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Symptom Management and Supportive Care

Efficacy of Prophylactic Treatment for Oxycodone-Induced Nausea and Vomiting Among Patients with Cancer Pain (POINT): A Randomized, Placebo-Controlled, Double-Blind Trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Opioid-induced nausea and vomiting • Prophylaxis • Antiemetics • Cancer pain • Oxycodone • Prochlorperazine

Abstract

Background. Although opioid-induced nausea and vomiting (OINV) often result in analgesic undertreatment in patients with cancer, no randomized controlled trials have evaluated the efficacy of prophylactic antiemetics for preventing OINV. We conducted this randomized, placebo-controlled, double-blind trial to evaluate the efficacy and safety of prophylactic treatment with prochlorperazine for preventing OINV.

Materials and Methods. Cancer patients who started to receive oral oxycodone were randomly assigned in a 1:1 ratio to receive either prochlorperazine 5 mg or placebo prophylactically, given three times daily for 5 days. The primary endpoint was the proportion of patients who had a complete response (CR) during the 120 hours of oxycodone treatment. CR was defined as no emetic episode and no use of rescue medication for nausea and vomiting during 5 days. Key secondary endpoints were the proportion of patients with emetic episodes, proportion of patients with moderate or severe nausea, quality of life, and proportion of treatment withdrawal.

Results. From November 2013 through February 2016, a total of 120 patients were assigned to receive prochlorperazine ($n = 60$) or placebo ($n = 60$). There was no significant difference in CR rates (69.5% vs. 63.3%; $p = .47$) or any secondary endpoint between the groups. Patients who received prochlorperazine were more likely to experience severe somnolence ($p = .048$).

Conclusion. Routine use of prochlorperazine as a prophylactic antiemetic at the initiation of treatment with opioids is not recommended. Further research is needed to evaluate whether other antiemetics would be effective in preventing OINV in specific patient populations. ***The Oncologist*** 2018;23:367–374

Implications for Practice: Prophylactic prochlorperazine seems to be ineffective in preventing opioid-induced nausea and vomiting (OINV) and may cause adverse events such as somnolence. Routine use of prophylactic prochlorperazine at the initiation of treatment with opioids is not recommended. Further research is needed to evaluate whether other antiemetics would be effective in preventing OINV in specific patient populations.

Introduction

Pain is one of the most common symptoms in patients with cancer [1–3]. About 38% to 80% of patients with advanced cancer experience moderate to severe pain [1–3], and opioids are generally effective for alleviating cancer pain [4–6]. However, the use of opioids often causes nausea and vomiting, especially during the early period of treatment. Opioid-induced nausea and vomiting (OINV) occur in up to 60% of patients who start to receive opioids [7–11].

Although many patients eventually develop tolerance to this side effect, nausea and vomiting during the early phase of treatment often lead patients to discontinue their opioid therapy, resulting in analgesic undertreatment [9–11]. Thus, appropriate management of OINV is expected to improve patient compliance, enhance analgesic efficacy, reduce opioid-induced complications, and improve the overall quality of life (QOL) [9–11].

