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ORIGINAL ARTICLE

Efficacy and safety of olanzapine combined with aprepitant, palonosetron, and dexamethasone for preventing nausea and vomiting induced by cisplatin-based chemotherapy in gynecological cancer: KCOG-G1301 phase II trial

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Abstract
Purpose Olanzapine is effective in chemotherapy-induced nausea and vomiting (CINV). In patients receiving highly emetogenic chemotherapy (HEC), its efficacy was reported as rescue therapy for breakthrough emesis refractory to triplet therapy (palonosetron, aprepitant, and dexamethasone). However, its preventive effects with triplet therapy for CINV are unknown. This study aimed to investigate efficacy and safety of preventive use of olanzapine with triplet therapy for CINV of HEC.
Methods This study is a prospective multicenter study conducted by Kansai Clinical Oncology Group. Forty chemo-naïve gynecological cancer patients receiving HEC with cisplatin (≥50 mg/m^2) were enrolled. Oral olanzapine (5 mg) was administered with triplet therapy a day prior to cisplatin administration and on days 1–5. The primary endpoint was complete response (no vomiting and no rescue) rate for the overall phase (0–120 h post-chemotherapy). Secondary endpoints were complete response rate for acute phase (0–24 h post-chemotherapy) and delayed phase (24–120 h post-chemotherapy) and complete control (no vomiting, no rescue, and no significant nausea) rate and total control (no vomiting, no rescue, and no nausea) rate for each phase. These endpoints were evaluated during the first cycle of chemotherapy.
Results Complete response rates for acute, delayed, and overall phases were 97.5, 95.0, and 92.5 %, respectively. Complete control rates were 92.5, 87.5, and 82.5 %, respectively. Total control rates were 87.5, 67.5, and 67.5 %, respectively. There were no grade 3 or 4 adverse events.
Conclusions Preventive use of olanzapine combined with triplet therapy gives better results than those from previously reported studies of triplet therapy.

Keywords Olanzapine · Chemotherapy-induced nausea and vomiting · Cisplatin · Highly-emetogenic chemotherapy · Antiemetic therapy

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Introduction

Despite developments in antiemetic therapies, chemotherapy-induced nausea and vomiting (CINV) remains one of the most distressing symptoms that reduce the quality of life (QOL) of patients receiving chemotherapy. Because CINV can cause comorbidities, such as anorexia, malnutrition, dehydration, and increased anxiety towards treatment, it is important to prevent and alleviate CINV as much as possible [1]. The Multinational Association of Supportive Care in Cancer (MASCC)/European Society of Medical Oncology (ESMO),

American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) have developed evidence-based guidelines for antiemetic drugs [2–4]. In accordance with these guidelines, the Japan Society of Clinical Oncology (JSCO) has published guidelines for the proper use of antiemetics [5].

These guidelines recommend triplet therapy with 5-hydroxytryptamine 3 receptor antagonist (5-HT_3RA), neurokinin-1 receptor antagonist (NK-1RA), and dexamethasone as the standard antiemetic therapy for highly emetogenic chemotherapy (HEC) [2–5]. Previous studies have reported that with triplet therapy, the complete response (no vomiting and no rescue therapy) rate to HEC is approximately 80 % in the acute phase (0–24 h post-chemotherapy) and approximately 60–70 % in both the delayed (24–120 h post-chemotherapy) and the overall phases (0–120 h post-chemotherapy), with the rate of patients with no nausea at approximately 40–50 % [6–10]. The outcomes of CINV treatment improved by combining doublet therapy (5-HT_3RA, dexamethasone) with palonosetron, a second-generation 5-HT_3RA [11]. However, when triplet therapy including NK-1 RA was used, the clinical trial outcomes for complete response rate were comparable to the outcomes from studies where palonosetron or first-generation 5-HT_3RA was used [12].

