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5HT$_3$RA plus dexamethasone plus aprepitant for controlling delayed chemotherapy-induced nausea and vomiting in colorectal cancer

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Abstract

Delayed chemotherapy-induced nausea and vomiting (CINV) is not well controlled in colorectal cancer (CRC) patients undergoing oxaliplatin (L-OHP)-based chemotherapy. Whether neurokinin-1 receptor antagonist addition to a first-generation 5HT$_3$ antagonist (1st 5-HT$_3$RA) and dexamethasone (DEX) is beneficial to these patients remains controversial. Furthermore, whether palonosetron (PALO) or aprepitant (APR) is more effective in controlling delayed CINV is unclear. We, therefore, investigated whether PALO+DEX or 1st 5-HT$_3$RA+DEX+APR was more effective in controlling delayed CINV, and the risk factors for delayed CINV, in CRC patients undergoing L-OHP–based chemotherapy. Data were pooled from two prospective observational Japanese studies and a phase III trial to compare CINV incidence between the PALO + DEX (PALO) and 5-HT$_3$RA+DEX+APR (APR) groups by propensity score–matched analysis. CINV risk factors were identified using logistic regression models. The CINV incidence was higher in the PALO group than in the APR group. Logistic regression analysis revealed alcohol consumption, motion sickness, and the PALO+DEX regimen as independent risk factors for delayed nausea, and female sex and the PALO+DEX regimen as those for delayed vomiting. Compared with prophylactic PALO + DEX, 1st 5-HT$_3$RA+DEX+APR was more effective in controlling delayed CINV. Thus, CRC patients receiving L-OHP–based chemotherapy should be treated with three antiemetics, including APR.

KEYWORDS

aprepitant, colorectal cancer, nausea, oxaliplatin, vomiting

Abbreviations: 5-HT$_3$Ras, 5-hydroxytryptamine-3 receptor antagonists; APR, aprepitant; CAPOX, capecitabine plus oxaliplatin; CINV, chemotherapy-induced nausea and vomiting; CRC, colorectal cancer; DEX, dexamethasone; ESMO, European Society for Medical Oncology; FOLFOX, fluorouracil plus leucovorin plus oxaliplatin; GRA, granisetron; HEC, high-emetic-risk chemotherapy; L-OHP, oxaliplatin; MEC, moderate-emetic-risk chemotherapy; MST, median survival time; NK1Ras, neurokinin-1 receptor antagonists; OLZ, olanzapine; PALO, palonosetron; RCT, randomized controlled trial.

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1 | INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide.[1] In the late 1990s, oxaliplatin (L-OHP), one of the key drugs for CRC treatment, was developed, and the 5-fluorouracil plus leucovorin plus oxaliplatin (FOLFOX) and capecitabine plus oxaliplatin (CAPOX) regimens were established. Thus far, these regimens have remained the standard cytotoxic drug combinations to provide approximately 20 months or more of median survival time (MST).[2] New molecular targeting agents have been continuously developed, and in combination with cytotoxic drugs such as L-OHP, they provide longer survival, ie, more than 30 months of MST.[3] It is important to note that the improvement in survival has been achieved not only with the development of antitumor agents but also with the development of supportive care.

Chemotherapy-induced nausea and vomiting (CINV) is one of the major adverse events during cancer chemotherapy. With the development of effective antiemetic agents such as 5-hydroxytryptamine-3 receptor antagonists (5-HT_3RAs) and neurokinin-1 receptor antagonists (NK1RAs), the management of CINV has been improving. Palonosetron (PALO) is a second-generation 5-HT_3RA indicated for the prevention of both acute and delayed CINV.[4] It has a higher affinity for the 5-HT_3 receptor and longer half-life than first-generation (1st) 5-HT_3RAs.[5,6] It has been proven superior to 1st 5-HT_3RAs in clinical trials conducted among patients receiving both moderate-emetic-risk chemotherapy (MEC)[7,8] and high-emetic-risk chemotherapy (HEC).[9,10]

Aprepitant (APR) is a selective NK1RA.[11] Several studies have demonstrated that adding APR to doublet antiemetic therapy with a 5-HT_3RA and dexamethasone (DEX) can control CINV in HEC regimens.[12-15] However, in a nationwide, prospective, observational multicenter study, the incidences of delayed nausea and vomiting in CRC patients receiving L-OHP–based chemotherapy were 37.9% and 12.6%, respectively.[16] In a multicenter, randomized controlled trial (RCT) in CRC patients treated with L-OHP–based chemotherapy (SENRI trial),[17] the "no nausea" rates of doublet antiemetic prophylaxis and triplet antiemetic prophylaxis including APR were 61.8% and 66.3%, respectively. In another RCT, the delayed total control (no vomiting, no nausea, and no rescue medication) rate was 48.1% with PALO+DEX.[18] Delayed CINV reduces patients' quality of life,[19] and remains a major problem for many CRC patients receiving L-OHP–based chemotherapy.