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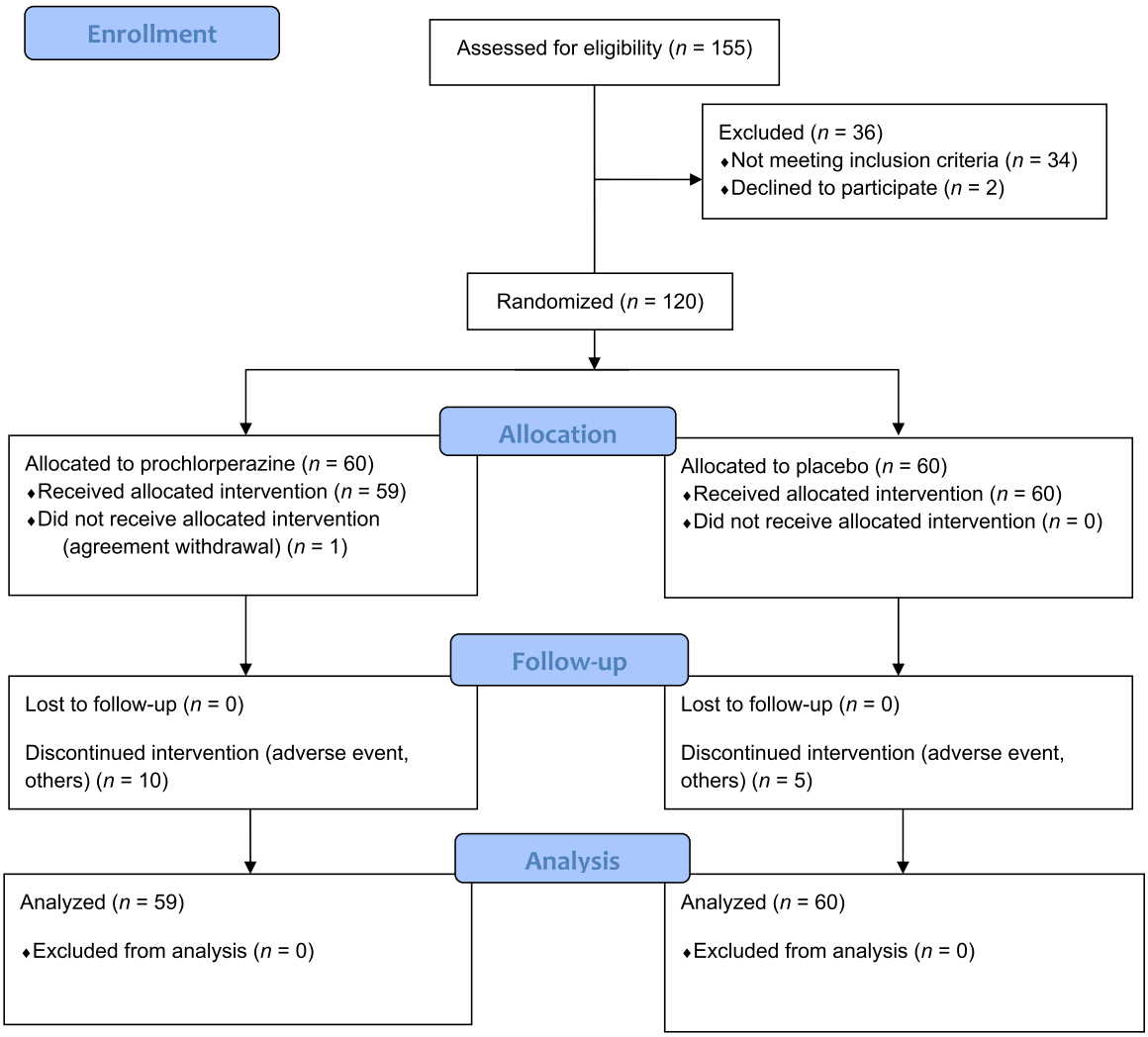

Figure 1. CONSORT 2010 Flow Diagram. Screening, randomization, and follow-up.

The efficacy of prophylactic antiemetics in patients with cancer has been tested in various clinical settings, including chemotherapy, radiation therapy, surgical procedures, and parenteral morphine administration in an emergency setting [12–15]. However, the efficacy of prophylactic antiemetics for the prevention of OINV in patients with cancer pain remains to be fully elucidated [16–21]. To date, several preliminary observational studies have investigated the efficacy of antiemetic prophylaxis against OINV among patients with cancer pain [16–20]. However, to our knowledge, no randomized controlled trial has evaluated the efficacy of prophylactic treatment with antiemetics for the prevention of OINV [22].

In particular, a placebo controlled trial is lacking, and the use of placebo as a commentator is of importance. We thus conducted this randomized, placebo-controlled, double-blind trial to evaluate the efficacy and safety of prophylactic antiemetic treatment with prochlorperazine for the prevention of OINV in patients with cancer.

