

# Risk factors for delayed chemotherapy-induced nausea and vomiting with low-emetic-risk chemotherapy: a prospective, observational, multicenter study

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**Purpose:** Improvement in the control of delayed chemotherapy-induced nausea and vomiting (CINV) is needed. There is limited information on antiemetic prophylaxis for patients undergoing low-emetic-risk chemotherapy (LEC), and the optimal antiemetic treatment is not well understood. Therefore, we analyzed the risk factors for delayed CINV to aid in the development of individualized treatments.

**Patients and methods:** This prospective multicenter study was conducted in 13 hospitals and included patients with solid cancers undergoing LEC. A total of 222 patients were enrolled between September 2013 and November 2014. The participants completed a daily diary for 5 days after the commencement of the first cycle of LEC to describe the daily incidence of CINV (yes/no). Furthermore, the participants described the severity of nausea and the amount of food intake with the help of VAS.

**Results:** Two hundred and ten patients provided their data that were analyzed using multivariate logistic regression to examine the risk factors for delayed CINV. History of CINV, Eastern Cooperative Oncology Group performance status score  $\geq 1$ , acute CINV, and single-day antiemetic prophylaxis were identified as independent risk factors for delayed CINV.

**Conclusion:** The current use of antiemetic prophylaxis according to the recommended guideline appears to effectively control delayed CINV in patients undergoing LEC. Therefore, patients with the abovementioned risk factors should be carefully observed, and their treatment should be adjusted according to their symptoms. The use of multiple-day dexamethasone may be beneficial for those patients who develop acute CINV, especially when it is accompanied by anorexia.

**Keywords:** adverse effects, antiemetics, prophylaxis, quality of life

## Introduction

CINV is a well-known potential adverse effect of cancer chemotherapy that impairs the patients' quality of life, including that of patients undergoing LEC.<sup>1,2</sup> The control of delayed CINV, a particularly important issue, remains unresolved. In fact, in our previous study, delayed CINV was observed more frequently than that of predicted CINV, and the severity of nausea gradually increased from day 1, peaking on days 4 and 5.<sup>3</sup> Both treatment- and patient-related risk factors need to be considered to ensure the optimal control of CINV.<sup>4-12</sup> However, until recently, the lack of clinical trials performed in patients treated with LEC has made it difficult

to identify patients at risk of CINV. Moreover, antiemetic guidelines recommend the use of a single agent, such as low-dose dexamethasone on the first day of chemotherapy, stating that it is not necessary to administer antiemetics to prevent delayed CINV in patients undergoing LEC; however, this recommendation is not based on the results of clinical trials, rather it reflects a consensus among experts in the field.<sup>13–16</sup> Identifying patients at a high risk of delayed CINV while undergoing LEC may enhance the clinical management by health care providers to reduce the incidence and severity of delayed CINV. Therefore, in this study, we aimed to assess both risk factors and a candidate treatment strategy for delayed CINV in patients with solid cancers undergoing LEC.

## Patients and methods

### Study design

The study design, including patient enrollment, data collection, and treatment, has been described previously.<sup>3</sup> Briefly, this prospective, observational, multicenter study was conducted from September 2013 to November 2014 in 13 hospitals affiliated with the National Hospital Organization in Kyushu, Japan. Adult patients beginning LEC were consecutively recruited at the study sites.

This study is registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol ID: UMIN000020800).

### Patients

Men and women  $\geq 20$  years of age who were LEC-naïve and scheduled to undergo at least 1 cycle of a single-day cytotoxic LEC were eligible for inclusion in this study. The intended cancer treatment comprised at least one of the following injectable agents: docetaxel, paclitaxel, gemcitabine, pemetrexed, liposomal doxorubicin, eribulin, and 5-fluorouracil. Patients were excluded from the study if they had undergone treatment with chronic systemic corticosteroid therapy, concurrent abdominal or pelvic radiation therapy, or had undergone LEC within 120 hours (5 days) of initiating chemotherapy. Patients were also excluded if they had brain metastases or had vomited in the 24-hour period preceding chemotherapy initiation.

Patients were provided with a diary before the commencement of chemotherapy and were asked to record their digestion-related symptoms (development and severity of nausea, frequency of vomiting, food intake, and the number of salvage treatments received) each day during a 5-day period

after commencing LEC. The incidence of nausea was identified by patients. A 100 mm linear VAS was used to quantify food intake (100 mm, no oral food intake; 0 mm, eating as usual) and severity of nausea (100 mm, worst nausea; 0 mm, no nausea). Before or at the time of the initial chemotherapy treatment, we recorded the following patient information on a case report form: initials, sex, hospital number, date of birth, treatment history, alcohol consumption, history of motion sickness, ECOG performance status, cancer chemotherapy regimen, and antiemetic as well as salvage antiemetic treatments. The patients were asked to send their completed diaries to the Central Office using the preaddressed return envelopes provided. Likewise, the investigators sent their case reports to the Central Office in such return envelopes.

