Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Hironobu Hashimoto, Masakazu Abe, Osamu Tokuyama, Hideaki Mizutani, Yosuke Uchitomi, Takuhiro Yamaguchi, Yukari Hoshina, Yasuhiko Sakata, Takako Yanai Takahashi, Kazuhisa Nakashima, Masahiko Nakao, Daisuke Takei, Sadamoto Zenda, Koki Mizukami, Satoru Iwasa, Michiru Sakurai, Noboru Yamamoto, Yuichiro Ohe

Summary

Background Olanzapine 10 mg added to standard antiemetic therapy including aprepitant, palonosetron, and dexamethasone has been recommended for the prevention of chemotherapy-induced nausea and vomiting. Guidelines suggest that a dose reduction to 5 mg should be considered to prevent sedation. In several phase 2 studies, olanzapine 5 mg has shown equivalent activity to olanzapine 10 mg and a favourable safety profile in relation to somnolence. We evaluated the efficacy of olanzapine 5 mg combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting caused by cisplatin-based chemotherapy.

Methods This was a randomised, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy of olanzapine 5 mg with triplet-combination antiemetic therapy done in 26 hospitals in Japan. Key inclusion criteria were patients with a malignant tumour (excluding those with a haemopoietic malignancy) who were scheduled to be treated with cisplatin (≥50 mg/m²) for the first time, age between 20 and 75 years, and with Eastern Cooperative Oncology Group performance status of 0–2. Eligible patients were randomly assigned (1:1) to receive either oral olanzapine 5 mg or placebo once daily on days 1–4 combined with aprepitant, palonosetron, and dexamethasone (dosage based on the standard antiemetic therapy against highly emetogenic chemotherapy). Patients were randomly assigned to interventions by use of a web entry system and the minimisation method with a random component, with sex, dose of cisplatin, and age as factors of allocation adjustment. Patients, medical staff, investigators, and individuals handling data were all masked to treatment assignment. The primary endpoint was the proportion of patients who achieved a complete response, defined as absence of vomiting and no use of rescue medications in the delayed phase (24–120 h). All randomly assigned patients who satisfied eligibility criteria received a dose of cisplatin 50 mg/m² or more, and at least one study treatment, were included in efficacy analysis. All patients who received any treatment in this study were assessed for safety. This study is registered at UMIN Clinical Trials Registry, number UMIN000024676.

Findings Between Feb 9, 2017, and July 13, 2018, 710 patients were enrolled; 356 were randomly assigned to receive olanzapine and 354 were assigned to receive placebo. All eligible patients were observed 120 h after cisplatin initiation. One patient in the olanzapine group and three in the placebo group did not receive treatment and were excluded from all analyses. One patient in the olanzapine group discontinued treatment on day 1 and was excluded from the efficacy analysis. In the delayed phase, the proportion of patients who achieved a complete response was 280 (79% [95% CI 75–83] of 354 patients in the olanzapine group and 231 (66% [61–71] of 351 patients in the placebo group (p<0·0001). One patient had grade 3 constipation and one patient had grade 3 somnolence related to treatment in the olanzapine group.

Interpretation Olanzapine 5 mg combined with aprepitant, palonosetron, and dexamethasone could be a new standard antiemetic therapy for patients undergoing cisplatin-based chemotherapy.

Funding Japan Agency for Medical Research and Development.

Introduction

Chemotherapy-induced nausea and vomiting is an unpleasant adverse event that can affect many patients. When not treated with antiemetics, the incidence of vomiting in patients treated with highly emetogenic chemotherapy exceeds 90%.[1] Currently, the standard antiemetic therapy for cisplatin—a highly emetogenic chemotherapy agent—involves triplet-combination therapy with a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, neurokinin-1 (NK1)

Lancet Oncol 2019

Published **Online** December 11, 2019 https://doi.org/10.1016/S1470-2045(19)30678-3