In the SENRI trial,[17] complete response and protection in the delayed phase were achieved significantly more often in the triplet group than in the doublet group (85.0% vs 75.4%, and 79.7% vs 69.4%, respectively). Kitayama et al[20] reported that PALO+DEX showed equivalent antiemetic efficacy compared with that of APR plus granisetron (GRA) plus DEX in MEC in a prospective randomized crossover study. Tsuji et al[16] suggested that patients receiving L-OHP–based regimens seem to benefit from doublet therapy involving PALO or triplet therapy involving APR. These results suggest that patients receiving L-OHP–based regimens need doublet or triplet antiemetic prophylaxis with PALO or APR, respectively. However, it is unclear whether PALO or APR is more effective in controlling delayed CINV in CRC patients receiving L-OHP–based chemotherapy. Therefore, in this study, we investigated whether PALO+DEX or 1st 5-HT_3RA+DEX+APR was more effective in controlling delayed CINV, as well as the risk factors for delayed CINV, in CRC patients treated with L-OHP–based chemotherapy.

2 | MATERIALS AND METHODS

2.1 | Study design

Pooled data of 404 patients who participated in two multicenter, prospective observational studies[21,22] and one randomized trial[17] were analyzed. Individual study results were previously published or presented at the annual meeting of the European Society for Medical Oncology (ESMO). The study flowchart is shown in Figure 1. The studies were conducted in patients who were scheduled to receive L-OHP–based chemotherapy (FOLFOX or CAPOX) in Japan and were approved by the institutional review board or independent ethics committee of the sites involved in the studies. Written informed consent was obtained from all participating patients before any related study procedure was initiated. All procedures performed were in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

2.2 | Data collection

Any nausea and vomiting developing within 24 hours after chemotherapy was defined as acute CINV, while nausea and vomiting developing between 24 hours and 7 days after the start of the chemotherapy as delayed CINV. Patients enrolled in any of the three studies were required to be at least 20 years of age, have CRC, and be chemotherapy-naïve. Data collection included data from the 7-day diaries started by the patients on the day of chemotherapy; the CINV data were based on patient self-reports in the diaries. Eligible patients received an L-OHP–based regimen as chemotherapy, and PALO + DEX (PALO group) or 1st 5-HT_3RA + DEX+APR (APR group) as antiemetic prophylaxis, which was administered within 1 h before the scheduled chemotherapy.

2.3 | Statistical analysis

Patient demographics and the incidence of CINV were analyzed using descriptive statistics (Chi-square test). Propensity score matching was used to reduce the imbalance between the PALO and APR groups. Propensity scores to determine matched pairs between the groups were obtained using five variables (age, sex, drinking habit, a history of motion sickness, and antiemetic prophylaxis) that could potentially influence the development of CINV among patients with

