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Is area under the curve the best parameter for carboplatin induced emetic risk stratification?

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ABSTRACT

Carboplatin (CBDCA)-induced emetic risk is currently classified on the basis of CBDCA-area under the curve (CBDCA-AUC). We investigated the utility of three CBDCA dosage parameters for predicting emesis by CBDCA. Patients with thoracic cancer treated with CBDCA were included. The endpoints were complete response (CR) and total control (TC). CR was defined as no vomiting and no use of rescue medication during the overall assessment period, whereas TC was defined as no vomiting, nausea, nor use of rescue medication during the overall assessment period. The parameters of CBDCA were defined as follows: (1) CBDCA-AUC; (2) CBDCA/body surface area (BSA): the administered dose of CBDCA per body surface area (mg/m^2); and (3) total CBDCA/body: the total administered dose of CBDCA (mg). Eighty-five patients were evaluated. The median CBDCA/BSA but not CBDCA-AUC was higher in patients with non-CR compared to those with CR. Receiver operating characteristic curve analysis revealed that the AUC of CBDCA/BSA for predicting non-CR was higher than that of CBDCA-AUC. CBDCA/BSA shows greater potential for predicting CBDCA-induced emetic risk compared with CBDCA-AUC, which is the parameter in current antiemetic guidelines.

Keywords: carboplatin, chemotherapy-induced nausea and vomiting (CINV), moderate emetic risk regimen, antiemetic treatment, antiemetic guideline recommendations

Abbreviations:
AUC: area under the curve
BSA: body surface area
CBDCA: carboplatin
CI: confidence interval
CINV: chemotherapy-induced nausea and vomiting
CR: complete response
eGFR: estimated glomerular filtration rate
MIC: minimum inhibitory concentration
NK1: neurokinin-1
OR: odds ratio
ROC: receiver operating characteristic
TC: total control

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INTRODUCTION

Despite the development of molecular targeted therapies, such as epidermal growth factor receptor (EGFR) kinase inhibitors for EGFR-mutated non-small cell lung cancer, platinum compounds remain key anticancer agents in treating several advanced solid tumors.[1-3] Among these, carboplatin (CBDCA)—a second-generation platinum agent—is widely used to treat lung cancer, gynecologic cancers, the head and neck cancer, and breast cancer, etc.[4]

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and important adverse events in patients treated with CBDCA. CBDCA is categorized as either high-emetic-risk chemotherapy when the CBDCA-area under the blood-concentration time curve (CBDCA-AUC) is ≥4 (mg/ml·min), or moderate-emetic-risk chemotherapy (MEC) when the CBDCA-AUC is <4 (mg/ml·min) according to National Cancer Community Network (NCCN) guidelines. In the guidelines of the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO)/Multinational Association of Supportive Care in Cancer (MASCC), CBDCA is classified as a MEC.[5-8] In the NCCN and ASCO guidelines, antiemetic strategies are based on the CBDCA-AUC. Specifically, a triple-antiemetic strategy involving a neurokinin-1 (NK1) receptor antagonist, a serotonin receptor antagonist, and dexamethasone is recommended for patients undergoing treatment with CBDCA-AUC of ≥4, whereas the use of NK1 receptor antagonists is unnecessary for patients undergoing treatment with CBDCA-AUC of <4.[5] In contrast, ESMO/MASCC guidelines recommend using this triple antiemetic strategy regardless of the CBDCA-AUC.

The risk stratification of CBDCA-induced CINV based on CBDCA-AUC in these guidelines is mainly based on expert consensus, and it is unclear whether the current cutoff value of 4 is optimal. In fact, the dose adjustment procedure of CBDCA using AUC is based on a pharmacokinetic study that investigated the relationship between AUC and efficacy/myelosuppression but not CINV.[9] In the retrospective cohort study that investigated the efficacy and safety of CBDCA plus pemetrexed regimen, similar incidence of nausea and vomiting was reported between patients treated with CBDCA AUC ≥ 4 and those treated with CBDCA AUC < 4 (any grade: 63.3% and 70.8%, p=0.325, according to the National Cancer Institute-Common Toxicity Criteria ver3.0).[10] Furthermore, in terms of cisplatin, another platinum agent as well as CBDCA, the dose of cisplatin per body surface area (BSA) was an independent risk factor for CINV.[11] However, the data regarding useful CBDCA dosage parameters for predicting CINV risk are insufficient. Additionally, few studies have investigated the association between CBDCA-AUC and CINV.