### Statistical analyses

Patient demographics, clinical characteristics, and antiemetic treatments prescribed for the acute and delayed phases were summarized using contingency tables. Independent risk factors for delayed CINV incidence (dependent variable) were evaluated using logistic regression analysis with backward elimination method. The following independent factors were included in the model: sex, CINV history, development of acute CINV, opioid use, motion sickness, morning sickness, alcohol consumption, ECOG performance status, antiemetic prophylaxis, LEC other than taxane, and age. The severity patterns of nausea and food intake in relation to the occurrence of acute CINV were evaluated by the transition of the VAS score (without conducting further statistical analysis). All reported *P*-values corresponded to two-sided tests; and *P*-values  $< 0.05$  were considered statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

### Ethics approval and informed consent

All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committees of each participating institution, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from individual participants, prior to their inclusion in the study.

## Results

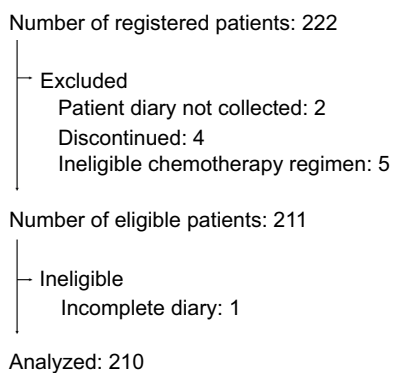
### Participants

In this study, 222 patients were enrolled who were undergoing LEC for the first time. After excluding patients who withdrew

within 5 days of undergoing LEC or who did not submit a diary, the data of 210 patients (94.6% of all patients enrolled) were finally analyzed (Figure 1). Table 1 summarizes the demographic and clinical characteristics of the 210 patients.

### Antiemetic treatment

The CINV guidelines recommend the use of single-day antiemetic agents (e.g., dexamethasone) for patients undergoing LEC.<sup>13–16</sup> Such patients should not undergo routine antiemetic prophylaxis during the delayed phase. However, 78 patients (37.1%) received antiemetic agents on multiple days. Table 2 summarizes the antiemetic treatments prescribed for the acute and delayed phases in the first cycle of LEC.



**Figure 1** Enrollment of patients.

**Notes:** A total of 222 patients were registered, and 211 patients’ diaries were paired with the case report forms and staff reports. One patient who had an incomplete diary was excluded from the analysis; hence, the data of 210 patients (94.6% of all patients registered) were finally analyzed.

**Table 1** Patient demographics and clinical characteristics (n=210)

Variable	Category	n (%)
Sex	Male	82 (39.0)
	Female	128 (61.0)
Age (years), median (range)		64 (27–86)
ECOG performance status	0	141 (67.1)
	1	59 (28.1)
	≥2	10 (4.8)
		54 (25.7)
Number of prior chemotherapies	0	138 (65.7)
	1	18 (8.6)
	≥2	93 (44.3)
		63 (30.0)
Primary cancer diagnosis	Breast cancer	21 (10.0)
	Lung cancer	17 (8.1)
	Pancreatic cancer	16 (7.6)
	Gastric cancer	105 (50.0)
	Other	45 (21.4)
Antineoplastic agents	Docetaxel	34 (16.2)
	Paclitaxel	19 (9.0)
	Gemcitabine	7 (3.3)
	Pemetrexed	

**Abbreviation:** ECOG, Eastern Cooperative Oncology Group.

### Incidence of delayed CINV

Delayed CINV (of any grade) was reported by 27.3% of the patients who underwent the single-day antiemetic prophylaxis and by 11.5% of the patients who underwent the multiple-day antiemetic prophylaxis. Among patients who developed acute CINV, 68.8% and 33.3% who underwent the single- and multiple-day prophylaxis, respectively, developed delayed CINV (Table 2). The antiemetic most commonly used on day 2 or later, for multiple-day prophylaxis was dexamethasone.

### Analysis of risk factors

Univariate and multivariate logistic regression analyses were performed to determine the degree of delayed CINV risk associated with various CINV-related factors. The multivariate analysis identified the history of nausea and/or vomiting, ECOG performance status score ≥1, acute CINV, and single-day antiemetic prophylaxis as independent risk factors for delayed CINV (Table 3).

