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Efficacy of Single-dose First-generation 5-HT_3 Receptor Antagonist and Dexamethasone for Preventing Nausea and Vomiting Induced by Low-dose Carboplatin-based Chemotherapy

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Abstract. *Background: Carboplatin (CBDCA) is known to exhibit a high emetic risk among moderate-emetic risk anticancer drugs, and the dose of CBDCA varies in different therapies. In concurrent chemoradiotherapy (CCRT) for non-small cell lung cancer (NSCLC), the weekly administration of CBDCA (area under the curve (AUC) 2 mg/ml/min) and paclitaxel (PTX: 40 mg/m^2) is frequently applied as standard therapy. However, the optimal antiemetic measures in the use of such low-dose CBDCA remain unclear. In this study, we retrospectively assessed the antiemetic effect of a single-dose of a first-generation 5-hydroxytryptamine-3 receptor antagonist (5-HT_3RA) and dexamethasone in the weekly CBDCA+PTX therapy in CCRT. Patients and Methods: The subjects were patients with NSCLC who were administered weekly CBDCA+PTX therapy in CCRT between January 2011 and December 2016 at our Department. As an antiemetic measure, a first-generation 5-HT_3RA, azasetron (10 mg, orally) or granisetron (3 mg, intravenously), and dexamethasone (9.9 mg, intravenously) were administered on day 1. The patients were evaluated for the following efficacy end-points for the first cycle: Complete response (CR; defined as no vomiting or retching episodes with no rescue medication) in the acute phase (0-24 hours), delayed phase (>24-120 hours), and overall phase (0-120 hours). Other efficacy endpoints evaluated were no vomiting or retching, and no nausea in all phases. Results: The subjects we assessed in this study were 46 patients who were administered weekly CBDCA+PTX therapy in CCRT. For the overall, acute, and delayed phases, the complete response rates were 89.1%, 100%, and 89.1%, respectively. The rate of no nausea in the overall, acute, and delayed phases was 78.3%, 100%, and 78.3%, respectively. The rate of no vomiting in the overall, acute, and delayed phases was 95.7%, 100%, and 95.7%, respectively. Conclusion: A single dose of a first-generation 5-HT_3RA and dexamethasone had a favorable suppressive effect on nausea and vomiting in weekly CBDCA+PTX therapy for NSCLC.*

Chemotherapy-induced nausea and vomiting (CINV) lowers patients' quality of life (QOL) and adherence to treatment, and in the worst case, it can affect the treatment effect and curability. CINV frequently occurs in patients treated with anticancer drugs, and patients complain that it is the most bothersome adverse event during treatment (1). However, antiemetics with a novel mechanism have been developed successfully, including 5-hydroxytryptamine-3 receptor antagonist (5-HT_3RA) in the 1990s and a neurokinin 1 receptor antagonist (NK_1RA), aprepitant, in the 2000s. Furthermore, guidelines for antiemesis in cancer chemotherapy have been reported by medical oncology societies and associations of supportive care in cancer, including the American Society of Clinical Oncology (ASCO) (2), Multinational Association of Supportive Care in Cancer (MASCC) (3), National Comprehensive Cancer Network (NCCN) (4), and Japanese Society of Clinical Oncology (JSCO) (5), which excluded CINV from the top list of bothersome side effects (6).