Based on these backgrounds, we hypothesized that the dose of CBDCA per BSA (CBDCA/BSA [mg/m^2]) or total dose of CBDCA per body (total CBDCA /body) has better utility for predicting CINV risk compared to CBDCA-AUC, which lead us to conduct the current retrospective cohort study. The aim of this study was to explore the optimal CBDCA parameter for predicting the risk of CINV. In this study, we investigated the utility of three CBDCA dosage parameters (CBDCA-AUC, CBDCA/BSA, total CBDCA/body) for predicting CINV.

MATERIALS AND METHODS

Study design and Patients

This study was a retrospective cohort study, which was approved by institutional review board

of Nagoya University Hospital. We included all patients with thoracic malignant tumor such as lung cancer, thymic cancer who were treated with CBDCA-based therapy regimens from 2011 to 2014 in our hospital for this retrospective cohort study.

Data collection

Individual medical charts were retrospectively reviewed, and the following data were collected: age, sex, ECOG performance status (PS), history of alcohol consumption (habitual or non-habitual), prophylactic antiemetic treatment (granisetron/aprepitant/dexamethasone [GAD] or palonosetron/dexamethasone [PD]), and combination agent with CBDCA (pemetrexed or an agent other than pemetrexed). We adopted combination agent with CBDCA as a clinical factor which possibly affect the emetic events such as nausea and vomiting based on previous evidence. Concretely, previous reports showed pemetrexed plus CBDCA had higher risk of nausea and vomiting compared to paclitaxel plus CBDCA.[12,13]

The parameters of CBDCA were defined as follows: (1) CBDCA-AUC, the actual dose of CBDCA divided by (25 + estimated glomerular filtration rate [eGFR]); (2) CBDCA/BSA, the administered dose of CBDCA per BSA (mg/m^2); (3) total CBDCA/body, the total administered dose of CBDCA (mg). To determine the total dose of CBDCA in our clinical practice, we estimated GFR using one of the following three methods: (i) eGFR, (ii) Cockcroft calculation without calibration by +0.2 mg/dl of serum creatinine, or (iii) Cockcroft calculation with calibration by +0.2 mg/dl of serum creatinine.[14] Therefore, we needed to calibrate the CBDCA-AUC of each patient to evaluate the association between CBDCA-AUC and CINV. We recalculated the CBDCA-AUC for each patient using eGFR in patients whose GFR was estimated using method (ii) or (iii) as follows:

$$\text{CBDCA} - \text{AUC} = \frac{\text{Total administered dose of CBDCA}}{\text{eGFR}+25}\ (\text{mg/ml}\cdot\text{min})$$

On the basis of this calibration, the CBDCA-AUC of each patient was calculated to the second decimal place.

Outcomes and Endpoints

The data regarding severity of nausea (classified into four grades: none, mild, moderate, or severe), the incidence of vomiting, and the use of rescue antiemetic drugs were retrospectively reviewed for outcome analysis.

The endpoints were complete response (CR) and total control (TC) for the evaluation of CINV. We monitored nausea and vomiting in the 5 days from the initiation of CBDCA therapy. CR was defined as no vomiting and no use of rescue medication during the overall assessment period, and TC was defined as no vomiting, no nausea, and no use of rescue medication during the overall assessment period. Patients who did not achieve CR/TC were categorized as non-CR/non-TC.

Statistical analysis

Data were analyzed using JMP version 13.0. We considered p values of <0.05 to indicate statistical significance. Comparisons of two groups (CR/TC or non-CR/non-TC) were performed using Fisher's exact test or Wilcoxon rank sum test. The cutoff value for each parameter of CBDCA was determined using the Youden index method in the receiver operating characteristic curve (ROC) analysis. The odds ratio (OR) with 95% confidence interval (CI) for each CBDCA parameter for CR or TC failure was evaluated using univariate and multivariate analyses with

logistic regression. The adjusted clinical factors were sex, which was confirmed as a robust risk factor for emesis, and clinical factors with $p < 0.10$ using Fisher's exact test.