Subjects, Materials, and Methods

Study Design and Participants

This study was a single-center, double-blind, 1:1 placebo-controlled, randomized trial designed to evaluate the efficacy of oral prochlorperazine for the prevention of nausea and vomiting in patients receiving oral oxycodone for cancer pain. The study was approved by the Ethics Committee at Nagoya University Hospital and was conducted according to the Declaration of Helsinki. All patients provided written informed consent for participation in this study prior to enrollment. The study is registered at University Hospital Medical Information Network (UMIN000012502).

Patients with cancer of any primary site who required oral oxycodone were enrolled in this study. The eligibility criteria included an age of $\geq$20 years, a life expectancy of 1 month or longer, an Eastern Cooperative Oncology Group (ECOG) performance status [23] of 0 to 3, aspartate transaminase and alanine transaminase levels $\leq$5$\times$ the upper limit of the normal range in the institution (ULN), a total bilirubin level of $\leq$3$\times$ ULN, and a creatinine clearance (Cockcroft-Gault) of $\geq$30 mL/min. Patients were excluded if they were already receiving any strong opioids (i.e., morphine, oxycodone, fentanyl, or methadone); had vomiting, retching, or nausea of any causes; had received radiotherapy to the head, abdomen, or pelvis within 6 days before and during the study period; had received new drugs with emetic or antiemetic action within 48 hours before study initiation; or had a history of hypersensitivity or any contraindication to prochlorperazine.

Table 1. Patient characteristics

Characteristic	Prochlorperazine group ($n = 60$)	Placebo group ($n = 60$)	All patients ($n = 120$)
Age, years, median (range)	69.5 (33–81)	70.0 (38–88)	70.0 (33–88)
Sex			
Male	37	38	75
Female	23	22	45
Primary tumor site			
Lung	19	23	42
Breast	5	7	12
Kidney, urinary tract	8	4	12
Head and neck	6	3	9
Pancreas	5	4	9
Colon	3	4	7
Liver	2	4	6
Soft tissue	1	5	6
Bile duct	3	2	5
Stomach and esophagus	3	1	4
Skin	2	2	4
Unknown	1	1	2
Uterus	1	0	1
Adrenal cortex	1	0	1
ECOG performance status			
0	9	8	17
1	25	26	51
2	14	10	24
3	12	16	28
Pain intensity (worst 11-point NRS)			
Mean	7.17	7.48	7.30
SD	1.90	1.94	1.91
Anticancer treatment			
None	45	43	88
Cytotoxic	3	3	6
Molecular-targeted drugs	3	3	6
Immune checkpoint inhibitor	1	0	1
Radiotherapy	8	11	19
History of opioid therapy			
Opioid naïve	43	43	86
Weak opioids (tramadol)	17	17	34
Concomitant medication[a]			
Nonopioid analgesics	52	53	105
Coanalgesics (pregabalin)	12	9	21
Steroids	8	7	15
Anxiolytics/antipsychotics	10	14	24
Total oxycodone dose (mg)[a]			
Mean	75.42	81.46	78.46
SD	39.99	56.97	49.17

[a]All oxycodone consumption during study period. $n = 119$. One patient in the prochlorperazine group withdrew consent after randomization.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NRS, numeric rating scale; SD, standard deviation.

We also excluded patients who had received new chemotherapeutic agents for at least 1 week or longer before treatment with the study drug and during the study period. Patients who had received palonosetron or fosaprepitant within the last 120 hours, aprepitant within the last 72 hours, and steroids or 5-HT3 antagonists within the last 48 hours as a part