### Severity of nausea and amount of food intake

Figures 2 and 3 shows the daily mean VAS scores for severity of nausea and the amount of food intake, respectively, on days 1–5 postchemotherapy. Because the low incidence of vomiting precluded the observation of a visible difference in vomiting, the incidence of nausea alone was assessed. In patients who developed acute CINV, those who underwent multiple-day antiemetic prophylaxis had a lesser reduction in food intake than those who underwent the single-day antiemetic prophylaxis.

### Discussion

This study demonstrated both risk factors and a candidate treatment strategy for delayed CINV in patients with solid cancers undergoing LEC. History of CINV, ECOG performance status score ≥1, CINV in the acute phase, and undergoing single-day prophylactic antiemetics were found to be the independent risk factors for delayed CINV in patients undergoing LEC.

We found that younger age was not a risk factor for CINV; this finding is consistent with previous reports.<sup>17,18</sup> However, it differs from the widely accepted clinical view that younger patients are more prone to CINV than that of older patients. It is possible that age was not identified as a risk factor in this study because of the age strata bias—the median age of the participants in this study was found to be 64 years.

Single-day antiemetic prophylaxis was identified as a risk factor for delayed CINV. Patients undergoing multiple-day

**Table 2** Incidence of delayed CINV

		All patients		Patients who developed acute CINV	
		n	(%)	n	(%)
Single-day (n=132)	DEX day 1	22/89	(24.7)	8/13	(61.5)
	5HT3RA day 1	1/3	(33.3)	0/0	(0)
	5HT3RA day 1+DEX day 1	12/37	(32.4)	3/3	(100)
	PALO day 1+DEX day 1	0/2	(0)	0/0	(0)
	DEX day 1+Meto day 1	1/1	(100)	0/0	(0)
	Total	36/127	(27.3)	11/16	(68.8)
Multiple-day (n=78)	DEX days 1–4	3/43	(7.0)	2/5	(40.0)
	5HT3RA day 1+DEX days 1–4	1/22	(4.5)	0/1	(0)
	PALO day 1+DEX days 1–4	0/2	(0)	0/0	(0)
	5HT3RA day 1+DEX days 1–4+APR days 1–3	2/5	(40)	0/0	(0)
	Other	3/6	(50)	0/0	(0)
	Total	9/78	(11.5)	2/6	(33.3)

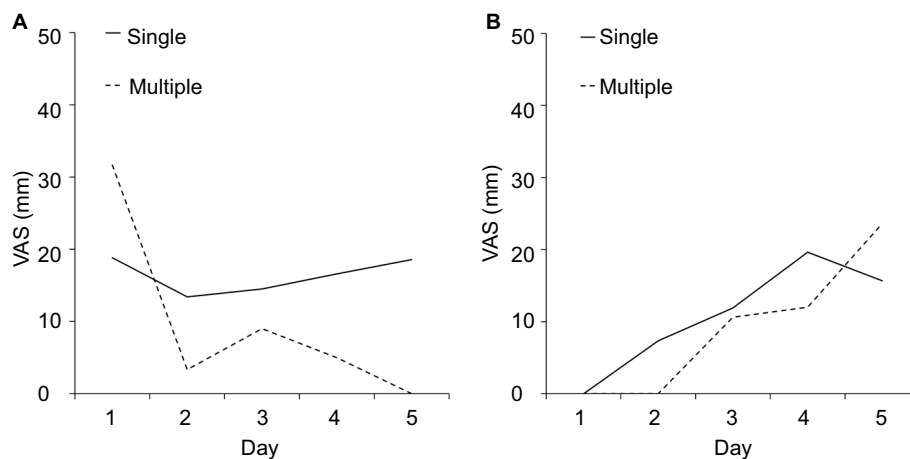
**Abbreviations:** 5HT3RA, the first generation 5-hydroxy-tryptamine 3 receptor antagonist; APR, aprepitant; CINV, chemotherapy-induced nausea and vomiting; DEX, dexamethasone; Meto, metoclopramide; PALO, palonosetron (the second generation 5HT3RA).