RESULTS

Patient characteristics

A total of 85 patients were included in this study. The patient characteristics and CBDCA parameters are presented in Table 1. The median age of our cohort was 67 years (range 27–80 years), and 43.5% of patients were men. The majority of patients had a good PS (PS0: 47.1% and PS1: 47.1%). Of the total study cohort, 41.2% of patients had habitual alcohol consumption and 11.8% received opioid treatment as supportive care at the time of starting CBDCA-based chemotherapy. In terms of prophylactic antiemetic therapy, 30.6% of patients received GAD, and 69.4% of patients received PD. We also found that 50.6% of patients received pemetrexed as a combination agent of CBDCA. Regarding CBDCA parameters, the median of CBDCA-AUC, CBDCA/BSA, and total CBDCA/body was 5.01 (range 1.90–7.01), 303 mg/m^2 (range 114–431), and 480 mg (range 193–810), respectively.

Table 1 Patient characteristics (n = 85)

Variables		No. of patients (%)
Age, median (range)		67 (27–80)
Sex	Male	37 (43.5)
	Female	48 (56.5)
ECOG PS	0	40 (47.1)
	1	40 (47.1)
	2	5 (5.9)
Alcohol consumption	Habitual	35 (41.2)
	Non-habitual	50 (58.8)
Opioid user	Yes	10 (11.8)
	No	75 (88.2)
Prophylactic anti emetic treatment	GAD	26 (30.6)
	PD	59 (69.4)
Combination agent	Pemetrexed	43 (50.6)
	Others	42 (49.4)
Albumin (g/dl), median		3.7 (2.1–4.8)
CBDCA-AUC (mg·min/mL), median (range)		5.01 (1.90–7.01)
CBDCA/BSA (mg/m^2), median (range)		303 (114–431)
Total CBDCA/body (mg), median (range)		480 (193–810)

ECOG PS: European Cooperative Oncology Group performance status
Others: paclitaxel, S1, and gemcitabine were included in others.
GAD: granisetron, aprepitant and dexamethasone
PD: palonosetron and dexamethasone
CBDCA: carboplatin
AUC: area under curve
BSA: body surface area

Comparison of patient characteristics and CBDCA parameters between patients with CR and non-CR

Table 2A shows patients characteristics and CBDCA parameters in relation to CR status. The overall rate of CR was 72.9% (62 of 85). The difference in the rate of CR among patients treated with pemetrexed and those treated with other agents was close to statistical significance (62.8% vs. 83.3%, p = 0.050), but other baseline characteristics were not statistically significantly different between patients who achieved CR and those who did not.

The median CBDCA-AUC was similar between patients who did and did not achieve CR (4.94 (range 1.90–6.57) vs. 5.25 (range 4.12–7.01), p = 0.169), while the median CBDCA/BSA and total CBDCA/body were statistically significantly higher in patient with non-CR compared to those in patients with CR (339 mg/m^2 (range 185–411) vs. 290 mg/m^2 (range 114–431), p = 0.011; 510 mg (range 300–670) vs. 455 mg (range 193–810), p=0.042).

Table 2A Patient characteristics and CBDCA parameters according to CR achievement (n = 85)

		No. of patients with CR (%)	No. of patients with Non-CR (%)	p value
Age	≥67	34 (75.6)	11 (24.4)	0.629
	<67	28 (70.0)	12 (30.0)	
Sex	Male	25 (67.6)	12 (32.4)	0.339
	Female	37 (77.1)	11 (22.9)	
ECOG PS	0	31 (77.5)	9 (22.5)	0.466
	1–2	31 (68.9)	14 (31.1)	
Alcohol consumption	Yes	27 (77.1)	8 (22.9)	0.621
	No	35 (70.0)	15 (30.0)	
Opioid user	Yes	7 (70.0)	3 (30.0)	1.000
	No	55 (73.3)	20 (26.7)	
Antiemetic drugs	GAD	21 (80.8)	5 (19.2)	0.427
	PD	41 (69.5)	18 (30.5)	
Albumin (g/dL)	<3.7	28 (80.0)	7 (20.0)	0.321
	≥3.7	34 (68.0)	16 (32.0)	
Combination agent	Pemetrexed	27 (62.8)	16 (37.2)	0.050
	Others	35 (83.3)	7 (16.7)	
CBDCA-AUC (mg·min/mL), median (range)		4.94 (1.90–6.57)	5.25 (4.12–7.01)	0.169
CBDCA/BSA (mg/m^2), median (range)		290 (114–431)	339 (185–411)	0.011†
Total CBDCA/body (mg), median (range)		455 (193–810)	510 (300–670)	0.042†