It appears that female gender is a risk factor for CINV. The CINV Study Group of Japan and JSCO conducted a large-scale prospective multicenter collaborative trial throughout Japan to investigate risk factors of CINV [13]. Multivariate analysis revealed that from a gender standpoint, female gender had significantly poorer prognosis for acute-phase nausea and vomiting, as well as for delayed-phase nausea and vomiting (odds ratios 3.087, 3.514, 1.420, and 2.159, respectively). The Kansai Clinical Oncology Group (KCOG), with which we are affiliated, conducted a prospective multicenter phase II trial (KCOG-G1003) to investigate the efficacy and safety of triplet therapy (palonosetron, aprepitant, and dexamethasone) for HEC including a cisplatin dose of ≥50 mg/m^2 in 96 women with gynecological cancer [14]. The complete response rate for the overall phase was 54.2 %, and the percentage of patients with no nausea was low (30.2 %). Therefore, while greater prevention and alleviation of CINV, particularly in female patients, is much desired, no established antiemetic regimens exceeding triplet therapy have been developed.

The antiemetic guidelines list olanzapine, an atypical antipsychotic, as an effective agent to treat triplet therapy-refractory CINV. Reports of a randomized controlled trial indicate that olanzapine has antiemetic effects on CINV that are superior to those of aprepitant, dexamethasone, and azasetron, particularly in the delayed phase [15–17]. Furthermore, it has been reported that the efficacy of olanzapine is higher than that of metoclopramide as a rescue therapy for triplet therapy-refractory CINV [18]. As olanzapine has a different mechanism of action than the agents that comprise triplet therapy, when used in combination with triplet therapy, olanzapine may increase the antiemetic effect. However, it is important to note that the efficacy and safety of the four agents used in combination for the prevention of CINV have not been verified.

At our facility, we have preventively administered olanzapine in combination with triplet therapy starting from the next cycle of chemotherapy in patients with gynecological cancer undergoing HEC, including cisplatin, who developed triplet therapy-refractory emesis. In a retrospective study, we reported that nausea disappeared or alleviated in approximately 90 % of patients throughout the combined usage of olanzapine and triplet therapy [19, 20]. Based on this experience, we conducted a prospective multicenter phase II trial (KCOG-G1301) to investigate the efficacy and safety of a four-drug combination regimen with triplet therapy combined with olanzapine, to prevent CINV in patients with gynecological cancer receiving HEC including cisplatin at a dose of ≥50 mg/m^2.

Patients and methods

Patient selection

The trial was conducted between October 2013 and February 2015 at four institutions affiliated with the KCOG. The subject sample consisted of chemotherapy-naïve patients with gynecological cancer receiving chemotherapy with HEC containing cisplatin at a dose of ≥50 mg/m^2.

The enrollment eligibility criteria of patients were as follows: chemotherapy-naïve gynecological cancer, receiving HEC containing cisplatin at a dose of ≥50 mg/m^2, aged 20–80 years; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2; bone marrow activity met the criteria for starting administration of chemotherapy; liver and renal function met the criteria for starting administration of chemotherapy; and provided written and informed consent.

The exclusion criteria of patients were as follows: had previously received chemotherapy; were receiving chemotherapy in combination with radiation therapy; had a body mass index (BMI) of ≥35; had abnormal glucose tolerance (hemoglobin A1c ≥6.5 and fasting blood sugar ≥126 mg/dL); had creatine phosphokinase exceeding the reference value by 2.5-fold; had emetic episodes requiring administration of antiemetics the day prior to chemotherapy; were undergoing treatment with antipsychotics; had a family history of neuroleptic malignant syndrome; had active infection; and had large amounts of fluid accumulation in the body cavities (ascites, pleural effusion, and pericardial effusion). Also excluded were women who were pregnant, were hoping to become pregnant, were breastfeeding, and had a smoking habit.