See **Online/Comment** https://doi.org/10.1016/S1470-2045(19)30791-0

Department of Pharmacy (H Hashimoto BS, T Y Takahashi PhD), **Innovation Center for Supportive, Palliative and Psychosocial Care** (Y Uchitomi MD, S Zenda MD), **Data Management Section** (Y Hoshina MS), **Department of Gastrointestinal Medical Oncology** (S Iwasa MD), **Department of Experimental Therapeutics** (N Yamamoto MD), **and Department of Thoracic Oncology** (Y Ohe MD) **National Cancer Center Hospital, Tokyo, Japan; Department of Gynaecologic Oncology** (M Abe MD), **Division of Thoracic Oncology** (K Nakashima MD), **and Department of Pharmacy** (M Sakurai MS), **Shizuoka Cancer Center, Nagaizumi, Japan; Department of Gynaecology** (O Tokuyama MD) **and Department of Pharmacy** (M Nakao MS), **Osaka City General Hospital, Osaka, Japan; Department of Respiratory Medicine** (H Mizutani MD) **and Department of Pharmacy** (D Takei BS), **Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan** (Prof T Yamaguchi PhD) **Saitama Cancer Center, Ina, Japan; and Department of Pharmacy, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan** (Y Sakata B, K Mizukami BS)

Correspondence to:
Dr Masakazu Abe, Department of Gynaecologic Oncology, Shizuoka Cancer Center, Nagaizumi 411–8777, Japan
ma.abe@scchr.jp

Research in context

Evidence before this trial

We searched PubMed for articles published between January 1, 2000, and December 31, 2018, with the terms "CINV", "highly emetogenic chemotherapy", "HEC", and "olanzapine", with no language restrictions. Olanzapine has been investigated as an antiemetic agent because it suppresses various receptors associated with nausea and vomiting. American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines recommend a combination of olanzapine 10 mg with the 5-hydroxytryptamine-3 receptor antagonist, neurokinin-1 receptor antagonist, and dexamethasone, for patients treated with highly emetogenic chemotherapy including cisplatin. In these guidelines, the recommended dose of olanzapine was 10 mg, based on the study by Navari and colleagues. However, several guidelines suggested that a dose of 5 mg should be considered in patients at risk of sedation. We previously did a randomised phase 2 study comparing 5 mg and 10 mg olanzapine combined with standard antiemetic therapy in patients receiving cisplatin. In the delayed phase (24–120 h after initiation of highly emetogenic chemotherapy) the proportion of patients achieving complete response were 78% in the 10 mg group and 86% in the 5 mg group. The most common treatment-related adverse event was somnolence (53% in the 10 mg group *vs* 45% in the 5 mg group).

Added value of this study

To our knowledge, the J-FORCE study was the first randomised, double-blind, placebo-controlled, phase 3 study to show that olanzapine 5 mg plus triplet-combination therapy results in a significant improvement compared with standard care (triplet-combination therapy) in the proportion of patients achieving complete response during the delayed phase, in patients treated with a cisplatin-based regimen.

Implications of all the available evidence

Our finding regarding the difference in complete response is clinically relevant as it exceeded the minimum difference of 10% for most efficacy assessments, which is the threshold recommended by the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) guideline. Our findings showed that olanzapine 5 mg combined with aprepitant, palonosetron, and dexamethasone could be a new standard antiemetic therapy in patients undergoing cisplatin-based chemotherapy.

receptor antagonist, and dexamethasone. However, the efficacy of this approach in the delayed phase (24–120 h after initiation of therapy with cisplatin) is insufficient.[2,3]

Olanzapine is an antipsychotic drug that targets multiple receptors and acts as an antagonist against various substances, including dopamine, serotonin, adrenaline, histamine, and muscarine.[4–6] Olanzapine has been investigated as an antiemetic drug because it is thought to suppress various receptors, including those for dopamine, serotonin, epinephrine, histamine, and muscarine. The guidelines established by the American Society of Clinical Oncology and National Comprehensive Cancer Network recommend a combination of olanzapine 10 mg with the aforementioned triplet-combination therapy (5-HT3 receptor antagonist, NK1 receptor antagonist, and dexamethasone) against highly emetogenic chemotherapy agents (HEC), including cisplatin.[7,8] However, these guidelines state that reduction of the dose of olanzapine to 5 mg should be considered for patients older than 75 years, and those who have excessive sedation while receiving olanzpine 10 mg.[7,8] Moreover, the guidelines established by the European Society for Medical Oncology and Multinational Association of Supportive Care in Cancer warn clinicians about excessive sedation following treatment with olanzapine 10 mg.[9] Triplet-combination therapy is a standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based chemotherapy. However, several studies that investigated this triplet combination therapy with olanzapine included a large proportion (60%) of participants treated with an anthracycline regimen.[10,11] Therefore, whether a four-drug combination therapy is effective for cisplatin-based regimens remains unclear, but we expected that olanzapine 5 mg would provide sufficient antiemetic efficacy for patinents receiving chemotherapy for the first time.