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In these guidelines, anticancer drugs are classified into high (emetic risk >90%), moderate (30%-90%), low (10%-30%), and minimal (<10%) based on the emetic risk. Furthermore, owing to its wide range of emetic risk (30-90%), moderate emetic risk chemotherapy (MEC) was further classified into three categories in the 2016 MASCC guidelines (3). Carboplatin (CBDCA) is ranked as the highest risk drug among MEC in the 2016 MASCC guidelines, and the three-drug combination therapy of 5-HT_3RA, dexamethasone, and NK_1RA is recommended. Among MEC, for drugs with a risk of nausea/vomiting in the delayed phase such as oxaliplatin, doxorubicin, and cyclophosphamide, the administration of 5-HT_3RA and dexamethasone on day 1 and that of dexamethasone during the delayed phase are recommended. For other drugs that are considered low-risk in the delayed phase, the administration of 5-HT_3RA and dexamethasone on day 1 is recommended, but routine treatment for prevention of delayed emesis is not recommended. On the other hand, the emetic risk of anticancer drugs depends on not only the drug, but also its dose, and some drugs such as cyclophosphamide and cytarabine are classified into different categories of emetic according to the dose (2-5). In reports showing the efficacy of the three-drug combination of 5-HT_3RA, NK_1RA, and dexamethasone with the use of CBDCA, as recommended in the 2016 MASCC guidelines, high-dose CBDCA (area under the curve (AUC) 5-6 mg/mL/min) was administered (7-11). The standard treatment for locally advanced, unresectable, stage III non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy (CCRT), in which weekly administration of CBDCA (AUC 2 mg/ml/min) and paclitaxel (PTX: 40 mg/m^2) is frequently used as chemotherapy combined with radiotherapy owing to its favorable tolerability (12). As the dose of CBDCA is low (AUC: 2 mg/ml/min) in this therapy, a first-generation 5-HT_3RA and dexamethasone are administered on day 1 as an antiemetic measure, and the routine administration of antiemetics to prevent delayed emesis is not conducted at the Gifu University Hospital.

In this study, we assessed the antiemetic effect of a 1-day administration of a first-generation 5-HT_3RA and dexamethasone in the weekly CBDCA+PTX treatment in CCRT by a retrospective chart review.

Patients and Methods

Patients. Patients with non-small cell lung cancer (NSCLC) who were administered weekly CBDCA (AUC 2 mg/ml/min) and PTX (40 mg/m^2) combination chemotherapy with a concurrent thoracic radiotherapy at the Department of Respiratory Medicine, Gifu University Hospital, Japan between January 2011 and December 2016, were analyzed retrospectively. The exclusion criteria of patients were as follows: previous chemotherapy; regular administration of antiemetic medicine, such as corticosteroids, antidopamine agonists, phenothiazine tranquilizers, and antihistamine drugs; introduction of or increased administration of opioid within 1 week before chemotherapy; nausea and/or vomiting due to organic causes such as brain metastasis or tumor infiltration of the bowel, or other gastrointestinal abnormality.

Treatment. Chemotherapy consisted of CBDCA (AUC 2 mg/ml/min) and PTX (40 mg/m^2), which were administered through an intravenous drip infusion on a weekly basis. For prevention of CINV, a combination of oral azasetron (10 mg) or intravenous granisetron (3 mg) with intravenous dexamethasone (9.9 mg) was administered as a 30-min infusion prior to chemotherapy on day 1. For PTX, oral diphenhydramine (50 mg) and intravenous ranitidine (50 mg) were added on day 1 to prevent anaphylaxis.

Radiotherapy was administered at 2 Gy five times per week. In the radical cure treatment, a total of 60 Gy was administered and in the preoperative CCRT, a total of 40 Gy was administered.

Evaluation of the control of CINV. All patients were provided with a checklist for a daily assessment of CINV. Using the checklist, patients made a daily recording of nausea and vomiting episodes up to 5 days after chemotherapy. Physicians, pharmacists, and nurses recorded nausea, and vomiting control and rescue antiemetic therapy in the electronic medical record after verifying the data.

The patients were evaluated for the following efficacy endpoints for the first cycle: Complete response (CR; defined as no vomiting or retching episodes with no rescue medication) in the in the acute phase (0-24 hours), delayed phase (>24-120 hours) and overall phase (0-120 hours). The other efficacy endpoints evaluated were no vomiting or retching and no nausea in all phases.

Nausea and vomiting were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Ver. 4.0 for evaluation.