Study treatment

All patients who enrolled in this trial were administered triplet therapy and olanzapine. Triplet therapy (5-HT_3RA, NK-1RA, and dexamethasone) was administered in accordance with recommendations in the Japanese guideline [5]. The 5-HT_3RA palonosetron was administered intravenously on day 1 at a dose of 0.75 mg, 30–60 min prior to cisplatin administration. Although 0.25 mg dose of palonosetron is recommended in international guidelines, 0.75 mg is recommended in the Japanese guideline because of results from phase II studies done in Japan. Therefore, we decided to use 0.75 mg dose of palonosetron in this study [11]. The NK-1RA aprepitant was orally administered 60–90 min prior to cisplatin administration at a dose of 125 mg on day 1, then 80 mg on days 2 and 3. Dexamethasone was intravenously administered 30–60 min prior to cisplatin administration at a dose of 9.9 mg (12 mg as dexamethasone phosphate) on day 1 and then intravenously administered at a dose of 6.6 mg (8 mg as dexamethasone phosphate) or orally administered at a dose of 8 mg on days 2–4.

Olanzapine was orally administered at a dose of 5 mg on the day prior to cisplatin administration and then once on days 1–5 at bedtime.

Metoclopramide was used as rescue therapy for breakthrough emesis. The decision of whether or not to use rescue therapy was made by each individual patient.

Evaluation of parameters

The enrolled patients were hospitalized for treatment from the day prior to and up to day 6 of chemotherapy. We recorded medical information on each patient at the time of hospitalization (age, height, weight, BMI, cancer type and staging, medical history, family history, ECOG performance status, laboratory results, and chemotherapy regimen).

Patients were given a self-recorded symptom diary to record their symptoms over the 5-day period. On the day prior to chemotherapy, patients recorded their experience of emesis during pregnancy, history of motion sickness, and alcohol-intake history. The 24-h period after cisplatin administration was considered as day 1, and each subsequent 24 h period was counted as 1 day. Patients recorded their degree of nausea, presence/absence of vomiting or retching, presence/absence of rescue therapy, and adverse events in the symptom diary every 24 h for the 120-h period after cisplatin administration. The degree of nausea was evaluated by the individual patients using an 11-point (0–10) numeric rating scale (NRS).

The acute phase was defined as 0–24 h after cisplatin administration, the delayed phase was 24–120 h after cisplatin administration, and the overall phase was 0–120 h after cisplatin administration.

The primary endpoint was the overall phase complete response (no vomiting and no rescue therapy) rate. The secondary endpoints were complete response rate in the acute phase and the delayed phase, and the complete control (no vomiting, no rescue therapy, and no significant nausea: NRS of 0–2) rate, total control (no vomiting, no rescue therapy, and no nausea: NRS of 0) rate, rate of patients with no nausea, and adverse events in the acute phase, delayed phase, and overall phase. Safety endpoints, including adverse events and laboratory tests, were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE Version 4.0).

These endpoints were evaluated during the first cycle of chemotherapy.

Statistical analysis

Statistical analyses were performed using the statistical software R (Version 2.13.0). The treatment outcomes of the acute phase and delayed phase were compared using the McNemar's test, and $P < 0.05$ was considered statistically significant.

Establishment of sample size

The sample size of the present trial was calculated as follows. In the aforementioned KCOG-G1003 trial, the overall phase complete response rate for triplet therapy in patients with gynecological cancer receiving HEC containing cisplatin at a dose of ≥50 mg/m^2 was 54.2 % [14]. On the basis of this result, we set the unacceptable response rate at 55 %. In a retrospective comparative study conducted by the Shizuoka Cancer Center, 20 patients with gynecological cancer who developed grade 3 nausea (CTCAE Version 4.0) despite triplet therapy were given preventive administration of olanzapine at a dose of 5 mg combined with triplet therapy for subsequent cycles. As a result, 50 % of patients did not develop nausea [19]. Therefore, of the 45 % of patients who did not reach complete response state with triplet therapy, it was estimated that 50 % reached complete response state with combined use of olanzapine and triplet therapy. Thus, when triplet therapy was combined with olanzapine, the complete response rate was assumed to reach approximately 75 %, and desirable response rate was set at 75 %. On the basis of this estimation, a sample of 35 patients was required for the present trial to reach a significance level of 5 % (one-sided) and 80 % statistical power. In anticipation of a 10–20 % rate of exclusion, the planned number of enrollments was 40 patients.