We have done three phase 2 studies investigating the efficacy and safety of the triplet-combination therapy with olanzapine 5 mg against chemotherapy-induced nausea and vomiting caused by cisplatin-based regimens.[12–14] The four-drug combination therapy including olanzapine 5 mg showed a good antiemetic effect in a phase 2 study involving patients with gynaecological cancer (n=40);[12] in a single-centre, phase 2 study involving patients with lung cancer (n=30);[13] and in a randomised, phase 2 study (n=153), which was planned to evaluate the efficacy and safety of two doses (10 mg and 5 mg) of olanzapine.[14] In the latter study, complete response in the delayed phase was achieved in 59 (78%; 80% CI 70–84; p=0·010) of 76 patients in the 10 mg arm and 66 (86%; 72–91; p<0·001) of 77 patients in the 5 mg groups. Olanzapine 5 mg showed equivalent efficacy and a lower incidence of adverse events (including somnolence) than did olanzapine 10 mg.[12]

The objective of this phase 3 (J-FORCE) study was to test the superiority of olanzapine 5 mg compared with placebo plus triplet-combination therapy for the prevention of chemotherapy-induced nausea and

vomiting caused by cisplatin-based chemotherapy in the delayed phase.

Methods

Study design and participants

This was a randomised, double-blinded, placebo-controlled, phase 3 study done in 26 Japanese hospitals (cancer centres, private hospitals, public hospitals, and university hospitals; appendix p 9).

The study included patients with a malignant tumour (excluding those with a haemopoietic malignancy) who were scheduled to be treated with first-line cisplatin (≥50 mg/m²). Additionally, patients eligible for inclusion in the study had to be aged 20 years or older and aged 75 years or younger. The other inclusion criteria were an Eastern Cooperative Oncology Group performance status 0–2; absence of symptomatic brain metastasis or carcinomatous meningitis; absence of treatment with the 5-HT3 receptor antagonist aprepitant, NK1 receptor antagonists, corticosteroids (including dexamethasone), dopamine antagonists, phenothiazine tranquilisers, antihistaminic drugs, benzodiazepines, barbiturates, and several other drugs (including haloperidol, droperidol) within 48 h before registration; and adequate organ function (ie, total bilirubin concentration of 2·0 mg/dL or less, aspartate aminotransferase and alanine aminotransferase concentrations of 100 U/L or less. We excluded patients aged 76 years or older because results from our phase 2 study suggested that risk of falls was increased in this patient group due to sedation when receiving olanzapine 10 mg.[14] Patients were excluded if they had one or more of the following events: unstable angina, myocardial infarction, cerebral haemorrhage, cerebral infarction, or active gastroduodenal ulcer within 6 months before registration. Patients were also excluded if they had a convulsive disorder requiring anticonvulsant treatment; ascites retention requiring therapeutic puncture; gastrointestinal obstruction (such as having gastropyloric constriction or intestinal obstruction); diabetes for which the patient was receiving treatment with either insulin or oral hypoglycemic group, or both; or HbA_{1c} (National Glycohemoglobin Standardization Program) of 6·5% or more at the time of registration. The full inclusion and exclusion criteria can be found in the protocol.

The study was done in compliance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (guidelines established by the Japanese Government), and the protocol (appendix p 10) was approved by the Ethics Committees of all participating institutions. All patients included in this study provided written, informed consent. The trial protocol was approved by the Japan Supportive, Palliative and Psychological Oncology Group Protocol Review Committee and the institutional review boards of each participating institution.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either olanzapine 5 mg or placebo, plus the triplet-combination.

The registration and randomisation were done using the web entry system, which required a personal account and password. Inquiries about patient registration and the web entry system were managed at the data management section in the National Cancer Center Hospital and by the study secretariat. The minimisation method with a random component was applied for randomisation, using gender (male *vs* female), dose of cisplatin (≥70 mg/m² *vs* <70 mg/m²), and age (≥55 years *vs* <55 years) as factors of allocation adjustment. The allocation information was independently maintained by the pharmacists who prepared the study drugs (dispensing pharmacists) to ensure the double-blinding of the study. Patients, medical staff, investigators, and individuals who handled the data were masked to treatment assignment.