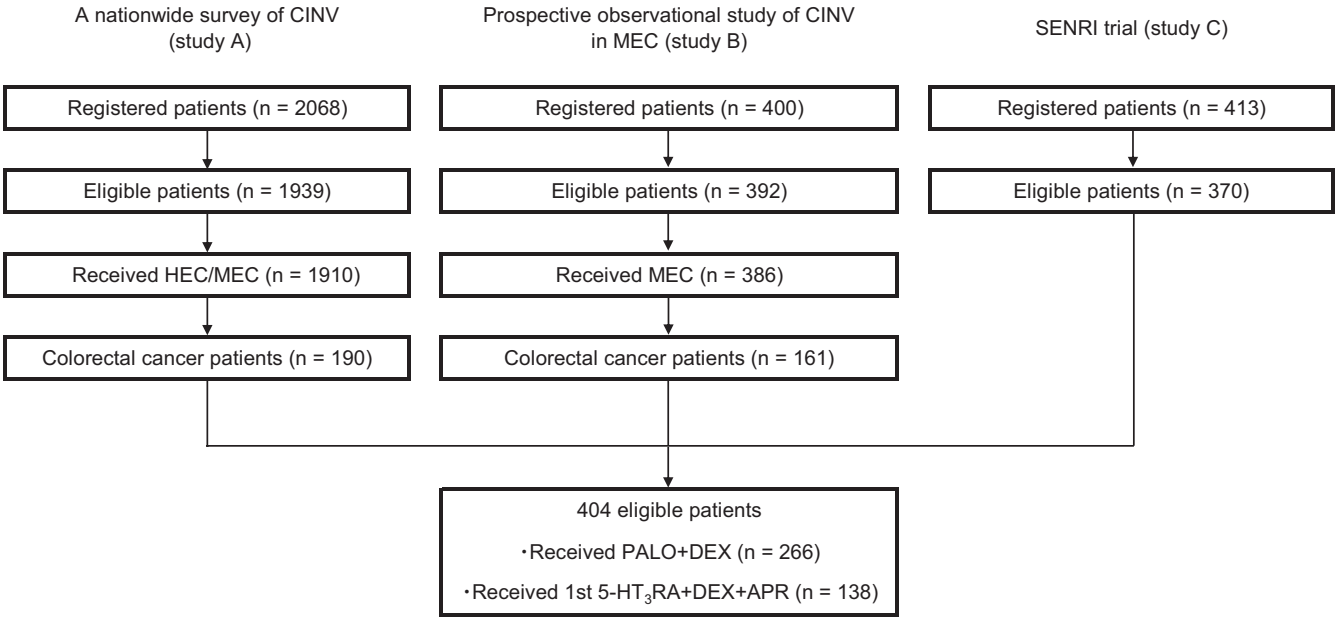

FIGURE 1 Patient selection diagram. A total of 404 colorectal cancer patients who received oxaliplatin-based chemotherapy were selected from a total of 2881 patients in two prospective observational studies and a randomized controlled trial. APR, aprepitant; CINV, chemotherapy-induced nausea and vomiting; DEX, dexamethasone; HEC, high-emetic-risk chemotherapy; 1st 5-HT3RA, first-generation 5-hydroxytryptamine-3 receptor antagonists; MEC, moderate-emetic-risk chemotherapy; PALO, palonosetron

lung cancer. The scores were evaluated using a logistic regression model in this study. Patients were matched at a 1:1 ratio by using the caliper matching method within 0.2 of the standard deviation from the propensity score logit.

Independent risk factors for CINV were evaluated using logistic regression analysis with the backward elimination method. $P < .05$ (two-sided) was considered significant, except for independent risk factors (significance level was $P < .1$). All statistical analyses were performed using SAS 9.4 (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics

A total of 272 patients were included in the analysis: 136 received PALO+DEX and 136 received 1st 5-HT_3RA+DEX+APR. Patients' baseline characteristics, including sex, age, motion sickness, and drinking habits, are shown in Table 1.

3.2 | Propensity score matching analysis

Propensity score matching was used to adjust for differences in the patients' baseline characteristics that could potentially influence the development of CINV between the two groups. The matching was done at a ratio of 1:1, and we obtained the score-matched pairs for subsequent analyses. After propensity score matching, variables between the two groups were found to not be significantly different (Table 1).

3.3 | Control of CINV

The propensity score–matched incidence patterns of nausea and vomiting after chemotherapy are shown in Figure 2. The incidence of delayed vomiting significantly differed between the PALO and APR groups (12.5% vs 4.4%, $P = .017$). The incidence of nausea did not significantly differ between the PALO group (43.4%) and the APR group (32.4%).

3.4 | Risk factors for CINV

The results of the univariate and multivariate logistic regression analyses of risk factors for delayed CINV are shown in Table 2. Sex, age, drinking habits, motion sickness, and antiemetic prophylaxis were analyzed. Motion sickness, drinking habit, and the PALO + DEX regimen were identified as risk factors for delayed nausea, while female sex and the PALO + DEX regimen were identified as risk factors for delayed vomiting.

4 | DISCUSSION

In the present study, we evaluated whether PALO or APR was useful for preventing delayed CINV in CRC patients treated with L-OHP–based chemotherapy. Compared with prophylaxis with PALO+DEX, prophylaxis with 1st 5-HT_3RA+DEX+APR significantly reduced the incidence of delayed vomiting. Along with female sex, the PALO+DEX regimen was identified as a risk factor for delayed vomiting. Although there was no significant difference in the incidence

TABLE 1 Patient characteristics

	Before propensity score matching					After propensity score matching				
	PALO group (N = 266)		APR group (N = 138)			PALO group (N = 136)		APR group (N = 136)		
Characteristics	n	(%)	n	(%)	*P*-value	n	(%)	n	(%)	*P*-value
Sex										
Male	154	(57.9)	81	(58.7)	0.877	67	(49.3)	80	(58.8)	0.114
Female	112	(42.1)	57	(41.3)		69	(50.7)	56	(41.2)	
Age, years										
<60	104	(39.1)	40	(29.0)	0.044	40	(29.4)	40	(29.4)	1.000
≥60	162	(60.9)	98	(71.0)		96	(70.6)	96	(70.6)	
Motion sickness										
No	228	(85.7)	116	(84.1)	0.417	113	(83.1)	114	(83.8)	0.979
Yes	34	(12.8)	22	(15.9)		22	(16.2)	22	(16.2)	
Drinking habit										
No	160	(60.2)	108	(78.3)	<0.001	108	(79.4)	108	(79.4)	1.000
Yes	104	(39.1)	28	(20.3)		28	(20.6)	28	(20.6)	

Abbreviations: APR, aprepitant; PALO, palonosetron.