† indicates statistical significance (p < 0.05).
ECOG PS: European Cooperative Oncology Group performance status
Others: paclitaxel, S1, and gemcitabine were included in others.
GAD: granisetron, aprepitant and dexamethasone
PD: palonosetron and dexamethasone
CBDCA: carboplatin
AUC: area under curve
BSA: body surface area
SD: standard division
CR: complete response
Non-CR: non-complete response

Comparison of patient characteristics and CBDCA parameters between patients with TC and non-TC

Table 2B shows the patient characteristics and CBDCA parameters according to TC achievement. The TC rate in our cohort was 65.9%, 56 of 85 patients achieved TC. There were no patient characteristics which showed statistically significant difference between patient with TC and those with non-TC.

In terms of CBDCA parameters, median of CBDCA-AUC was similar between patient with TC and those with non-TC (4.94 (range 1.90–6.57) vs. 5.25 (range 4.12–7.01), p=0.080), while total CBDCA/body and CBDCA/BSA were statistically significantly higher in patient with non-TC compared to those in patients with TC (345 mg/m^2 (range 185–426) vs. 284 mg/m^2 (range 114–431), $p < 0.001$; and 530 mg (range 300–698) vs. 450 mg (range 193–810), p=0.006).

Table 2B Patient characteristics and CBDCA parameters according to TC achievement (n = 85)

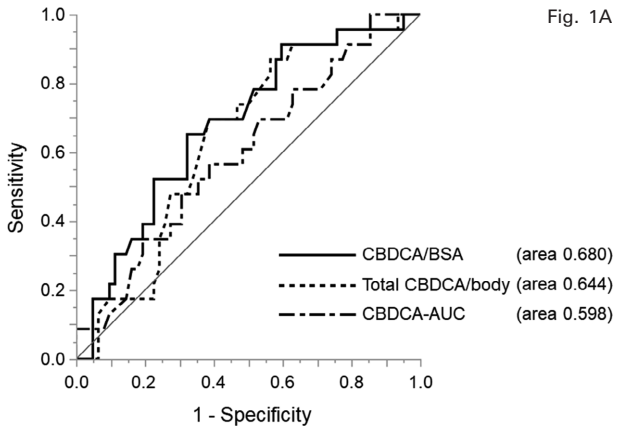
		No. of patients with TC (%)	No. of patients with Non-TC (%)	p value
Age	≥67	33 (73.3)	12 (26.7)	0.170
	<67	23 (57.5)	17 (42.5)	
Sex	Male	22 (59.5)	15 (40.5)	0.357
	Female	34 (70.8)	14 (29.2)	
ECOG PS	0	29 (72.5)	11 (27.5)	0.258
	1–2	27 (60.0)	18 (40.0)	
Alcohol consumption	Yes	24 (68.6)	11 (31.4)	0.817
	No	32 (64.0)	18 (36.0)	
Opioid user	Yes	6 (60.0)	4 (40.0)	0.729
	No	50 (66.7)	25 (33.3)	
Antiemetic drugs	GAD	18 (69.2)	8 (30.8)	0.805
	PD	38 (64.4)	21 (35.6)	
Albumin (g/dL)	<3.7	26 (74.2)	9 (25.7)	0.245
	≥3.7	30 (60.0)	20 (40.0)	
Combination agent	Pemetrexed	24 (55.8)	19 (44.2)	0.067
	Others	32 (76.2)	10 (23.8)	
CBDCA-AUC (mg·min/mL), median (range)		4.94 (1.90–6.57)	5.25 (4.12–7.01)	0.080
CBDCA/BSA (mg/m^2), median (range)		284 (114–431)	345 (185–426)	<0.001†
Total CBDCA/body (mg), median (range)		450 (193–810)	530 (300–698)	0.006†