Ethical considerations

The present study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies. The protocol was approved by the ethical review

board of each participating facility. Prior to trial participation, all patients provided written, informed consent. This trial was registered with the University Hospital Medical Information Network (UMIN) clinical trial registry (no. UMIN000011857).

Results

Patient characteristics

Patient characteristics are shown in Table 1. Median age was 57 years and median BMI 22. The disease had reached stage I or II in 65 % of patients, and ECOG performance status score was 0 or 1 in 97.5 %. High risk factors for CINV, experience of emesis during pregnancy, history of motion sickness, and no alcohol intake history were found in 50.0, 32.5, and 52.5 % of patients, respectively. Cisplatin dosage was 50 mg/m^2 in 37 patients; 60 mg/m^2, in 1 patient; and 80 mg/m^2, in 2 patients. A multiagent regimen was administered to 97.5 % of patients.

Table 1 Patient characteristics

	Number	Percentage
Total	40	100.0
Age (years)		
Median (range)	57 (25–76)	
Body mass index		
Median (range)	22 (18–34)	
ECOG performance status		
0	30	75.0
1	9	22.5
2	1	2.5
Gynecological malignancy		
Cervical cancer	20	50.0
Endometrial cancer	19	47.5
Vulval cancer	1	2.5
Stage		
Stage I	15	37.5
Stage II	11	27.5
Stage III	4	10.0
Stage IV	8	20.0
Recurrence	2	5.0
Risk factors		
Experience of emesis during pregnancy	20	50.0
History of motion sickness	13	32.5
No alcohol intake history	21	52.5
Cisplatin dose		
50 mg/m^2	37	92.5
60 mg/m^2	1	2.5
80 mg/m^2	2	5.0
Chemotherapy regimen		
Cisplatin/paclitaxel	19	47.5
Cisplatin/adriamycin	16	40.0
Cisplatin/etoposide	2	5.0
Cisplatin/irinotecan	1	2.5
Cisplatin/adriamycin/cyclophosphamide	1	2.5
Cisplatin	1	2.5

Antiemetic effects

Antiemetic effects in the acute, delayed, and overall phases are shown in Table 2. The primary endpoint of overall phase complete response rate was 92.5 %. Secondary endpoints of complete response rate for the acute phase and delayed phase were 97.5 and 95.0 %, respectively. For the acute, delayed, and overall phases, the complete control rates were 92.5, 87.5, and 82.5 %, respectively, while the total control rates were 87.5, 67.5, and 67.5 %, respectively. The rate of no nausea in the overall phase was 67.5 %, and the rate of no significant nausea was 87.5 %. Although a statistically significant difference was observed for total control rate and no nausea between the acute phase and delayed phase ($P = 0.013$), no statistically significant difference was observed for the other endpoints.

The rates of no vomiting, no rescue therapy, no significant nausea, and no nausea according to treatment day are shown in Table 3. Of the patients who experienced vomiting, only one patient experienced episodes of vomiting on day 5. Rescue therapy was administered for one patient on day 1 and two patients on day 5. During the five-day period, the rate of patients with no significant nausea was ≥95 %. The rate of patients with no nausea was ≥80 % on days 1–4.

