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ORIGINAL ARTICLE

Patient-perceived symptomatic benefits of olanzapine treatment for nausea and vomiting in patients with advanced cancer who received palliative care through consultation teams: a multicenter prospective observational study

Isseki Maeda[1] · Eriko Satomi[2] · Daisuke Kiuchi[2] · Kaoru Nishijima[3] · Yoshinobu Matsuda[4] · Akihiro Tokoro[4] · Keita Tagami[5] · Yoshihisa Matsumoto[6] · Akemi Naito[7] · Tatsuya Morita[8] · Satoru Iwase[9] · On behalf of the Phase-R N/V Study Group · Hiroyuki Otani · Takuya Odagiri · Hiroaki Watanabe · Masanori Mori · Yosuke Matsuda · Hiroka Nagaoka · Meiko Mayuzumi · Yoshiaki Kanai · Nobuhiro Sakamoto · Keisuke Ariyoshi

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Abstract

Purpose To examine the safety, effectiveness, and patient-perceived benefit of treatment with olanzapine for nausea and vomiting (N/V) in patients with advanced cancer.

Methods We conducted a multicenter prospective observational study in a tertiary care setting (Trial registration number: UMIN000020493, date of registration: 2016/1/12). We measured the following: average nausea in the last 24 h using a Numeric Rating Scale (NRS: range 0–10) at baseline and day 2, patient-perceived treatment benefit (based on a 5-point verbal scale), and adverse events (AEs; using the Common Terminology Criteria for Adverse Events version 4).

Results The 85 participants (45% men) had a mean age of 58.7±15.8 years. Major causes of N/V were opioids (44%) and chemotherapy (34%). All patients received a daily dose of olanzapine of 5 mg or less as first-line treatment (N=35) or second- or later-line treatment (N=50). Nausea NRS decreased from 6.1±2.2 to 1.8±2.0 (differences: −4.3, 95% CI −3.7 to −4.9, p<0.001). The proportion of patients who did not experience vomiting episodes in the last 24 h increased from 40–89%. Mean decrease in nausea NRS by patient-perceived treatment benefit were as follows: −0.8 for "none" (n=4, 5%); −2.8 for "slight" (n=17, 20%); −3.3 for "moderate" (n=14, 16%); −4.7 for "lots" (n=25, 29%); and −6.1 for "complete" (n=25, 29%; p-for-trend<0.001). The most prevalent AE was somnolence (n=15, 18%).

Conclusion Short-term and relatively low-dose olanzapine treatment was effective for multifactorial N/V. Confirmatory studies with longer observation periods are needed to clarify the duration of the effect and adverse events.

Keywords Cancer · Palliative care · Olanzapine, Japan · Nausea · Vomiting

✉ Isseki Maeda
isseki.maeda@gmail.com

[1] Department of Palliative Care, Senri-Chuo Hospital, Toyonaka, Osaka, Japan

[2] Department of Palliative Medicine, National Cancer Center Hospital, Tokyo, Japan

[3] Department of Palliative Medicine, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

[4] Department of Psychosomatic Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Osaka, Japan

[5] Department of Palliative Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

[6] Department of Palliative Medicine, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

[7] Department of Palliative Care, Miyazaki Medical Association Hospital, Miyazaki, Japan

[8] Palliative and Supportive Care Division, Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan

[9] Department of Palliative Medicine, Saitama Medical University, Irima, Saitama, Japan

Introduction

The literature shows that nausea and vomiting (N/V) is the most common and distressing symptom in patients with advanced cancer [1, 2]. Moreover, studies have reported that, in patients with advanced cancer who received palliative care, the underlying causes of N/V are multifactorial [3, 4]. Chemotherapy-induced nausea and vomiting (CINV) has been most widely explored by researchers examining the symptomatic management of N/V. Some recent clinical guidelines have started recommending olanzapine, an atypical antipsychotic that has affinity for many neurotransmitter receptors [5, 6], as one of the first-line treatments for the prevention of CINV induced by highly or moderately emetogenic chemotherapy and a useful option to treat breakthrough CINV (i.e., N/V that occurs within five days of chemotherapy administration after the use of guideline-directed prophylactic antiemetic agents) [7, 8].