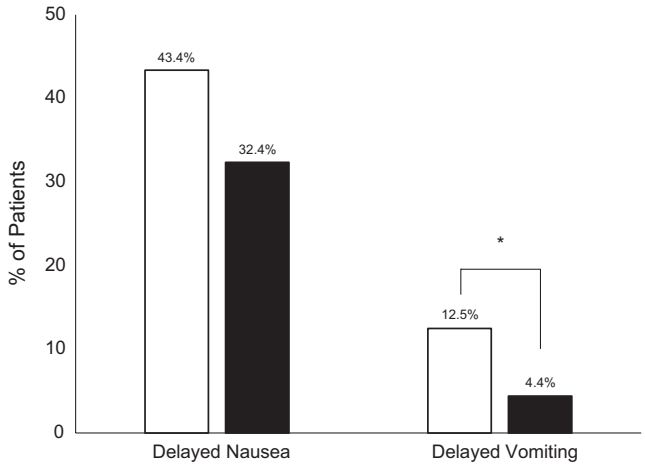

FIGURE 2 Incidence of nausea and vomiting. The incidence of delayed nausea and vomiting. White bars denote the palonosetron (PALO) + dexamethasone (DEX) regimen (PALO group), while black bars indicate the first-generation 5-hydroxytryptamine-3 receptor antagonists (1st 5-HT3RA) + DEX + aprepitant (APR) regimen (APR group). The incidence of delayed vomiting was significantly lower in the APR group than in the PALO group

of delayed nausea between the two groups, the PALO+DEX regimen was identified as a risk factor for delayed nausea, along with motion sickness and drinking habit.

The benefit of adding NK1RAs to a conventional doublet antiemetic prophylaxis remains controversial for MECs other than carboplatin-based regimens, and recommendations for using NK1RAs with MEC vary among guidelines.[23-25] Because few clinical trials have attempted to determine the optimal antiemetic prophylaxis for CRC patients receiving L-OHP–based regimens, evidence-based guidance in this setting is lacking.

Hesketh et al[26] reported that the addition of single-dose casopitant did not improve the overall control of CINV in patients receiving L-OHP–based MEC. Excellent control of CINV was achieved with the combination of ondansetron and DEX in this study population. On the other hand, Nishimura et al[17] reported that triplet antiemetic prophylaxis including APR was more effective than doublet antiemetic prophylaxis in preventing CINV in CRC patients receiving L-OHP–based regimens. In addition, the overall antiemetic effects of APR with or without PALO did not significantly differ. A recent meta-analysis[27] indicated that the addition of NK1RAs for patients undergoing L-OHP–based chemotherapy did not have a very pronounced effect. However, the two major studies cited above[17,26] that included CRC patients with similar L-OHP doses showed conflicting results. In the study by Hesketh et al,[26] the use of casopitant instead of APR may also have affected the difference in results. There are other reports that PALO+DEX or triplet antiemetic prophylaxis with APR is needed to control delayed CINV in patients receiving L-OHP–based chemotherapy.[16,20] A 10% absolute difference in the rates of nausea and vomiting seems to be clinically meaningful to the patient as defined by Multinational Association of Supportive Care in Cancer/ESMO.[28] In this study, the APR regimens reduced the incidence of delayed vomiting by 8.09% and that of delayed nausea by 11.03%, compared with the PALO group.