Table 2. Primary and secondary endpoints

Endpoints	Prochlorperazine group ($n = 59$)	Placebo group ($n = 60$)	p value
Primary endpoint			
Complete response: *n* (%)	41 (69.5)	38 (63.3)	.47
Secondary endpoints			
Patients with at least one emetic episode in 5 days, *n* (%)	14 (23.7))	16 (26.7)	.71
Patients requiring at least one rescue antiemetic in 5 days, *n* (%)	14 (23.7)	16 (26.7)	.71
Number of emetic episodes in patients with at least one emetic episode[a], median (range)	1.5 (1–7)	1.0 (1–7)	.79
Nausea (worst in 5 days)			
Present (≥1), *n* (%)	23 (39.0)	31 (51.7)	.16
Moderate (≥4), *n* (%)	17 (28.8)	21 (35.0)	.47
Severe (≥7), *n* (%)	6 (10.2)	10 (16.7)	.30
Quality of life (EORTC-C15-PAL), score (SD)			
Global health status	9.0 (21.7)	10.2 (17.5)	.76
Physical function	−1.7 (21.0)	0.6 (12.3)	.48
Emotional function	1.7 (16.0)	2.8 (16.1)	.70
Appetite	4.0 (26.3)	9.6 (24.8)	.23
Constipation	14.1 (34.6)	18.6 (32.9)	.47
Pain	−28.3 (26.3)	−26.8 (23.8)	.76
Dyspnea	−1.7 (13.0)	−2.8 (16.7)	.68
Sleep	−26.6 (32.6)	−26.6 (29.5)	1.00
Fatigue	−0.3 (20.6)	−1.1 (16.9)	.81
Nausea	20.9 (34.4)	17.0 (28.6)	.50
Treatment withdrawal, *n* (%)	10 (17.0)	5 (8.3)	.16

Complete response was defined as no emetic episode and no use of rescue medication for nausea and vomiting for 5 days. EORTC-C15-PAL: quality of life (QOL) scores were analyzed by analysis of covariance including treatment group and baseline QOL as covariates; variables were analyzed using a chi-square test or Mann-Whitney *U* test.

[a]The analysis was carried out among the patients who had at least one emetic episode (prochlorperazine group, $n = 14$; placebo group, $n = 16$).

Abbreviations: EORTC-C15-PAL, European Organisation for Research and Treatment of Cancer quality of life questionnaire for palliative care cancer patients; SD, standard deviation.

of chemotherapy-induced nausea and vomiting prophylaxis were also excluded.

Although we had acknowledged that a history of exposure to weak opioids could confound the results, we did not exclude patients who had used weak opioids (i.e., codeine and tramadol) in order to maximize patient enrollment and to more closely reflect the real-world situation, in which patients often will have received weak opioids before receiving oxycodone.

Randomization and Masking

Patients who satisfied all study entry criteria were randomly assigned (1:1) to the prochlorperazine group or the placebo group by a web-based randomization system using a stratified randomized model. Randomization was stratified according to sex, age (≤55, 56–69, ≥70 years), ECOG performance status (PS: 0, 1 vs. 2, 3), and pain score (numerical rating scale [NRS]: ≥7 vs. <7). A double-blind technique was used with a placebo identical in appearance to prochlorperazine tablets, which were encapsulated. The encapsulated prochlorperazine and placebo capsules were manufactured by an unblinded pharmacist who was not involved in providing direct care to the study patients.

Procedures

All patients received oral sustained-release oxycodone (5 mg or 10 mg) twice daily for cancer pain (10 mg/day or 20 mg/day). Patients were randomly assigned to receive either prochlorperazine 5 mg or matched placebo orally three times daily for 5 days (15 mg/day). The initial dose of prochlorperazine or placebo was administered 30 to 60 minutes before the administration of the initial dose of oxycodone on day 1. The rationale for choosing prochlorperazine as an antiemetic for this study included the following: (a) there was no empirical evidence one antiemetic could be superior to others for the management of OINV [22], (b) some international clinical guidelines and reviews list prochlorperazine as one of the first-line medications for OINV [6, 7], and (c) prochlorperazine is the most common antiemetic used in this setting in Japan [16–21].