Contrastingly, studies remark that there is limited evidence on the therapeutic effects of olanzapine for N/V non-related to chemotherapy/radiation in patients with advanced cancer [2, 9, 10]; although several studies—since 2002—have indicated that olanzapine is effective to improve N/V in such situations [11–17], most were small case series [12, 13, 15] or retrospective studies [14]. Olanzapine has been considered an alternative option for N/V that is refractory to standard therapy [2, 10]. Nonetheless, a recent pilot randomized study conducted in cancer patients with N/V nonrelated to chemotherapy/radiation indicated that olanzapine had large antiemetic effects compared with a placebo [18]; namely, we can expect that olanzapine will have a therapeutic effect for multifactorial N/V in patients receiving palliative care.

The US Food and Drug Administration defined Patient-Reported Outcome (PRO) as, any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [19]. Knowing which symptomatic changes are clinically important to patients has become increasingly important in the era of PRO [20, 21]. Still, none of the abovementioned studies has assessed patient perceptions (i.e., satisfaction, preference) for olanzapine treatment [11–18], with one exception [16]. Therefore, there is a paucity of information on patient-perceived symptomatic benefits of olanzapine for N/V.

Therefore, this study aimed to examine the safety and therapeutic effectiveness of olanzapine for N/V in patients with advanced cancer who received care from palliative care consultation teams. Additionally, to obtain in-depth insights in N/V management for patients with advanced cancer, we examined the relationship between changes in N/V and patient-perceived treatment benefits and examined the influence of this relationship on treatment response.

Methods

This manuscript is part of a larger multicenter prospective observational research project aimed at examining the safety and therapeutic effectiveness of palliative care treatment, named the Japan Pharmacological Audit Study of Safety and Effectiveness in the Real World (Phase-R; study identifier: UMIN000020493). Through the Phase-R, researchers have conducted real-world registry studies in the pharmacological management of delirium, opioid-induced constipation, and dyspnea [22, 23]. We affirm that all treatments and study-related observations were done within the context of routine clinical practice.

Participants

In this Phase-R N/V study, 12 palliative care consultation teams in tertiary care hospitals in Japan have participated. We recruited patient-participants through consecutive sampling; the inclusion criterion was being adult cancer patients with N/V for whom olanzapine administration was planned. The exclusion criterion was being patients who received olanzapine administration as a rescue medication prior to study enrollment. The administration of olanzapine, treatment line, dosage, and concomitant treatments were determined based on the clinical judgment of the palliative care physicians.

Data collection

Data collection was conducted at two timepoints: day 0 (i.e., baseline) and day 2.

At baseline, patient characteristics (i.e., age, sex, primary cancer site, ECOG [Eastern Cooperative Oncology Group] performance status) were recorded. Clinician's prediction of survival was recorded and categorized as "days," "weeks," or "months." Underlying causes of N/V were determined based on the clinical considerations of possibility (i.e., whether causative relationship was presumable?) and temporality (i.e., was there a reasonable temporal relationship?).

If a patient experienced termination of olanzapine administration before day 2 owing to death, deterioration, or discharge, the final available data were used to assess effectiveness and safety.

Outcome measures

At baseline and day 2, average nausea over the last 24 h (i.e., the primary outcome measure) was assessed using a Numeric Rating Scale (NRS; range: 0–10; a higher value indicates a

more severe symptom); daily number of vomiting episodes over the last 24 h was evaluated and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) grade: 0=none; 1=1–2 episodes; 2=3–5 episodes; and 3=6 or more episodes; and types and number of uses of rescue antiemetic medication over the last 24 h were recorded. At day 2, patient-perceived treatment benefit was measured by a 5-point verbal rating scale (1=none, 2=slight, 3=moderate, 4=lots, 5=complete), which was previously used in pain studies [24, 25].