† indicates statistical significance ($p < 0.05$).
ECOG PS: European Cooperative Oncology Group performance status
Others: paclitaxel, S1, and gemcitabine were included in others.
GAD: granisetron, aprepitant and dexamethasone
PD: palonosetron and dexamethasone
CBDCA: carboplatin
AUC: area under curve
BSA: body surface area
SD: standard division
TC: total control
Non-TC: non-total control

ROC curve analysis of CBDCA parameters for predicting non-CR and non-TC

The ROC analyses for non-CR and non-TC are shown in Figure 1. Interestingly, the AUC of CBDCA/BSA (0.680) and total CBDCA/body (0.644) for predicting non-CR were higher than that of CBDCA-AUC (0.598), although this was not statistically significant (p=0.293, p=0.513, respectively). The optimal cut-off values for predicting non-CR, as determined using the Youden index method, was 5.07 for CBDCA-AUC, 325 mg/m^2 for CBDCA/BSA, and 500 mg/body for total CBDCA/body (Figure 1A).

As well as the results of ROC analysis for predicting non-CR, the AUC of CBDCA-BSA (0.727) and total CBDCA/body (0.682) for predicting non-TC were higher than that of CBDCA-AUC (0.616), although this was not statistically significant (p=0.105, p=0.291, respectively). The optimal cut-off values for each CBDCA parameter for predicting non-TC, as determined by the Youden index method, were 5.49 for CBDCA-AUC, 339 mg/m^2 for CBDCA/BSA, and 500 mg/body for total CBDCA/body (Figure 1B).



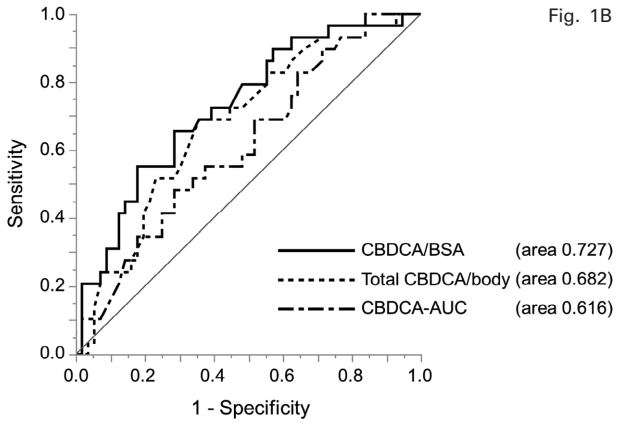


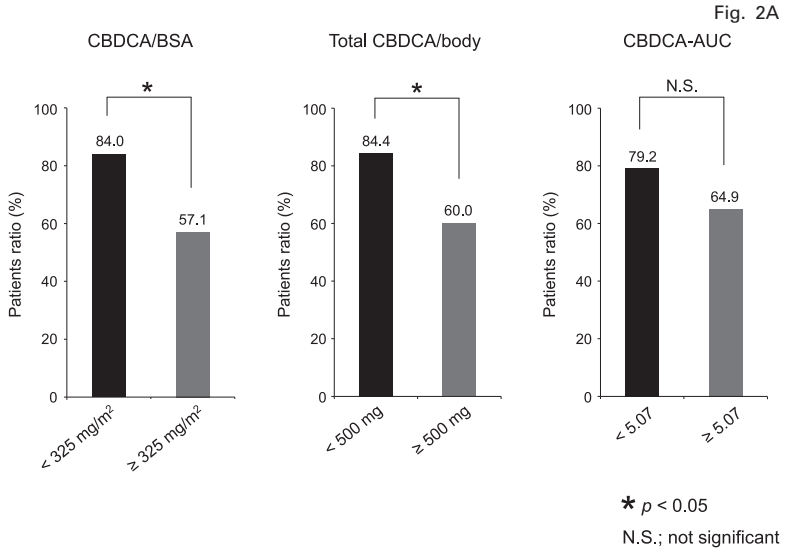
Fig. 1 The receiver operating characteristic curve (ROC) analysis for predicting non-complete response (CR) and non-total control (TC)

Fig. 1A: The receiver operating characteristic curve (ROC) analysis of each carboplatin (CBDCA) parameters for predicting patients with non-complete response (CR). The optimal cut off value is calculated by Youden index methods.