Risk analysis for chemotherapy-induced nausea during the overall period. Uni- and multivariate logistic regression analyses were performed to determine the risk of incomplete protection from nausea or vomiting during the overall period. The risk factors considered in this evaluation were patient-related factors such as sex, age, performance status (PS), smoking history, and alcohol consumption (habitual *versus* non-habitual) (13-15). The cutoff value for age was 60 years old according to our previous study (16). Odds ratios (OR) and 95% confidence intervals (CI) were determined.

Statistical analysis. The data were analyzed using IBM SPSS Statistics ver. 22 (IBM Japan Services, Tokyo, Japan). Parametric variables were analyzed using the Student's *t*-test, and non-parametric data were analyzed by the Mann-Whitney *U*-test or the Chi-square test. A *p*-value less than 0.05 was considered statistically significant.

Ethical considerations. The present study was carried out in accordance with the guidelines for human studies adopted by the Ethics Committee of the Gifu Graduate School of Medicine, and approved by the Japanese Government (approved no. 28-348 of the Institutional Review Board).

Results

Patient characteristics. Although the target subjects were 57 patients, we analyzed 46 subjects excluding 11 patients who met the exclusion criteria; those with a history of previous

chemotherapy (n=2), those for whom opioids were introduced or increased within a week prior to the initiation of chemotherapy (n=5), those who were regularly administered an antiemetic (n=3), and those with nausea/vomiting prior to the initiation of chemotherapy (n=1). The patient characteristics are shown in Table I. In five cases with stage IV, palliative radiotherapy was administered for local control.

Control of nausea and vomiting. The antiemetic effects in the acute, delayed, and overall phases are shown in Figure 1. For the overall, acute, and delayed phases, the complete response rates were 89.1%, 100%, and 89.1%, respectively. The rate of no nausea in the overall, acute, and delayed phases was 78.3%, 100%, and 78.3%, respectively. The rate of no vomiting in the overall, acute, and delayed phases was 95.7%, 100%, and 95.7%, respectively. The occurrence of nausea/vomiting by grade in the overall phase is shown in Table II. The rates of nausea were 2.2% (grade 1) and 19.8% (grade 2), whereas no occurrence was observed in grade 3 or higher. The rate of vomiting was 4.3% in grade 1, and no occurrence was observed in grade 2 or higher.

Risks for chemotherapy-induced nausea and vomiting in the overall phase. As shown in Table III, univariate analysis showed that female sex (OR: 3.50; 95% CI: 0.807-15.186, p=0.094), age <60 years (OR: 1.50; 95% CI: 0.314-7.168; p=0.611), PS >1 (OR: 0.35; 95% CI: 0.065-1.888; p=0.222), and no habitual alcohol consumption (OR: 3.96; 95% CI: 0.446–35.182; p=0.217), were not significant risk factors for complete control (no nausea, no vomiting, and no rescue medication) in the overall phase. However, no smoking history was shown as a significant risk factor for complete control in the overall phase using univariate (OR: 11.33; 95% CI: 1.684-76.259; p=0.013) and multivariate analysis (OR: 8.586; 95% CI: 1.169-63.050; p=0.035).

Table I. *Patient characteristics*.

Total Number	46	
Age (years)		
Median (Range)	64 (43-83)	
	No.	%
Gender		
Male	33	71.7
Female	13	28.3
ECOG performance status		
0	29	63.0
1	17	37.0
Stage		
IIA	3	6.5
IIIA	27	58.7
IIIB	10	21.7
IV	5	10.9
Recurrence	1	2.2
Histology		
Adenocarcinoma	17	37.0
Squamous cell carcinoma	26	56.5
Others	3	6.5
Habitual alcohol consumption		
Yes	12	26.1
No	34	73.9
Smoking history		
Yes	40	87.0
No	6	13.0

Table II. *Occurrence of nausea/vomiting by grade in the overall phase*.