Adverse events (AEs) were assessed using the CTCAE version 4 [26]. AEs potentially related to olanzapine (e.g., neuroleptic malignant syndrome, urinary retention, aspiration pneumonia, falls, cardiovascular events, hyperglycemia, somnolence, extrapyramidal symptoms, and sudden death) were recorded in all cases. Still, only serious adverse events (SAEs; defined as CTCAE Grade 3 or greater) that have a causal-relationship with olanzapine according to the NCI Guidelines [27] were reported. We used this empiric reporting rule because the frequency of disease-related AEs was very high and because regular examination was often skipped in the study sample (i.e., palliative care patients). All measurements were conducted by the responsible palliative care physicians.

Statistics

Sample size power calculations were conducted to detect an estimated treatment response rate (defined as patients reporting a 2 or greater value in the nausea NRS) of 40%; the calculations were based on a confidence interval (CI) width of 20% (i.e., ± 10%) and an alpha error of less than 5%. The results demonstrated the need for an analyzable sample of 92 patients; after considering sample attrition, the target population was set at 100 patients.

Descriptive statistics were used to report patient characteristics, underlying causes of N/V, treatment details (i.e., dose and treatment line of olanzapine administration, previous antiemetic use, and co-administered treatment), changes in N/V symptoms (i.e., changes in nausea NRS and number of vomiting episode), and AEs. The changes in nausea NRS between baseline and day 2 were tested using paired *t* test. Hedges' g was calculated to indicate effect size; based on a prior study [28], it was interpreted as follows: 0.2–0.5=small; 0.5–0.8=moderate; and 0.8 or greater=large. The associations between patient-perceived treatment benefit and nausea NRS changes at day 2 were visualized using a bar plot. Trend test was performed using multiple regression models.

Sensitivity analysis was conducted by imputing missing data for post-treatment nausea NRS that were missing owing to patient-related factors (e.g., conscious decline) in four patients.

Two-tailed *p* values less than 0.05 were considered statistically significant. All analyses were done using the SPSS ver. 25 (IL, USA).

Compliance with ethical standards

This study was conducted in accordance with the Declaration of Helsinki and the requirements set forth by the Japanese Ethical Guidelines for Epidemiology Research. The study protocol was reviewed and approved by the institutional review board of all participating sites.

At study enrollment, the following opt-out method was employed: patients and their families were informed about study details through leaflets or posters and were guaranteed that they would have the right to decline study participation at any given point in time without any type of prejudice. This recruit method was approved by the institutional review boards because all assessments and treatments were done within the context of daily clinical necessity, and because study participation did not impose excessive risks to patients; accordingly, the need for written informed consent was waived.

Results

Between January and December 2016 (i.e., 11 months), 101 patients were enrolled in the study. After 16 patients were excluded by the following reasons, 85 participants were included in the analysis. Reasons for exclusion were as follows: nausea NRS data from one institution was not available (*n*=7), baseline NRS data missing owing to patient-related factors (i.e., consciousness disturbance and cognitive impairment; *n*=5), and day 2 NRS data missing owing to patient-related factors (*n*=4; one of these four died from primary disease before day 2).

Patients' characteristics

Patients' mean age was 58.7±15.8 years and 45% were men (Table 1). The most frequent site of primary cancer was lung (34.1%), followed by gastrointestinal (18.8%), and head and neck (10.6%). Nearly 70% of the patients had reduced physical function (i.e., ECOG PS 2 or greater). Seven patients (8%) had a clinician's prediction of survival of "weeks," and 78 (92%) of "months." Active anticancer treatment was performed within 7 days before enrollment in 42 patients (49%); among these, 25 (29%) received intravenous chemotherapy, 8 (9%) received oral chemotherapy, and 18 (21%) received radiotherapy. Major causes of N/V were opioids (*n*=37, 44%), followed by chemotherapy (*n*=29, 34%), and