See Online for appendix

Regarding the study drugs, 0·25 g olanzapine (Zyprexa Fine Granules; Eli Lilly Japan KK; active drug) or 0·25 g lactose (placebo) were added into capsules (DB caps, Lonza Japan) to achieve effective masking.

Procedures

5-HT3 receptor antagonist (palonosetron hydrochloride [hereafter referred to as palonosetron] 0·75 mg) was administered intravenously to patients at a maximum of 30 min before the administration of cisplatin on the first day of anticancer therapy (day 1). NK1 receptor antagonist (oral aprepitant 125 mg or intravenous fosaprepitant 150 mg) were administered at a maximum of 1 h before the administration of cisplatin on day 1. When aprepitant was administered on day 1, aprepitant 80 mg was also orally administered after breakfast on days 2 and 3. Dexamethasone 12 mg was administered orally or intravenously (dependent on institution at a maximum of 30 min before administration of cisplatin on day 1. Dexamethasone 8 mg was also administered on days 2–4. When fosaprepitant was administered on day 1, the dose of dexamethasone on days 3 and 4 was increased to 16 mg, because blood concentration of fosaprepitant decreases on days 3 and 4.[15] Olanzapine or placebo were administered after dinner for 4 days from the day of initial administration of cisplatin. Two capsules were orally administered on each occasion. The patients were admitted to hospital and observed for 120 h after initiation of cisplatin.

Patients recorded the following items into their symptom diary every 24 h: the number of vomiting episodes and the time of first vomiting; severity of nausea using a Likert scale (0, no nausea; 1, mild nausea; 2, moderate nausea; 3, severe nausea); number of rescue

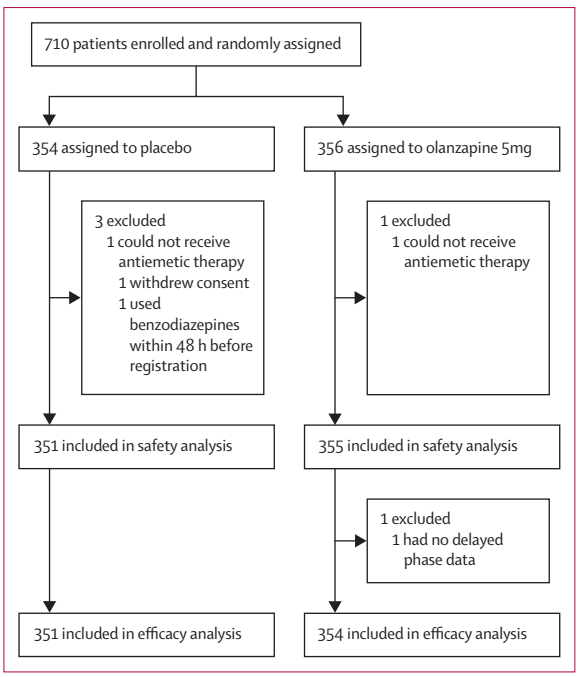

Figure 1: **Trial profile**

medications and the time of the first administration; severity of appetite loss (0, not at all; 1, a little bit; 2, quite a bit; 3, very much); severity of sleepiness in the daytime; the incidence of concentration impairment due to sleepiness; and frequency of sleepiness (0, not at all; 1, a little bit; 2, quite a bit; 3, very much).

Adverse events (constipation, hiccups, somnolence, insomnia, dry mouth, dizziness) were assessed every 24 h during patients' hospital admission by clinical study personnel or attending physicians, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0, Japanese version established by the Japan Clinical Oncology Group.

After the completion of the study period, the patients assessed the degree of their satisfaction regarding the antiemetic therapy using a seven-point categorical scale (0, very satisfied; 1, satisfied; 2, somewhat satisfied; 3, rather satisfied; 4, rather dissatisfied; 5, dissatisfied; 6, very dissatisfied), and entered the result of this assessment into their symptom diary.

Outcomes

The primary endpoint was the proportion of patients achieving complete response in the delayed phase (24–120 h from the initiation of cisplatin). Complete response was defined as a condition in which a patient does not experience vomiting or retching and does not require additional treatment with antiemetics. The secondary endpoints were: proportion of patients who achieved a complete response in the acute phase (0–24 h from the initiation of cisplatin) and overall phase (0–120 h from the initiation of cisplatin); proportions of complete control—defined as a condition in which a patient does not report more than mild nausea (0 or 1 on a 4-grade categorical scale) during complete response in the acute, delayed, and overall phases; the proportions of total control—defined as a condition in which a patient does not report nausea during complete response in the acute, delayed, and overall phases; and incidence of adverse events. Time to treatment failure was defined as the time from the initiation of therapy with cisplatin to the first episode of vomiting or to the administration of a rescue antiemetic, whichever came first.