**Table 3** Risk factors for delayed CINV

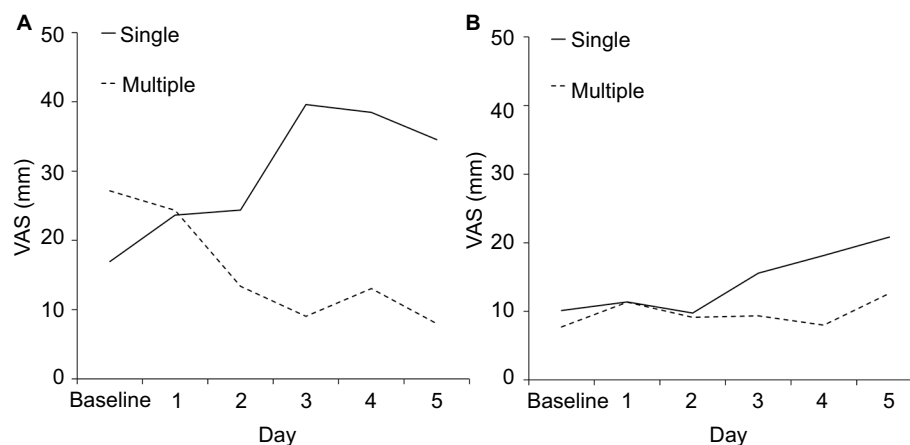
Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex (female)	1.33 (0.67–2.67)	0.42		
CINV history (yes vs no)	1.83 (0.94–3.56)	0.08	3.22 (1.45–7.13)	0.004
Development of acute CINV (yes vs no)	7.04 (2.77–17.86)	<0.001	7.40 (2.76–19.80)	<0.001
Opioid use (yes vs no)	2.33 (0.91–5.97)	0.08		
Motion sickness (yes vs no)	1.22 (0.53–2.82)	0.83		
Morning sickness (yes vs no)	1.17 (0.57–2.39)	0.67		
Alcohol consumption (yes vs no)	0.61 (0.30–1.24)	0.17		
ECOG PS ( $\geq 1$ )	2.11 (1.09–4.19)	0.03	2.23 (1.04–4.78)	0.04
Antiemetic prophylaxis (single-day vs multiple-day)	2.88 (1.30–6.36)	0.01	3.74 (1.49–9.42)	0.01
LEC other than taxane	2.21 (1.11–4.40)	0.02		
Age (per 1-year increase)	1.02 (0.99–1.05)	0.19		

**Note:** Logistic regression analyses were performed using the backward regression method.

**Abbreviations:** CINV, chemotherapy-induced nausea and vomiting; ECOG PS, Eastern Cooperative Oncology Group performance status; LEC, low-emetic-risk chemotherapy; OR, odds ratio.

**Figure 2** Severity of nausea.

**Notes:** Daily mean visual analog scale (VAS) scores for severity of nausea on days 1–5 after the initiation of low-emetic-risk chemotherapy in patients (A) with and (B) without acute chemotherapy-induced nausea and vomiting. The difference in the severity of nausea is shown between the single- and multiple-day antiemetic prophylaxis groups. VAS (100 mm, worst nausea; 0 mm, no nausea).



**Figure 3** Food intake.

**Notes:** Daily mean visual analog scale (VAS) scores for food intake during the first 5 days after the initiation of low-emetic-risk chemotherapy in patients (A) with and (B) without acute chemotherapy-induced nausea and vomiting. The difference in VAS-rated food intakes between the single- and multiple-day antiemetic prophylaxis groups is shown. VAS (100 mm, no oral food intake; 0 mm, eating as usual).

antiemetic prophylaxis experienced delayed CINV less frequently than those undergoing single-day antiemetic prophylaxis. However, the VAS-based evaluation of the severity of nausea revealed that patients experienced only mild nausea; hence, the change of antiemetic treatment, from the single-day to the routine multiple-day prophylaxis, was unnecessary for all patients undergoing LEC. “No significant nausea” has historically been defined as a VAS score <25.<sup>18,19</sup> However, a more robust and modern approach would be to use “no nausea” as the primary endpoint, especially in the context of LEC. This is the most patient-centered clinical outcome; this parameter was also used in a recent study.<sup>20</sup> In this study, we relied on the information provided by the patients when assessing the incidence of nausea. Therefore, we defined a VAS score of 0 mm as “no nausea.”

Of the patients who developed acute CINV, the incidence of delayed CINV was found to be higher in those undergoing single-day antiemetic prophylaxis than those undergoing multiple-day antiemetic prophylaxis. Therefore, acute CINV is a possible predictor of delayed CINV. Patients who underwent multiple-day antiemetic prophylaxis had less severe nausea and lesser reduction in food intake than patients who underwent single-day antiemetic prophylaxis. Molassiotis et al reported the symptom cluster related to nausea as loss of appetite, dry mouth, feeling drowsy and bloated, and vomiting; nausea, rather than vomiting, was associated with the loss of appetite and dry mouth.<sup>21</sup> Olver et al reported that fatigue often accompany chemotherapy-induced nausea.<sup>22</sup> In this study, dexamethasone was the most common antiemetic used to prevent delayed CINV. It improves anorexia and fatigue; thus, it may be useful in

patients experiencing these adverse effects. Ito et al suggested that administration of dexamethasone on days 1–3, compared to only day 1, reduces the incidences of nausea, anorexia, depression, and fatigue during the delayed phase.<sup>23</sup> Thus, in patients who develop acute CINV, dexamethasone may be useful in preventing nausea and anorexia in the delayed phase. However, because dexamethasone has several side effects, including insomnia, indigestion/epigastric discomfort, agitation, and increased appetite,<sup>24,25</sup> we need to be mindful of these side effects when using dexamethasone for delayed antiemetic prophylaxis.