Table 1 Patient characteristics

	Values
Age, years	58.7±15.8
Male	38 (44.7%)
Female	47 (55.3%)
Primary cancer site	
Lung	29 (34.1%)
GI	16 (18.8%)
Head and neck	9 (10.6%)
Gynecological	5 (5.9%)
Others	26 (30.6%)
ECOG-PS	
0–1	26 (30.6%)
2	21 (24.7%)
3	33 (38.8%)
4	5 (5.9%)
Clinical prediction of survival	
Months	78 (91.8%)
Weeks	7 (8.2%)
Days	0
IV chemotherapy within a week, yes	25 (29.4%)
Oral chemotherapy at enrollment, yes	8 (9.4%)
Radiation therapy at enrollment, yes	18 (21.2%)
Treatment line of olanzapine	
1st line	35 (41.2%)
2nd line	31 (36.5%)
3rd line	14 (16.5%)
4th or later line	5 (5.9%)

Values are mean ± SD, or *n* (%)

impaired gastric emptying (*n*=18, 21%) (Table 2). The number of underlying causes was one in 37 participants (44%), two in 30 (35%), and three or more in 18 (21%).

Olanzapine treatment and co-administered treatment

Olanzapine was mainly used as the first or second line antiemetic treatment; as third line, it was used in 17% of the cases, and as the fourth or later in 6% (Table 1). The most frequently used drugs in the previous treatment lines were metoclopramide (*N*=25), prochlorperazine (*N*=21), 5-HT3 antagonists (*N*=6), antihistamines (*N*=6), and benzodiazepines (*N*=5).

Daily dose of olanzapine was 2.5 mg in 66 patients (78%) and 5 mg in 18 patients (21%). Olanzapine administration was terminated before day 2 in five patients owing to non-response (*N*=1), improvement (*N*=3), and disease progression (*N*=1).

Table 2 Underlying Causes of Nausea and Vomiting

Underlying causes	N (%)
Chemotherapy-induced	29 (34.1%)
Radiotherapy-induced	17 (20.0%)
Hepatic failure	2 (2.4%)
Renal failure	2 (2.4%)
Hypercalcemia	2 (2.4%)
Opioids	37 (43.5%)
Other drugs	1 (1.2%)
Impaired gastric emptying	18 (21.2%)
Non occlusive visceral	16 (18.8%)
Malignant bowel obstruction	8 (9.4%)
Cranial	6 (7.1%)
Vestibular	5 (5.9%)
Cortical (anxiety)	4 (4.7%)
Others	7 (8.2%)
Unidentified	2 (2.4%)
Values are *n* (%)	

At the first administration of olanzapine, corticosteroids had already been given in 20 patients at a mean betamethasone-equivalent dose of 4.2±2.6 mg/day. Some patients received treatments prior to baseline assessment with the following drugs: antimuscarinic drugs, octreotide, and decompression tubes, which were used in one, one, and four patients, respectively.

Changes in N/V intensity after olanzapine treatment

Changes in nausea NRS before and after treatment are shown in Table 3. Overall, nausea NRS over the last 24 h significantly decreased from 6.1±2.2 to 1.8±2.0 (differences: −4.3, 95%

Table 3 Effectiveness of Olanzapine assessed by Nausea Numeric Rating Scale

Outcome measures	Values	
Numeric Rating Scale	Baseline	Day 2
	6.1±2.2	1.8±2.0*
Numeric Rating Scale reduction after treatment		
≥1	78 (90.6%)	
≥2	72 (84.7%)	
≥3	60 (70.6%)	
Numeric Rating Scale at day 2		
≤3	69 (81.2%)	
≤2	58 (68.2%)	
≤1	47 (55.3%)	
=0	30 (35.3%)	

*$p<0.001$ for pre-post comparison by paired *t* test

CI −3.7 to −4.9, $p<0.001$, Hedges' $g=2.0$) at day 2. A reduction in nausea NRS of 2 or greater was reported in 72 patients (85%). At day 2, nausea NRS was 3 or less in 69 patients (81%) and 0 in 30 patients (35%). Regarding the daily olanzapine dose (5 mg group [$N=18$] vs. 2.5 mg groups [$N=66$]), there was no significant difference in terms of changes in mean nausea NRS (−4.9 vs. −4.1, $p=0.29$), but there was a significant difference in the response rate (i.e., 2 or greater nausea NRS declines; 100% vs. 80%, $p=0.04$).