In this study, patients receiving 1-day DEX, not multi-day (3 or 4 days) DEX, accounted for 9.5% and 14.9% of the patients in the APR and PALO groups, respectively. A DEX-sparing strategy of antiemetic prophylaxis consisting of PALO + 1-day DEX for the prevention of CINV has been studied previously.[18,29,30] A meta-analysis[31] indicated that a DEX-sparing antiemetic regimen was not associated

TABLE 2 Risk factors for delayed nausea and vomiting

	Delayed nausea				Delayed vomiting			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex	1.792	0.005			3.426	<0.001	3.612	<0.001
Female vs male	(1.196-2.685)				(1.790-6.558)		(1.867-6.985)	
Age, years	1.360	0.145			1.392	0.294		
<60 vs ≥ 60	(0.900-2.056)				(0.750-2.582)			
Drinking habit	1.628	0.029	1.941	0.005	1.502	0.249		
No vs yes	(1.052-2.520)		(1.227-3.072)		(0.752-2.999)			
Motion sickness	2.391	0.003	2.606	0.002	1.542	0.282		
Yes vs no	(13.45-4.251)		(1.444-4.703)		(0.701-3.394)			
Antiemetics	1.570	0.039	1.983	0.003	4.009	0.002	4.184	0.002
PALO group vs APR group	(1.023-2.411)		(1.257-3.129)		(1.657-9.696)		(1.711-10.232)	

Abbreviations: APR, aprepitant; CI, confidence interval; OR: odds ratio; PALO, palonosetron.

with a significant loss in antiemetic control in patients undergoing MEC including L-OHP–based regimens, irrespective of the known risk factors for CINV. Therefore, differences in the dosing period of DEX do not appear to affect the results of this study.

Triplet antiemetic prophylaxis including APR has been reported to be promising from an economic perspective in Japan. Toda et al[32] reported that the antiemetic efficacy and cost-effectiveness of a three-drug combination involving APR, generic GRA, and DEX was superior to those of a two-drug combination involving PALO and DEX in patients who received MEC. Risk/benefit profiles and medication costs are important factors influencing treatment decisions, including antiemetic treatment.

The assessment of individual risk factors is an important step in the development of personalized treatments for CINV. Younger age, female sex, motion sickness, and a drinking habit are well-known patient-related risk factors for CINV in patients with various cancers.[16,21,33-35] In the present study, a drinking habit and history of motion sickness were identified as patient-related risk factors for delayed nausea. Female sex was identified as a patient-related risk factor for delayed vomiting. Moreover, previous studies have identified female sex as a strong risk factor for vomiting.[16,22,34] In this context, it is noteworthy that the doublet antiemetic prophylaxis, PALO+DEX, has been identified as an independent risk factor for both nausea and vomiting, along with these well-known patient-related risk factors.

Even with triplet antiemetic prophylaxis including APR, delayed CINV, particularly nausea, remains an important issue, and a salvage antiemetic treatment should be considered for high-risk patients. The overall antiemetic effects of APR did not significantly differ depending on whether it was combined with PALO or 1st 5-HT3RA in CRC patients undergoing L-OHP–based chemotherapy.[17] In patients receiving MEC, PALO and 1st 5-HT_3RA might have an equivalent effect on CINV control when used in combination with NK1RA and DEX.[17,36] Improvement in antiemetic treatments involving combinations of antiemetic agents with different mechanisms of action, such as olanzapine (OLZ), is needed for patients in whom risk factors for CINV have been identified.

OLZ is classified as a multiacting receptor-targeted antipsychotic that blocks dopamine D1, D2, D3, and D4 receptors; 5-TH2A, 5-HT2B, 5-HT3, and 5-HT6 receptors; histamine H1 receptors; and muscarinic acetylcholine receptors M1, M2, M3, and M4.[37] OLZ activity at multiple receptors that may be involved in nausea and vomiting suggests that it might have clinically significant antiemetic properties. Navari et al[37] revealed that the use of OLZ 10 mg significantly improved nausea prevention as well as the complete response rate among patients who were receiving HEC. Hashimoto et al[38] reported that OLZ 5 mg combined with APR, PALO, and DEX was more effective compared with placebo combined with these agents in patients undergoing cisplatin-based chemotherapy. Although the evidence on the effectiveness of OLZ for CINV management in MEC is insufficient, more aggressive antiemetic treatment options such as quadruple therapy including OLZ may be considered for these patients.

The present study has some limitations. First, it is not a blind RCT. Second, risk factors such as smoking habit and morning sickness could not be analyzed. Finally, the results of this study were obtained from the Japanese population. However, they are likely applicable to other Asian populations. Further research is needed to verify whether these results could be extrapolated to other populations. Despite these limitations, the findings indicate the basic antiemetic prophylaxis for L-OHP–based chemotherapy. Because data with a sufficient number of events from three prospective studies including an RCT have been analyzed using propensity score–matched analysis, it is considered to be of high quality.

In conclusion, treatment with the triplet antiemetic prophylaxis, involving APR, was more effective in controlling delayed CINV than prophylaxis with PALO+DEX. Thus, CRC patients receiving L-OHP–based chemotherapy should be treated with three antiemetics, including APR.

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DISCLOSURE

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