Fig. 1B: The receiver operating characteristic curve (ROC) analysis of each carboplatin (CBDCA) parameters for predicting patients with non-total control (TC). The optimal cut off value is calculated by Youden index methods.

Figure 2 shows the rate of CR and TC between patients with high CBDCA parameters and those with low CBDCA parameters according to the determined optimal cut-off values.

The CR rate was significantly higher among patients with low CBDCA/BSA (<325 mg/m^2) than those with high CBDCA/BSA (≥325 mg/m^2) (84.0% vs. 57.1%, p = 0.012) (Figure 2A). As well as CBDCA/BSA, the CR rate was significantly higher among patients with low total CBDCA/body (<500 mg) than those with high total CBDCA/body (≥500 mg) (84.4% vs. 60.0%, p = 0.015). In contrast, the CR rates of patients with low and high CBDCA-AUC (<5.07 and ≥5.07, respectively) were not statistically significantly different (79.2% vs. 64.9%, p = 0.220).



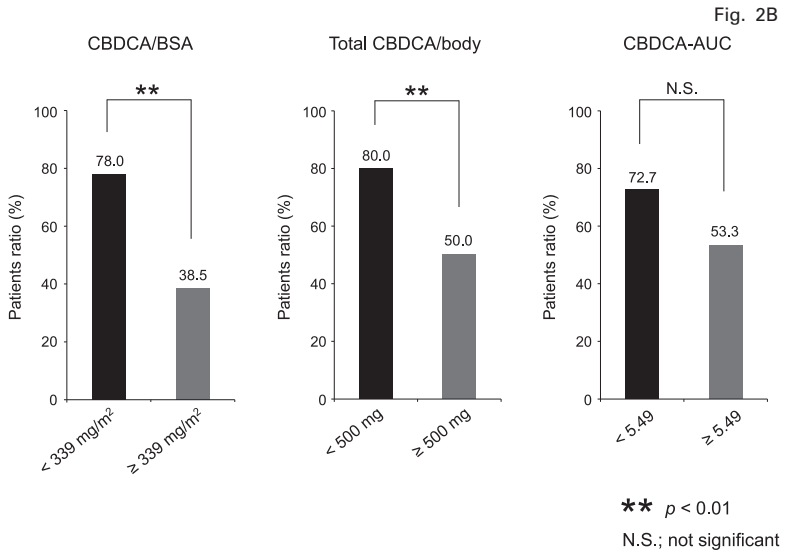


Fig. 2 The rate of complete response (CR) and total control (TC)

Fig. 2A: The rate of complete response (CR) in subgroup according to optimal cut-off value of each carboplatin (CBDCA) parameters. * indicates p value less than 0.05. N.S. indicates not significant.

Fig. 2B: The rate of total control (TC) in subgroup according to optimal cut-off value of each carboplatin (CBDCA) parameters. ** indicates p value less than 0.01. N.S. indicates not significant.

Similar to the results of the CR rate, the TC rate in patients with low CBDCA/BSA (<339 mg/m^2) was statistically significantly higher compared to that in patients with high CBDCA/BSA (≥339 mg/m^2) (78.0% vs.38.5%, p=0.001) (Figure 2B). The TC rate was significantly higher among patients with low total CBDCA/body (<500 mg) compared with those with high total CBDCA/body (≥500 mg) (80.0% vs. 50.0%, p = 0.006). In contrast, the TC rates among patients with low and high CBDCA-AUC (<5.49 and ≥5.49, respectively) were not significantly different (72.7% vs. 53.3%, p = 0.095).

Univariate and multivariate analyses of CBDCA parameters for predicting non-CR and non-TC

Based on the optimal cut off values determined by Youden index methods, we performed univariate and logistic regression multivariate analysis for predicting non-CR and non-TC on each CBDCA parameters.