All underlying causes were not significantly associated with response rate ($p>0.2$), except for patients with opioid-induced N/V; these patients revealed a lower response rate than those with other underlying causes (75.7% vs. 91.7%, $p=0.04$; Supplement Fig. 1). Chemotherapy/radiation-related and non-related causes and the number of underlying causes were not associated with response rate (Supplement Figs. 2 and 3). In the sensitivity analysis, results did not change if the missing data on nausea NRS at day 2 were imputed in four patients—using the baseline values.

As shown in Table 4, the proportion of patients without vomiting episodes in the past 24 h increased from 40 to 89% at day 2. at day 2, a decrease in the daily number of vomiting episodes was observed in 46 patients (54%), including four who had severe vomiting episodes at baseline, whom no longer showed any episodes at day 2; still, one patient (1%) experienced the deterioration of the vomiting symptom by one grade. The proportion of patients who needed rescue antiemetics significantly decreased after treatment (60% to 15%, $p<0.001$). A total of 13 patients (15%) required the following rescue antiemetic before day 2: metoclopramide ($N=7$), antihistamines ($N=4$), and benzodiazepines ($N=2$).

Associations between patient-perceived treatment benefit and changes in nausea NRS

Patient-perceived treatment benefit was "none" in 4 patients (5%), "slight" in 17 (20%), "moderate" in 14 (16%), "lots" in 25 (29%), and "complete" in 25 (29%). Results showed that the larger the perceived benefit, the larger the decrease in nausea NRS (p-for-trend<0.001). The mean decrease in nausea NRS in each group was as follows: −0.8 in "none;" −2.8 for "slight;" −3.3 for "moderate;" −4.7 for "lots;" and −6.1 for "complete." No patients with a perceived benefit of "lots" or "complete" experienced a vomiting episode at day 2, except for one case with perceived benefit of "lots;" this patient experienced 1–2 daily episodes.

AEs after olanzapine treatment

AEs observed after olanzapine treatment are shown in Table 5. At baseline, mild-to-moderate somnolence was frequently observed in patients with CTCAE grade 1 (28; 33%) and grade 2 (1; 1.2%). At day 2, somnolence worsened or newly developed in the following 15 patients (18%): grade 1 in 11 patients, grade 2 in three, and grade 3 in one. Details are shown in Supplement Table. The proportion of patients who experienced worsened somnolence (i.e., worsening of at least one CTCAE grade) approximately doubled in the higher dose group, though the difference did not reach statistical significance (14% in 2.5 mg group vs. 28% in 5 mg group, $p=0.15$).

During the observational period, two patients experienced falls, one developed extrapyramidal symptoms, and two developed other SAEs (e.g., G3 anemia and G4 febrile neutropenia, one patient for each). Possible causal relationship with olanzapine treatment was assumed only in one case of extrapyramidal symptoms. No other SAEs (i.e., neuroleptic malignant syndrome, cardiovascular event, and sudden death) were recorded. Since all non-somnolence AEs occurred in patients on 2.5 mg olanzapine, it is likely that the dose of olanzapine was not associated with these AEs.