The use of immediate-release oxycodone as rescue medication, as well as increasing the dose of sustained-release oxycodone, was allowed at any time depending on the pain intensity. For patients who developed nausea and vomiting, metoclopramide, haloperidol, domperidone, or chlorpheniramine maleate was used for rescue treatment according to the preference of the treating physician.

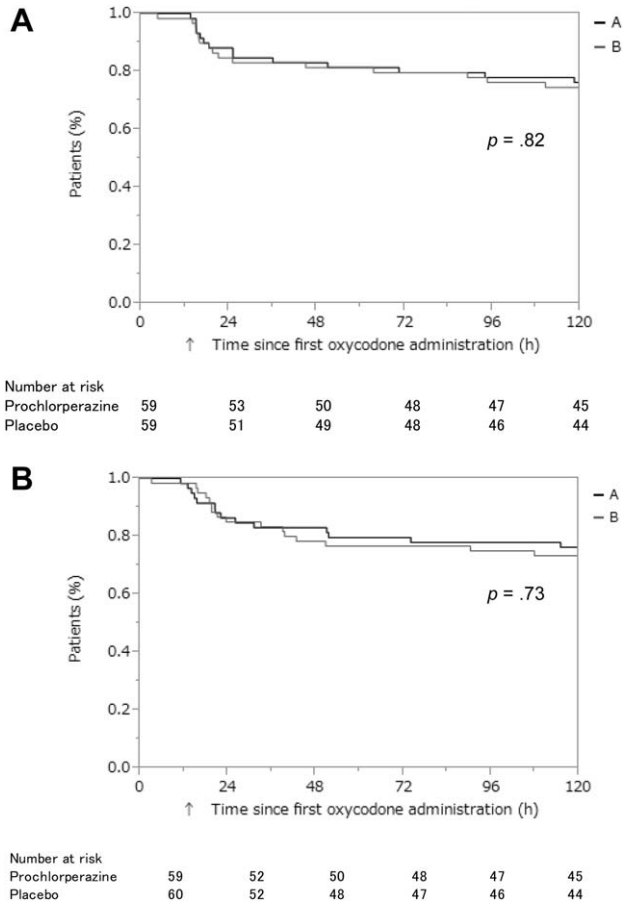

Figure 2. Time to first emetic episode and first rescue antiemetic medication. Time-to-event endpoints were analyzed using Kaplan-Meier methods and were tested using the log-rank test. **(A)**: Time to first emetic episode. **(B)**: Time to first rescue antiemetic medication.

Abbreviations: A, Prochlorperazine group; B, Placebo group; h, hours.

Patients completed a daily diary during the study period of 5 days every 24 hours, which included information on the presence or absence of emetic episodes (if present, the times when episodes occurred), the use of rescue antiemetics (if required, the time when used), oxycodone dosage, the intensity of worst nausea according to an 11-point Likert-type NRS from 0 (none) to 10 (worst), and adverse effects. The NRS of nausea was formatted according to the Japanese version of the Edmonton Symptom Assessment Schedule [24, 25]. Compliance of outpatients with diary completion was checked via telephone contact. The QOL data were recorded by the patients before the study and on day 7 after the study period using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL questionnaire [26, 27].

Outcome Measures

Owing to the lack of established outcome measures in this setting, we decided to adopt commonly used outcome measures for chemotherapy-induced nausea and vomiting [28, 29]. The primary endpoint of this study was the proportion of patients who had a complete response (CR) during the 120 hours of treatment with oxycodone [28, 29]. CR was defined as no emetic episode and no use of rescue medication for nausea and vomiting. An emetic episode was defined as one episode of vomiting or retching. Distinct emetic episodes were defined as episodes that were separated by the absence of emesis or retching for 5 minutes or longer [28, 29].

Furthermore, we investigated multiple secondary endpoints as follows: the proportion of patients who had at least one emetic episode during the study period; the proportion of patients who required rescue antiemetics during the study period; the cumulative number of emetic episodes in patients who had at least one emetic episode during the study period; the proportions of patients with nausea, moderate nausea ($\geq$4), and severe nausea ($\geq$7) [30]; QOL as assessed by the EORTC QLQ-C15-PAL questionnaire; the proportion of patients in whom oxycodone treatment was withdrawn for any reason; and the times to the first emetic episode and the first use of rescue antiemetics for nausea and vomiting. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.0) [31].