Safety

During treatment, no grade 3 or 4 adverse events were observed. The main adverse events were somnolence and constipation. Grade 1 somnolence was observed in 33 patients (82.5 %); however, it did not impede the patient's daily life and was found to be acceptable by the patients. Grade 1 and 2 constipation was observed in 29 patients (72.5 %) and was controlled with laxatives. We observed dry mouth in seven patients (17.5 %), dizziness in two (5 %), and finger tremor in two (5 %); all of which were grade 1. These adverse events did not affect their daily life and did not require treatment. Somnolence was an adverse event clearly thought to be caused by olanzapine; however, no patients requested to discontinue olanzapine, and all patients completed the protocol-based treatment.

Blood tests were conducted approximately 14 days after chemotherapy. Elevated levels of alanine aminotransferase and aspartate aminotransferase of grade 1 or 2 were observed in seven patients receiving cisplatin/paclitaxel and two patients receiving cisplatin/adriamycin. However, no increase

Table 2 Efficacy according to study phase

	Study phase	Percent	95 % CI	*P* value[a]
Complete response	Acute	97.5	(86.8–99.9)	1.000
	Delayed	95.0	(83.1–99.4)	
	Overall	92.5	(79.6–98.4)	
Complete control	Acute	92.5	(79.6–98.4)	0.683
	Delayed	87.5	(73.2–95.8)	
	Overall	82.5	(67.2–92.7)	
Total control	Acute	87.5	(73.2–95.8)	0.013
	Delayed	67.5	(50.9–81.4)	
	Overall	67.5	(50.9–81.4)	
No vomiting	Acute	100.0	(92.8–100.0)	1.000
	Delayed	97.5	(86.8–99.9)	
	Overall	97.5	(86.8–99.9)	
No rescue therapy	Acute	97.5	(86.8–99.9)	1.000
	Delayed	95.0	(83.1–99.4)	
	Overall	92.5	(79.6–98.4)	
No nausea	Acute	87.5	(73.2–95.8)	0.013
	Delayed	67.5	(50.9–81.4)	
	Overall	67.5	(50.9–81.4)	
No significant nausea	Acute	95.0	(83.1–99.4)	0.248
	Delayed	90.0	(76.3–97.2)	
	Overall	87.5	(73.2–95.8)	

95 % CI 95 % confidence interval

[a] Comparison of acute phase and delayed phase (McNemar's test)

in bilirubin levels was observed. We diagnosed elevated levels of alanine aminotransferase and aspartate aminotransferase as side effects of paclitaxel and adriamycin. There were no other abnormalities observed in the biochemical profiles or glucose tolerance.

Discussion

This study is, to the best of our knowledge, the first prospective trial to investigate the efficacy and safety of preventive olanzapine combined with triplet therapy for HEC containing cisplatin at a dose of ≥50 mg/m^2.

The most important finding in this trial is that a regimen combining four agents resulted in an overall phase complete response rate of ≥90 %. We believe that this outcome is better than other outcomes of triplet therapy reported till date. Acute emesis is the main factor for poor prognosis in delayed emesis [21]. Furthermore, once emesis has been experienced, anticipatory emesis and emesis in subsequent cycles of chemotherapy are likely to occur [22, 23]. Therefore, it is very important to control CINV upon initial administration of chemotherapy in order to achieve subsequent control of CINV.

The second important finding is that delayed emesis was controlled in almost the same level of acute phase, although prevention and alleviation of delayed emesis are known to be more difficult than those of acute emesis. There was no statistically significant difference between the acute phase and delayed phase in terms of complete response rate; complete control rate; and rates for no vomiting, no rescue therapy, and no significant nausea. For no nausea and total control rate, there was a statistically significant difference of approximately 20 % between the acute and delayed phases. However, in terms of outcomes per treatment day, the rate of no nausea reached ≥80 % from days 1 to 4 (0–96 h after cisplatin administration), which were considered good outcomes.