Table 3A shows a univariate analysis and multivariate analyses for predicting non-CR. In multivariate analysis, CBDCA/BSA (adjusted Odds (OR) 3.15 [95% confidence interval (CI): 1.08–9.16, p=0.035]) and total CBDCA/body (adjusted OR 3.04 [95% CI: 1.04–8.93], p=0.043) were independent risk factors for predicting non-CR. In contrast, CBDCA-AUC (adjusted OR 1.78 [95% CI: 0.64–4.98, p=0.272]) was not statistically significant for predicting non-CR.

Table 3A Univariate analysis and Multivariate analysis for non-CR (n = 85)

Variables		Univariate analysis		Multivariate analysis†	
		OR (95% CI)	p value	OR (95% CI)	p value
CBDCA-AUC (mg·min/mL)	<5.07	1		1	
	≥5.07	2.06 (0.78–5.43)	0.145	1.78 (0.64–4.98)	0.272
CBDCA/BSA (mg/m^2)	<325	1		1	
	≥325	3.94 (1.43–10.81)	0.008††	3.15 (1.08–9.16)	0.035††
Total CBDCA/body (mg)	<500	1		1	
	≥500	3.61 (1.30–10.08)	0.014††	3.04 (1.04–8.93)	0.043††

OR: odds ratio

† OR were adjusted by sex and the combination of pemetrexed in multivariate analysis.

†† indicates statistical significance (p < 0.05).

Table 3B shows a univariate analysis and multivariate analyses for predicting non-TC. In multivariate analysis, CBDCA/BSA (adjusted OR 4.63 [95% CI: 1.59–13.47, p=0.005]) and total CBDCA/body (adjusted OR 3.56 [95% CI: 1.30–9.76], p=0.014) were independent risk factors for predicting non-TC. In contrast, CBDCA-AUC (adjusted OR 2.15 [95% CI: 0.80–5.76, p=0.128]) was not statistically significant for predicting non-TC. Collectively, CBDCA-AUC was not predictive for both non-CR and non-TC, while CBDCA/BSA and total CBDCA/body were associated with both non-CR and non-TC.

Table 3B Multivariate analysis for non-TC (n = 85)

Variables		Univariate analysis		Multivariate analysis†	
		OR (95% CI)	p value	OR (95% CI)	p value
CBDCA-AUC (mg·min/mL)	<5.49	1		1	
	≥5.49	2.33 (0.92–5.92)	0.075	2.15 (0.80–5.76)	0.128
CBDCA/BSA (mg/m^2)	<339	1		1	
	≥339	5.66 (2.08–15.41)	<0.001††	4.63 (1.59–13.47)	0.005††
Total CBDCA/body (mg)	<500	1		1	
	≥500	4.00 (1.53–10.43)	0.005††	3.56 (1.30–9.76)	0.014††

OR: odds ratio

† OR were adjusted by sex and the combination of pemetrexed in multivariate analysis.

†† indicates statistical significance ($p < 0.05$).

DISCUSSION

The current study demonstrates that CBDCA/BSA and total CBDCA/body, but not CBDCA-AUC, are useful parameters for predicting the risk of CINV. To the best of our knowledge, this is the first study to investigate the utility of these parameters as predicting factors for CBDCA-induced nausea and vomiting.

The current antiemesis guidelines of ASCO and NCCN recommends that triple antiemetic strategy with NK1 receptor antagonist, 5-HT3 receptor antagonist, and dexamethasone should be selected for patients treated with CBDCA-AUC ≥ 4.[5,7,8] These recommendations are based on the fact that most phase III studies of triple antiemetic strategy for CBDCA regimen have included only patients treated with CBDCA having AUC ≥4.[15-18] Although the MASCC/ESMO guidelines universally recommend triple antiemetic therapy for CBDCA-induced nausea and vomiting,[5,6] few studies have demonstrated the benefits of such a strategy for patients with CBDCA-AUC <4. In fact, Jordan et al discussed this issue for patients treated with lower doses of CBDCA in their systematic review of NK1 receptor antagonists.[19] Besides these backgrounds, the ROC analysis of CBDCA-AUC in the present study indicated AUC of 0.598 for predicting non-CR and 0.616 for predicting non-TC, both of which would not be considered acceptable (AUC < 0.7) in terms of statistical consensus.[20]