Discussion

In this short-term observational study of vulnerable patients receiving palliative care, olanzapine administration showed

Table 4 Number of vomiting episodes prior 24 h at baseline and day 2

		Day 2				
		0 episodes	1–2 episodes	3–5 episodes	6+ episodes	
Baseline	0 episodes	33 (38.8%)	1 (1.2%)	0 (0%)	0 (0%)	34 (40.0%)
	1–2 episodes	29 (34.1%)	3 (3.5%)	0 (0%)	0 (0%)	32 (37.6%)
	3–5 episodes	10 (11.8%)	2 (2.4%)	1 (1.2%)	0 (0%)	13 (15.3%)
	6+ episodes	4 (4.7%)	1 (1.2%)	0 (0%)	1 (1.2%)	6 (7.1%)
		76 (89.4%)	7 (8.2%)	1 (1.2%)	1 (1.2%)	85 (100%)

Values are *n* (%)

Number of vomiting episodes was categorized according to the CTCAE grade

Table 5 Adverse Events during 2-day observation

	Baseline	Day 2
Death from all cause	N/A	0
Malignant syndrome	0	0
Urinary retention	1 (1.2%)	0
Aspiration pneumonia	1 (1.2%)	0
Falls	0	2 (2.4%)
Somnolence*		
Grade 1	28 (32.9%)	11 (12.9%)
Grade 2	1 (1.2%)	3 (3.5%)
Grade 3		1 (1.2%)
Cardiovascular	1 (1.2%)	0
Hyperglycemia	0	0
Sudden death	N/A	0
Other SAEs	4 (4.7%)	2 (2.4%)†
Extrapyramidal	0	1 (1.2%)

Values are *n* (%)

*Assessed by CTCAE somnolence grade

†CTCAE grade 3 anemia, and CTCAE grade-4 febrile neutropenia (n=1 for each)

rapid and significant improvement in patients' N/V symptoms with a large effect size. Serious adverse events, including somnolence and extrapyramidal symptoms, were uncommon. Patient-reported symptomatic benefits were large if they experienced a large decline in nausea NRS and no vomiting episodes.

The most important finding of this study relates to olanzapine treatment showing a rapid and a significant improvement in N/V for patients with advanced cancer who had a variety of underlying causes for these symptoms—including opioid-induced N/V and other visceral pathologies. As shown in previous reports, the underlying causes of N/V in palliative care populations are multifactorial [3, 4]. Indeed, in the current study, 57% of the patients had multiple causes of N/V; nonetheless, even in such complex cases, olanzapine showed a significant large impact on relief of N/V. The daily dose of olanzapine was 2.5 mg in 78% and 5 mg in 21% of the patients, which was similar to previous multicenter studies conducted in palliative care settings in Japan [29] and may be applicable to real-world palliative care practice. Based on a dose-to-dose comparison, a daily dose of 5 mg of olanzapine may provide symptomatic benefits to a greater number of patients than a lower dose of olanzapine. If a patient can tolerate adverse events such as worsening somnolence, 5 mg may be a more appropriate dose.

The second important finding is that patient-perceived treatment benefit of olanzapine for N/V was demonstrated for the first time. Patient-perceived symptomatic benefit responses of "slight" or greater were associated with a nausea NRS reduction of more than 2 points. Additionally, the reduction in nausea NRS was larger and the number of vomiting episodes was zero in patients who reported "lots" or "complete" effect of the treatment. Although the minimal clinically important differences for N/V in palliative care populations has yet to be determined [30, 31], the findings of the current study may provide useful insights. A reduction in nausea NRS of 2 points or greater may represent a minimal clinically important difference. To achieve greater clinical benefit, such as "lots" or more, greater NRS reductions (i.e., nausea NRS reduction of 4or greater) and resolution of vomiting may be required.