The third important finding was that there was no major problem in the acceptability of the four-agent combination regimen containing olanzapine. Although approximately 80 % of patients experienced grade 1 somnolence, none of the patients requested to discontinue olanzapine due to somnolence. Furthermore, no grade 3 or 4 adverse events were observed. To date, no grade 3 or 4 adverse events have been reported in studies of CINV using olanzapine [15–20, 24–26]. The decision of whether to use olanzapine in the second and subsequent cycles of chemotherapy was left to the discretion of the individual patients. All patients requested the use of olanzapine.

Table 4 lists the outcomes of the present trial and the outcomes of the subgroup analysis performed in the KCOG-G1003 trial with patients divided into those receiving first-line chemotherapy and those with a history of chemotherapy. The results were not of a randomized controlled trial, and therefore, the results of the two trials cannot be simply compared. However, because the KCOG-G1003 and KCOG-G1301 were conducted using the same methods, we assume that a four-agent combination regimen containing olanzapine will have a higher therapeutic effect, especially in the delayed

Table 3 Efficacy for each treatment day

	Day 1 (0–24 h) Number of patient (%)	Day 2 (24–48 h)	Day 3 (48–72 h)	Day 4 (72–96 h)	Day 5 (96–120 h)
No vomiting	40 (100)	40 (100)	40 (100)	40 (100)	39 (97.5)
No rescue therapy	39 (97.5)	40 (100)	40 (100)	40 (100)	38 (95.0)
No significant nausea	38 (95.0)	39 (97.5)	38 (95.0)	38 (95.0)	38 (95.0)
No nausea	35 (87.5)	33 (82.5)	32 (80.0)	32 (80.0)	29 (72.5)

Table 4 Comparison of the KCOG-G1003 subgroup analysis and the present study

	Study phase	KCOG-G1003 [14]		Present study (n = 40)
		Non-chemo-naïve (n = 34)	Chemo-naïve (n = 62)	
Complete response (%)	Acute	94.1	83.9	97.5
	Delayed	52.9	58.1	95.0
	Overall	52.9	54.8	92.5
Complete control (%)	Acute	88.2	79.0	92.5
	Delayed	44.1	46.8	87.5
	Overall	44.1	45.2	82.5
Total control (%)	Acute	70.6	69.4	87.5
	Delayed	29.4	29.0	67.5
	Overall	26.5	27.4	67.5
No vomiting (%)	Acute	94.1	88.7	100.0
	Delayed	79.4	67.7	97.5
	Overall	79.4	67.7	97.5
No rescue therapy (%)	Acute	100.0	93.5	97.5
	Delayed	58.8	69.4	95.0
	Overall	58.8	64.5	92.5
No nausea (%)	Acute	73.5	74.2	87.5
	Delayed	35.3	32.3	67.5
	Overall	29.4	30.6	67.5
No significant nausea (%)	Acute	91.1	88.7	95.0
	Delayed	61.8	62.9	90.0
	Overall	61.8	62.9	87.5

phase. While a randomized phase III trial is needed to verify whether the four-agent combination therapy is superior to triplet therapy truly, we believe that the results of the present trial provide evidence to design such a randomized phase III trial.

Olanzapine is a multi-acting-receptor-targeted-antipsychotic agent and antagonist of several chemoreceptors including dopamine (D_1-D_5), serotonin (5-HT_{2a}, 5-HT_{2c}, 5-HT_3, and 5-HT_6), histamine (H_1), adrenaline (α_1), and acetylcholine-muscarine ($Achm_1$-$Achm_5$) [27]. Compared to conventional antipsychotics (prochlorperazine, haloperidol, and so on), and metoclopramide used to treat CINV, olanzapine induces less extrapyramidal symptoms and akathisia [28]. Furthermore, olanzapine has a stronger affinity with 5-HT_3 receptors and longer half-life than 5-HT_3 RA [29]. Although olanzapine is not a conventional antiemetic, it exhibits a strong antiemetic effect. For this reason, many reports have, in addition to CINV, described its efficacy for emesis in advanced cancer and cancer-related anorexia [29–31].