EORTC QLQ-C15-PAL is a QOL questionnaire designed for use in patients receiving palliative care [26, 27]. This questionnaire includes two functional subscales (emotional and physical), seven symptom subscales (e.g., nausea/vomiting, pain), and an overall QOL question. Each subscale is converted to a score of 0–100. High scores on a functional subscale correspond to better functioning, while high scores on a symptom subscale correlate with increased symptom burden.

Statistical Analysis

Previous observational studies estimated that nausea, vomiting, or both developed in 8% to 36% of the patients who received opioids with prophylactic antiemetics [16, 17, 20], as compared with 26% to 67% of untreated patients or the study group as a whole [4, 7–10, 16, 17]. Therefore, we assumed a CR rate of 80% in the prochlorperazine group and 55% in the placebo group and calculated that at least 108 patients would have to be accrued for the study to have an 80% power to detect significant differences between the groups in the primary endpoint at a two-sided significance level of 5%, using the χ^2 test. To allow for an estimated withdrawal or dropout rate of 10%, a target sample size of 120 patients (60 per arm) was selected.

Analyses of the efficacy results were performed on an intention-to-treat basis. Safety was evaluated in patients who received at least one dose of the study drug. No interim analyses were performed. The proportion of patients with a CR was calculated for each group and compared using the χ^2 test. As secondary endpoints, the proportions of patients with emetic episodes, patients requiring rescue antiemetics, patients with nausea (any, moderate, severe), and patients in whom treatment was withdrawn were calculated for each group and compared using the χ^2 test. The number of emetic episodes was compared between the groups using the Mann-Whitney *U* test. Time-to-event endpoints (i.e., first emetic episode and first use of rescue antiemetics) were analyzed using Kaplan-Meier methods and were tested using the log-rank test. An analysis of covariance model was used to analyze data from the EORTC QLQ-C15-PAL questionnaire, including treatment group and baseline QOL as covariates.

Subgroup analyses with respect to the primary endpoint were performed and included gender, primary tumor site, opioid-naïve status, and initial oxycodone dose as factors. Adverse events were analyzed with the use of the Cochran-

Table 3. Subgroup analyses

Subgroup	Prochlorperazine group ($n = 59$), n (%)	Placebo group ($n = 60$), n (%)	p value
Sex			
Male ($n = 74$)	27/36 (75.0)	24/38 (63.2)	.27
Female ($n = 45$)	14/23 (60.9)	14/22 (63.6)	.85
Primary tumor site			
Digestive system[a] ($n = 31$)	9/16 (56.3)	8/15 (53.3)	.87
Lung ($n = 41$)	15/18 (83.3)	16/23 (69.6)	.31
Opioid naïve or not			
Naïve ($n = 85$)	29/42 (69.1)	26/43 (60.5)	.41
Not naïve ($n = 34$)[b]	12/17 (70.6)	12/17 (70.6)	1.00
Oxycodone dose[c]			
10 mg ($n = 110$)	40/56 (71.4)	37/54 (68.5)	.74
20 mg ($n = 9$)	1/3 (33.3)	1/6 (16.7)	.57

Complete response rates are shown.
[a]Stomach, esophagus, colon, liver, bile duct, and pancreas. Analyzed using a chi-square test.
[b]All patients used tramadol.
[c]Initial starting dose of oxycodone (daily dose).

