduce CINV incidence without adversely affecting the therapeutic effects and survival rates in patients with urothelial carcinoma.

This study was limited by its retrospective design based on electronic medical records and a small sample size compared to the estimated ideal sample size ($n=53-108$), which may induce biases owing to insufficient statistical power (0.42-0.59 to detect a medium effect). Additionally, it is possible that the patients' memories and medical staff records were inaccurate, resulting in recall bias. As there was probably some information that was not recorded in the medical records, it should be noted that the occurrence of nausea/vomiting may have been underestimated. Furthermore, we did not examine the relationship between patient-related factors (e.g., age, sex, and history of alcohol intake) or genetic risk factors (6,24,25) and the incidence of CINV. Therefore, these results should be interpreted with caution.

In conclusion, GC split therapy and GCa therapy were superior to GC therapy in reducing the incidence of CINV in patients with urothelial carcinoma. In particular, GCa therapy is likely to be superior to GC and GC split therapy because carboplatin can be administered regardless of renal function and has few side effects such as nausea and vomiting.

Although further investigations on the therapeutic effects and other adverse events are required, split-dose cisplatin administration or the use of carboplatin instead of cisplatin may be useful in patients who experience CINV without compromising treatment effectiveness.

Acknowledgements

Not applicable.

Funding

This study was supported by a grant from The Encouragement of Scientific Research, Promoted Research Center Subsidy by Meijo University Research Institute.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AY, MM, KY and YN conceived and designed the current study. AY, YS, MI, MN, ATG, HH, NT and MM acquired the data. AY, YS, MI, MN, ATG and YN analyzed and interpreted the data. AY, YS and MI performed statistical analysis. AY and YS drafted the manuscript. AY and YN supervised the study and confirmed the authenticity of all the raw data. YN critically revised the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This survey was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (26). This study was approved by the Ethics Committee of Nagoya University

Graduate School of Medicine (approval no. 2016-0539-3), and written informed consent was waived because of the retrospective design. To protect personal information, all data obtained were handled after anonymization.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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