In a randomized controlled trial comparing the efficacy of palonosetron plus dexamethasone on day 1 with or without dexamethasone on days 2 and 3 for the prevention of CINV, patients receiving dexamethasone on multiple days experienced a significantly higher incidence of insomnia than that of patients receiving single-day dexamethasone. In another study, the incidence of adverse events potentially attributable to dexamethasone, such as abdominal pain and hiccups, tended to be lower in the single-day than in the multiple-day dexamethasone group, but this difference was not statistically significant.<sup>26</sup> Therefore, multiple-day dexamethasone could be a candidate alternative prophylactic antiemetic regimen for patients undergoing LEC. However, randomized comparative studies with large patient populations are needed to confirm the efficacy of the salvage treatment. Hesketh et al demonstrated that palonosetron was well tolerated and effectively prevented CINV in both acute and delayed phases in patients with the history of CINV.<sup>27</sup> Although palonosetron is a useful antiemetic treatment option, it is expensive and does not increase the appetite or improve fatigue.

Breakthrough CINV is also an important issue. In this study, rescue antiemetics were administered to 28.9% of the patients with breakthrough CINV during the delayed phase, while metoclopramide was prescribed most frequently in this study (data not shown). Guidelines on breakthrough CINV recommend the use of antiemetics with a different mechanism of action from those used as initial prophylaxis (e.g., dopamine receptor antagonists, glucocorticoids, and antipsychotic or anti-anxiety agents) or a first generation 5-hydroxytryptamine 3 receptor antagonist different from that used as initial prophylaxis.<sup>13–16</sup> However, the recommended treatment is unable to effectively control the breakthrough CINV.<sup>28</sup> Navari et al reported that olanzapine was significantly better than metoclopramide in controlling breakthrough CINV in patients undergoing HEC.<sup>29</sup> As reported, the repeated use of rescue palonosetron is useful in controlling breakthrough CINV in HEC or moderate-emetic-risk chemotherapy, even when it was already used as prophylaxis.<sup>30</sup> However, the repeated use of palonosetron does not appear to be reasonable in LEC from an economic point of view. The antiemetic treatment for breakthrough CINV is not well established, and optimal antiemetic regimen for breakthrough CINV in LEC is still unclear. Further studies are needed to establish the strategy to prevent and suppress breakthrough CINV. However, the novel strategy, multiple-day dexamethasone, as shown in this study, can be expected to reduce the incidence of breakthrough CINV in the delayed phase.

This study has some limitations. First, its design was neither randomized nor blinded, and the sample size was not very large. Second, more than half of the patients in this study had undergone prior chemotherapy treatment. Compared with chemotherapy-naïve patients, previous chemotherapy might have affected the incidence of CINV among patients in this study. Finally, patients who underwent taxane therapy (e.g., docetaxel or paclitaxel) accounted for ~70% of the study population. Despite these limitations, we believe that the results show the risk factors for delayed CINV in routine clinical practice, as opposed to a controlled trial design, and may therefore, be more realistic.

## Conclusion

The current use of antiemetic prophylaxis, according to the recommended guideline, controls the delayed CINV in patients undergoing LEC. However, patients with the identified risk factors (i.e., the history of nausea and/or vomiting, ECOG performance status score  $\geq 1$ , acute CINV, and single-day antiemetic prophylaxis) should be carefully observed, and treatment should be adjusted according to their

symptoms. The use of multiple-day dexamethasone may be beneficial in patients who develop acute CINV, especially when it is accompanied by anorexia.

## Abbreviations

CINV, chemotherapy-induced nausea and vomiting  
 ECOG, Eastern Cooperative Oncology Group  
 HEC, high-emetic-risk chemotherapy  
 LEC, low-emetic-risk chemotherapy  
 VAS, visual analog scale

## Data availability

All datasets supporting the results reported in this article are kept by the corresponding author and can be provided upon reasonable request.

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## Disclosure

The authors report no conflicts of interest in this work.

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