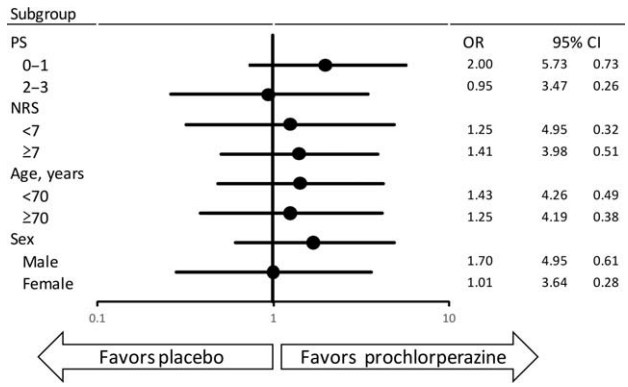

Figure 3. Forest plots of complete response
Abbreviations: CI, confidence interval; NRS, numeric rating scale; OR, odds ratio; PS, performance status.

Armitage trend test. All tests were two-sided, and p values of less than .05 were considered to indicate statistical significance. Statistical analyses were performed using JMP 11 software (SAS Institute, Inc., Cary, NC, www.sas.com).

Results

From November 2013 through February 2016, a total of 156 patients were screened, and 120 were randomly assigned, in a 1:1 ratio, to receive prochlorperazine ($n = 60$) or placebo ($n = 60$; Fig. 1). One patient in the prochlorperazine group withdrew consent after the collection of baseline data and was excluded from the efficacy analysis. Baseline patient characteristics were balanced between the groups (Table 1). The median age was 70.0 years, 63% of the patients were men, and the most common site of cancer was the lung (35%) followed by the breast (10%). The majority of patients were opioid naïve (72%).

Efficacy

There was no significant difference in the CR rate between the prochlorperazine group and the placebo group (69.5% vs. 63.3%, $p = .47$; Table 2). There was also no significant difference in any secondary endpoints between the groups (Table 2). Prochlorperazine had no impact on the median time to the first emetic episode or the first use of rescue antiemetic medication as compared with placebo (21.8 hours vs. 19.5 hours, $p = .82$; 21.3 hours vs. 22.3 hours, $p = .73$; Fig. 2). Ten patients in the prochlorperazine group discontinued the study because of severe vomiting ($n = 5$), delirium ($n = 2$), poor pain control ($n = 2$), or drug-induced hepatic dysfunction ($n = 1$). In the placebo group, five patients discontinued the study because of severe vomiting ($n = 3$), poor pain control ($n = 1$), or off-protocol drug use ($n = 1$).

On subgroup analyses, the CR rate did not differ significantly between the prochlorperazine group and placebo group in any subgroups investigated (Table 3). The CR rates in patients with cancer of the digestive system (stomach, esophagus, colon, liver, bile duct, and pancreas) were lower than the CR rate in patients with lung cancer. Additional subgroup analysis by the stratification factor in forest plots revealed no statistically significant interaction of CR (Fig. 3).

Adverse Events

Adverse events were reported in 58 (98.3%) patients in the prochlorperazine group and 57 (95%) patients in the placebo group. The most common adverse events were somnolence (72.3%), constipation (65.5%), appetite loss (44.5%), nausea (44.5%), and vomiting (24.4%). More patients in the prochlorperazine group experienced somnolence ($p = .048$) and delirium ($p = .09$; Table 4).

Other adverse events occurred with similar frequencies in both groups. Grade 4 hypercreatinemia occurred in one patient in the prochlorperazine group but was considered unrelated to the study drug.

Discussion

To the best of our knowledge, this is the first double-blind, randomized, controlled trial to evaluate the efficacy of prophylactic antiemetic treatment against OINV in patients with cancer. The efficacy of prophylactic antiemetic treatment was investigated only in observational studies, with conflicting

Table 4. Adverse events

Adverse events	Prochlorperazine group ($n = 59$)		Placebo group ($n = 60$)		p value
	≥Grade 3	All grades	≥Grade 3	All grades	
Somnolence	3	45	0	41	.048
Constipation	4	36	5	42	.30
Appetite loss	4	24	0	29	.85
Vomiting	0	14	1	15	.96
Dizziness	1	4	0	3	.32
Delirium	2	3	0	0	.09
Pneumonitis	1	1	1	1	.99
Hypercalcemia	1	1	0	0	.31
Liver dysfunction	1	1	0	0	.31
Hypercreatinemia	1	0	0	0	.31