Grade	Nausea		Vomiting	
	Number	%	Number	%
0	36	78.3	44	95.7
1	7	2.2	2	4.3
2	9	19.8	0	0

Discussion

In patients with locally advanced NSCLC for whom radical chest radiotherapy is applicable with combined chemotherapy, CCRT including a platinum agent is recommended (17). In Japan, weekly CBDCA+PTX therapy and CCRT are a standard therapy for unresectable stage III NSCLC (12), and we mainly conduct this therapy as CCRT at our hospital. In addition, preoperative CCRT, a therapy option for clinical stage IIIA (N2) in which lobectomy can be performed (18), is conducted with this treatment method at our hospital, and we perform surgery as well after approximately 40 Gy has been delivered.

CINV causes a decrease in physical strength and QOL, and it can reduce adherence to treatment and therapeutic effects. Therefore, sufficiently controlling CINV is very important. CBDCA is a key drug in chemotherapy for lung cancer and is routinely used in a number of regimens. CBDCA is a significant cause of emesis among moderate emetic risk agents, and a number of comparative tests between the two-drug (5-HT_3RA and dexamethasone) and three-drug (5-HT_3RA, dexamethasone, and NK_1RA) preventive measures have been performed. The CR rates in the overall phase were reported as 64.6% (two-drug) *vs*. 80.2% (three-drug) (7), 52% *vs*. 62% (8), 47.3% *vs*. 61.6% (9), and 67.2% *vs*. 80.3%, respectively (10), which hardly indicates that a sufficient effect is obtained by two drugs. The results show a favorable effect using a three-drug

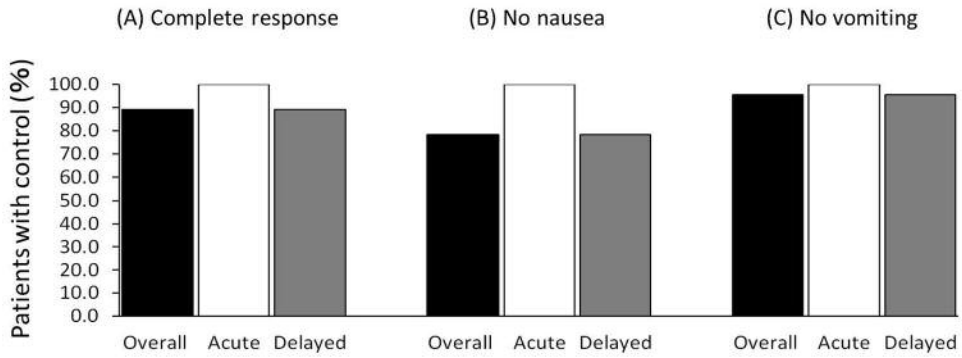

Figure 1. *Complete response (A). No nausea (B). No vomiting (C). The bar graph shows the percentages of patients whose nausea and/or vomiting were controlled in the overall phase (0-120 hours), the delayed phase (>24-120 hours), and the acute phase (24 hours). No vomiting: complete suppression rate of vomiting, complete response: no emetic episodes and no use of rescue medication, no nausea: complete suppression rate of nausea.*

Table III. *Risk analysis for complete control (no nausea, no vomiting and no rescue medication) in overall phase.* .

	Univariate analysis			Multivariate analysis		
	Odds ratio (OR)	95% Confidence Interval	*p*-Value	OR	95% Confidence Interval	*p*-Value
Female	3.50	(0.807-15.186)	0.094	2.124	(0.405-11.132)	0.373
Age < 60 years	1.50	(0.314-7.168)	0.611			
PS >1	0.35	(0.065-1.888)	0.222			
no habitual alcohol consumption	3.96	(0.446-35.182)	0.217			
non smoking history	11.33	(1.684-76.259)	0.013	8.586	(1.169-63.050)	0.035

combination including NK_1RA. In the 2016 MASCC guidelines for antiemesis, CBDCA was separated from the other MEC and the three-drug combination therapy of 5-HT_3RA, dexamethasone, and NK_1RA is recommended for antiemesis (3).