We found that CBDCA/BSA and total CBDCA/body have potential utility for predicting CBDCA-induced nausea and vomiting; for CBDCA/BSA, the AUC of the ROC for predicting non-TC was >0.7, which indicates good predictivity.[20] In addition, the TC rate of patients received CBDCA with ≥ 339 mg/m^2 (optimal cut off value by Youden Index) was only 38.5%, and those would be a good target for triple antiemetic strategy. A pharmacokinetic study investigating CBDCA treatment for patients with severe renal insufficiency could verify the results of the current study. Oguri et al investigated carboplatin concentrations in plasma in patients with eGFR < 30 ml/min/1.73 m^2.[21] Of these patients, target AUC were set as 4 or 5. However, any grade of nausea or vomiting was not noted in their study. In patients with severe renal insufficiency (eGFR < 30 ml/min/1.73m^2), total CBDCA/body must be below 275 mg with a target AUC of 5 because the estimated CBDCA clearance is equal to GFR (ml/min) + 25. The results of Oguri, et al suggested the incidence of CBDCA-induced nausea and vomiting to be low in patients receiving low total CBDCA/body with high CBDCA-AUC (4 or more). Consistent with these

previous reports, our results suggest that the association between CBDCA-AUC and CBDCA-induced nausea and vomiting is weak and further studies are warranted to identify new useful predictors of CBDCA-induced nausea and vomiting. The reason of the superiority of CBDCA/BSA to CBDCA-AUC is difficult to explain clearly.

However, we speculate that different mechanisms between the CBDCA-induced antitumor effect and CBDCA-induced emesis are a possible reason to explain the results of the current study. CBDCA exerts antitumor efficacy by inducing DNA crosslinks, whereas CBDCA causes CINV by increasing several cytokines such as substance P, resulting in stimulating neurokinin 1 (NK1) receptor. The association between CBDCA-AUC and antitumor effects or myelosuppression is well established by previous research, and both effects are induced by CBDCA-mediated DNA crosslink formation.[9] However, to our best knowledge, the association between the pharmacodynamics of CBDCA and CINV has not been investigated at this point. In antimicrobial research, several pharmacodynamic parameters are important for a given antibiotic agent, including (1) the ratio of maximum serum concentration (Cmax) to the minimum inhibitory concentration (MIC); Cmax/MIC, (2) the ratio of the AUC versus MIC; AUC/MIC, (3) the duration of the dosing interval that plasma concentrations exceed the MIC; Time above MIC.[22] These suggest that the relevant pharmacodynamic parameters predicting major effect or side effect of anticancer agents are different depends on the mechanism of drug action. As mentioned above, the mechanism of CINV caused by CBDCA is different from that of myelosuppression. Although pharmacodynamics of CBDCA for predicting CINV is not elucidated, it is possible that Cmax of CBDCA rather than AUC of CBDCA is the best pharmacodynamic parameters predicting CINV of CBDCA, and the dose of CBDCA/BSA might be well associated with Cmax of CBDCA. Because all of these are only speculative, further studies are warranted for investigating an optimal parameter for predicting CBDCA induced CINV.

Our study has several limitations, which should be acknowledged. The retrospective cohort analysis was based on patients recruited from a single institution. The results of multivariate analysis and optimal cut-off values for predicting non-CR and non-TC should be interpreted with caution because overfitting bias could exist. Because of the retrospective nature, the event rates for CR and TC in terms of vomiting and the use of rescue antiemetic drugs could be underestimated. Therefore, future multi-center prospective studies are required to validate the results of our study.

In conclusion, CBDCA/BSA shows greater potential than CBDCA-AUC for predicting the risk of CBDCA-induced emesis. Patients treated with high CBDCA/BSA may be good candidates for triple antiemetic therapy, regardless of CBDCA-AUC, whereas those receiving low CBDCA/BSA may not require NK1 receptor antagonists, even when the CBDCA-AUC is ≥4.

AUTHOR CONTRIBUTIONS

S.O. and K.I. equally contributed to this work.

CONFLICTS OF INTEREST

All authors declare no conflict interest in regard to the current study.

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