Grade ≥3 adverse events related to the study treatment are summarized. Grading of adverse events as per National Cancer Institute Common Toxicity Criteria (version 4.0). Hypercreatinemia was a grade 4 adverse event. Analyzed by Cochran-Armitage trend test.

results. A previous single-center study showed that interventions to promote the use of prophylactic medication might be effective in reducing the risk of opioid-induced nausea/vomiting [16]. On the other hand, a multicenter retrospective study of 619 patients, a single-center retrospective study of 280 patients, and another retrospective study in 416 patients reported that incidence of nausea or vomiting was similar regardless of prophylactic treatment with dopamine blockers [17–19]. In this study, there was no significant difference in the CR rates between the prochlorperazine group and placebo group. Other secondary endpoints (i.e., the number of patients who had emetic episodes, number of the patients who required antiemetics, intensity of nausea as evaluated with an NRS, median time to first emetic episode/use of rescue antiemetic medications, and quality of life subscales) did not differ significantly between the intervention group and control group. On the other hand, patients who received prochlorperazine were more likely to have severe somnolence and delirium. Therefore, we conclude that the routine use of prophylactic prochlorperazine at the initiation of treatment with opioids is not beneficial and rather might be detrimental to patients.

Our results demonstrated evidence that prochlorperazine is ineffective to prevent OINV, but it is still unclear whether the use of other antiemetics, such as olanzapine, would have resulted in beneficial outcomes, and this remains a topic for future research. Of note, we found a higher incidence of nausea and vomiting in patients with cancer of the digestive system; that is, about 50% of patients had emetic episodes after initial administration of oral oxycodone. Future research thus could focus on this high-risk subgroup of patients.

Determining which outcome measure is most appropriate as a primary endpoint is challenging in many areas of palliative-care research. There are no established outcomes that can be used in clinical trials assessing the efficacy of a medication to prevent OINV. In this study, we measured a variety of outcomes as secondary endpoints, and the results have the same directions. The set of outcomes adopted in this study, such as the CR rate, number of emetic episodes/rescue use of antiemetics, intensity of nausea, and the time to the first emetic episode/rescue use of antiemetics, provide interpretable findings and can be used in further studies.

Our study had several limitations. First, the study population was heterogeneous in terms of primary tumor sites and exposure to weak opioids. Although the majority of our patients had lung or breast cancer and subgroup analyses demonstrated no statistically significant difference in primary endpoints, there is a possibility that different outcomes might have been obtained in patients with homogeneous primary tumors arising in other sites. We included patients who had received weak opioids to increase feasibility, and about one third of our study patients had previously received tramadol. While subgroup analyses did not detect any significant difference in CR rates, there is also a possibility that trial on purely opioid-naïve patients might obtain different results. Second, this was a single-center study performed in Japanese patients, which might limit the generalizability of the findings to other populations. Third, we used oxycodone at a starting dose of 10 mg/day in most patients in this study because these dose levels are most commonly used and are approved by the Ministry of Health, Labor, and Welfare in Japan. Although the doses might be considered low in other parts of the world [4], titration of oxycodone was performed simultaneously in this study and we believe it is unlikely that the use of a higher starting dose of oxycodone would have led to different results. Fourth, we adopted CR rates as the primary endpoint of this study. The use of other measures might have led to different results, although we believe this is unlikely because all secondary outcomes had the same direction. Finally, the lack of a significant difference in emetic episodes between men and women may be related to the small number of subjects.

Conclusion

Prophylactic prochlorperazine seems to be ineffective in preventing OINV and might rather cause adverse events such as somnolence. Routine use of prophylactic prochlorperazine at the initiation of treatment with opioids is not recommended. Further research is needed to evaluate whether other antiemetics would be effective in preventing OINV in specific patient populations.

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Disclosures

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