The main neurotransmitters known to be associated with CINV include acetylcholine-muscarine (Achm), dopamine (D_2), histamine (H_1), serotonin (5-HT_2, 5-HT_3), and neurokinin (NK-1). Chemoreceptors of these transmitters are found in the central nervous system. H_1 and Achm receptors are found in the vestibular apparatus, 5-HT_3, NK-1, and D_2 receptors in the chemoreceptor trigger zone (CTZ), and 5-HT_2, 5-HT_3, NK-1, D_2, H_1, and Achm receptors in the vomiting center. It is thought that emesis is induced via the network formed by these receptors [32]. Olanzapine acts as an antagonist of the four chemoreceptors excluding the NK-1 receptor; due to its high permeability across the blood brain barrier [33], it is thought to affect the vestibular apparatus, CTZ, and vomiting center. For these reasons, the combined usage of olanzapine with triplet therapy is thought to exhibit an antagonist effect on most of the chemoreceptors involved in emesis.

Several phase III randomized controlled trials have investigated the efficacy of olanzapine in preventing CINV. In a study that compared olanzapine and aprepitant in patients receiving cisplatin-based chemotherapy or doxorubicin/cyclophosphamide, the rate of patients who experienced no nausea in the delayed phase was 69 vs. 38 %, indicating significantly better outcomes in the olanzapine group [15]. In a study that compared olanzapine and dexamethasone in patients receiving HEC or moderate emetogenic chemotherapy (MEC), the delayed outcome in patients receiving HEC revealed a significantly higher response rate in the olanzapine group (no nausea 69 vs. 30 %, no vomiting 78 vs. 56 %) [16]. In a study that compared olanzapine

and metoclopramide as rescue therapy in patients receiving HEC who experienced breakthrough emesis despite triplet antiemetic therapy, no vomiting was experienced in 70 vs. 31 % of patients, and no nausea was experienced in 68 vs. 23 %, indicating significantly better outcomes in the olanzapine group in the 72-h period following rescue therapy [18]. In a study that compared olanzapine and $5HT_3$ RA (azasetron) in patients receiving HEC or MEC, the response rate in the delayed phase was higher in the olanzapine group (no nausea 76.8 vs. 46.2 %, no vomiting 84.3 vs. 67.6 %). Furthermore, a QOL survey using the Quality of Life Questionnaire C30 revealed that the olanzapine group had significantly better QOL for global health status, emotional functioning, social functioning, fatigue, nausea/vomiting, insomnia, and appetite loss [17]. Based on the results of these phase III randomized controlled trials and those of the present study, we believe that olanzapine is an extremely effective agent for the control of CINV.

We note three obvious limitations of the present study. First, the entire study sample consisted of patients with gynecological cancer; therefore, it is unclear whether the same effects can be achieved in male patients and in chemotherapy regimens of other cancer types. Second, in most patients, cisplatin dose was 50 mg/m^2. Further studies should be performed to verify whether similar results can be achieved with higher doses. Third, the optimal dose of olanzapine required to control CINV is unclear. Further studies are needed to verify whether the same outcomes can be achieved at a dose of 2.5 mg and if the effect is increased at a dose of 10 mg. Finally, QOL evaluation was not performed in this study. QOL evaluation should be considered in a further study.

Based on the results of the present study, we are planning a phase III randomized controlled trial to verify the efficacy and safety of a four-agent combination regimen containing olanzapine with triplet therapy to prevent CINV caused by cisplatin-based HEC.

Conclusions

We administered preventive olanzapine combined with triplet therapy to chemotherapy-naïve patients with gynecological cancer receiving chemotherapy with HEC containing cisplatin ≥50 mg/m^2. These results were superior to those of triplet therapy studies reported to date and suggested that a four-agent combination regimen containing olanzapine is an effective regimen in the prevention of CINV in HEC.

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Conflict of interest The authors declare that they have no competing interests.

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