Low-dose (AUC2) CBDCA has been shown to be effective in the single use of chemotherapy or CCRT for lung cancer (12), head and neck cancer (19), and ovarian cancer (20) and is widely used. The antiemetic measures in low-dose (AUC2) CBDCA remain unclear in the guidelines. In weekly CBDCA+PTX therapy, the administration of 5-HT_3RA and dexamethasone on day 1 and that of dexamethasone on days 2-3, which is a standard antiemetic therapy in MEC, results in a significantly high total dose of dexamethasone during the treatment owing to its weekly administration, and this might cause side effects such as hyperglycemia and susceptibility to infection. Furthermore, conducting the three-drug combination therapy newly recommended in the 2016 MASCC guidelines has a high cost owing to high cost of NK_1RA.

In this study, we analyzed the suppressive effect of a single-dose of a first-generation 5-HT_3RA and dexamethasone on nausea/vomiting in the weekly CBDCA+PTX therapy of CCRT for lung cancer. In the ASCO guidelines, almost equal efficacy is shown for all first-generation 5-HT_3RA agents, and the antiemetic effect of oral agents and injections are also equal (2). We previously reported that the oral administration of azasetron (10 mg) and intravenous injection of granisetron (3 mg), both are first-generation 5-HT_3RAs, have similar antiemetic effect in chemotherapy using CBDCA (21). In this study, as first-generation 5-HT_3RAs, the oral administration of azasetron (10 mg) and intravenous injection of granisetron (3 mg) were analyzed. The current study showed that the CR rate of a single-dose of a first-generation 5-HT_3RA and dexamethasone in the overall phase was 89.1%, with no nausea observed in 78.3% and no vomiting in 95.7% in the overall phase, which were significantly favorable results. Furthermore, in five patients who could not achieve CR in the first cycle, switching to a second-generation 5-HT_3RA, palonosetron (n=1), adding olanzapine (n=2), switching to palonosetron and adding aprepitant (n=1), or switching to palonosetron and adding olanzapine (n=1) in the subsequent course allowed all five patients to achieve CR. It was demonstrated that administration of palonosetron, even when the administration

of dexamethasone on days 2-3 is omitted in MEC therapy, yields a CR rate similar to that obtained when dexamethasone is administered for three days (22-24). Aprepitant is known to be highly effective for the prevention of vomiting (25). However, it has been reported that olanzapine, an atypical antipsychotic agent, is more potent than aprepitant in preventing chemotherapy-induced nausea (26, 27). Aprepitant exhibits an inhibitory effect on a drug-metabolizing enzyme, CYP3A4, and it is important to consider the drug interaction. The administration of olanzapine is contraindicated in diabetic patients. Considering the complications, we use these drugs properly as additional therapy for cases in which antiemetic control with general prophylaxis is unfavorable.

Sex, age, PS, smoking history, and alcohol consumption are known risk factors for nausea and vomiting (12-14). Although we performed a subgroup analysis including these risk factors, the risk of CINV was only shown in patients with no smoking history who were administered CBDCA (AUC2). For non-smokers, there is a possibility that it may be necessary to consider strengthening antiemetic therapy, but further research is warranted.

There are several limitations in the present study. First, the present study was a non-randomized single-center study. Second, the small number of patients were induced CINV cases.

In conclusion, a single-dose of a first-generation 5-HT_3RA and dexamethasone in the weekly CBDCA+PTX treatment is a potential standard antiemetic therapy because the control rate of nausea/vomiting is rather favorable, nausea/vomiting can be favorably controlled by adding an antiemetic in the subsequent course in patients whose emesis was not favorably controlled, and the cost of antiemetics is low.

Conclusion

A single-dose of a first-generation 5-HT_3RA and dexamethasone showed a favorable suppressive effect on nausea/vomiting induced by low-dose CBDCA, which indicated that this is a useful supportive therapy.

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