Previous studies have reported on the therapeutic usefulness of olanzapine for N/V in patients with advanced cancer who received palliative care [11–17]. However, a systematic review remarked that the evidence level in these previous studies was low [10]. Case reports/series and retrospective study were suffered from selection bias. All available four observational studies [11, 14, 15, 17] had relatively small numbers of patients (N=15–40) and used empiric symptom measures for evaluating N/V. Recently, Navari et al. conducted the first pilot randomized placebo-controlled trial in this area in patients with advanced cancer and chronic nausea nonrelated to recent chemotherapy and radiotherapy. [18] In the study, fifteen patients received 5 mg of oral olanzapine for 7 days. The difference between arms in changes in nausea scores over 7 days was −8 (95% CI −8 to −7) on a 0–10 NRS scale, favoring olanzapine arm [18]. The current study was a multicenter prospective observational study with a relatively large sample size (n=85) and using validated outcome measures. We observed a rapid and significant antiemetic effect of olanzapine in patients with advanced cancer with multifactorial and complicated underlying causes of N/V. Additionally, the current study strengthens the evidence on the topic by showing patient-reported symptomatic benefits of olanzapine treatment.

Limitations

First, because this was an observational study without control arms, we cannot rule out that mechanisms other than the pharmacological actions of olanzapine might have contributed to our findings; for instance, we cannot rule out the possibility that some patients spontaneously recovered from N/V owing to influences from concurrent cancer treatment (e.g., such as CINV and radiation-induced N/V). Moreover, modifications in factors that are well-known underlying causes (e.g., opioid modification and constipation management) of N/V might also have influenced the results. Nonetheless, we remark that it is highly unlikely that participants incurred in dramatic physical condition changes during the short study period (i.e., 2 days). Although we believe that the short observation

period we set in this study was reasonable because the onset of effect of olanzapine has been reported to be hours to days [11, 13, 14, 17, 18], the duration of effect and adverse events should be observed over a longer observation period.

Second, the open-label nature of this study and the reporting on AEs based on empirical knowledge might have affected the results; for example, rater bias might have occurred because the persons who conducted the assessments present in this study and who prescribed olanzapine to patients were the unblinded palliative care physicians responsible for each patient. Owing to the empiric reporting rules we applied, the AEs in this study might be underestimated, especially in mild intensity events. Additionally, data from some participants were excluded from analysis because post-treatment nausea NRS data were missing owing to patients incurring in severe somnolence. Notwithstanding, we believe that the impact of these limitations was small because the number of excluded cases was also small and the results did not change in the sensitivity analysis using the baseline carried forward method described in prior research [32].

Third, the generalizability of our findings to end-of-life patients and patients with non-cancer advanced diseases is limited because our study was conducted in consultation palliative care settings. Moreover, this study might be underpowered because some patients were excluded due to missing data in nausea NRS, while we were able to detect statistical significance in the main results because treatment effect of olanzapine was greater than prespecified.

This study demonstrated the effectiveness of olanzapine for multifactorial N/V in patients with advanced cancer. Olanzapine showed the patient-perceived symptomatic benefit over a short period of time, and its effect size was large. Serious adverse events early in the course of treatment were uncommon. Confirmative studies with longer observation periods are needed to obtain further insights into the duration of the effect as well as adverse events of this treatment.

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Author contribution Isseki Maeda: conceptualization, formal analysis, and writing—original draft. Eriko Satomi: conceptualization and writing—original draft. Daisuke Kiuchi: resources and writing—review and editing. Kaoru Nishijima: resources and writing—review and editing. Yoshinobu Matsuda: resources and writing—review and editing. Akihiro Tokoro: resources and writing—review and editing. Keita Tagami: resources and writing—review and editing. Yoshihisa Matsumoto: resources and writing—review and editing. Akemi Naito: resources and writing—review and editing. Tatsuya Morita: conceptualization and writing—review and editing, supervision. Satoru Iwase: conceptualization, supervision, and funding acquisition.

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Data availability Data are available from the corresponding author upon reasonable request.

Code availability Code is available from the corresponding author upon reasonable request

Declarations

Ethics approval and consent to participate This study was conducted in accordance with the Declaration of Helsinki and the requirements set forth by the Japanese Ethical Guidelines for Epidemiology Research. Study protocol was reviewed and approved by institutional review boards of all participating sites. Opt-out methods were employed and written informed consent was waived according to the Japanese Ethical Guidelines for Epidemiology Research and the guidance of institutional review boards.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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