Statistical analysis

Based on the complete response proportions reported in patients treated with the triplet-combination therapy in previous studies, the proportion of patients who would achieve a complete response in the placebo group was assumed to be 65%.[16] Moreover, a 10% improvement in this proportion (following the addition of olanzapine 5 mg) is considered clinically significant in the design of a superiority trial. The sample size was calculated to be 329 patients per group (658 patients in total), with a significance level of 2·5% in a one-sided test and a detection power of 80%. The planned number of patients for enrolment was set at 690 patients, with consideration of a 5% of ineligible and untreated patients.

95% CIs were calculated for the proportion of patients achieving a complete response, complete control, and total control and the intergroup differences were analysed using the Mantel–Haenszel test after adjustment for allocation adjustment factors (age ≥55 years or <55 years, sex, and dose of cisplatin ≥70 mg/m² or <70 mg/m²). The significance level was set at 2·5% in the one-sided test. Time course changes every 24 h from day 1 to day 5 in patients achieving a complete response, complete control, and total control was analysed in a similar manner; p values were generated using the Generalized Estimating Equation with unstructured working correlation. For the time to treatment failure, we calculated the estimates of the median and the 95% CI in each group using the Kaplan–Meier method and analysed the inter-group differences using a log-rank test. Additional prespecified analyses were done for number of vomiting episodes and the time of first vomiting; severity of nausea; number of rescue medications and the time of the first administration; severity of appetite loss; severity of sleepiness in the daytime; the incidence of concentration impairment due to sleepiness; and frequency of sleepiness. We analysed inter-group differences using the Mantel test. The significance level in the two-sided test was set at 5%.

All randomly assigned patients who satisfied eligibility criteria received a dose of cisplatin 50 mg/m² or more, and at least one study treatment, were included in efficacy analysis. All patients who received any treatment in this study were assessed for safety.

	Olanzapine group (n=355)	Placebo group (n=351)
Age, years		
Median age	65 (22–75)	66 (30–75)
≥55	292 (82%)	290 (83%)
<55	63 (18%)	61 (17%)
Sex		
Male	237 (67%)	234 (67%)
Female	118 (33%)	117 (33%)
ECOG performance status		
0	228 (64%)	214 (61%)
1	121 (34%)	136 (39%)
2	6 (2%)	1 (<1%)
Cancer type		
Head and neck	33 (9%)	25 (7%)
Lung	179 (50%)	183 (52%)
Oesophageal	75 (21%)	79 (23%)
Gastric	20 (6%)	19 (5%)
Gynaecological	34 (10%)	34 (10%)
Urological	3 (1%)	1 (<1%)
Other	11 (3%)	10 (3%)
Planned cisplatin dose		
≥70 mg/m²	265 (75%)	262 (75%)
<70 mg/m²	90 (25%)	89 (25%)
Concurrent radiotherapy		
Yes	76 (21%)	79 (23%)
No	279 (79%)	272 (77%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

	Olanzapine group (n=354)	Placebo group (n=351)	$p_{interaction}$*
Complete response†			
Day 1	336 (95%)	311 (89%)	0·47
Day 2	325 (95%)	296 (84%)	..
Day 3	321 (91%)	285 (81%)	..
Day 4	317 (90%)	283 (81%)	..
Day 5	311 (88%)	268 (76%)	..
Complete control‡			
Day 1	333 (94%)	309 (88%)	0·27
Day 2	324 (92%)	290 (83%)	..
Day 3	319 (90%)	274 (78%)	..
Day 4	317 (90%)	276 (79%)	..
Day 5	305 (86%)	263 (75%)	..
Total control§			
Day 1	304 (86%)	283 (81%)	0·061
Day 2	277 (78%)	238 (68%)	..
Day 3	271 (77%)	233 (66%)	..
Day 4	280 (79%)	231 (66%)	..
Day 5	261 (74%)	234 (67%)	..

Data are n (%). *Generalised Estimating Equation with unstructured working correlation. †Average difference, 7·9% (95% CI 4·5–11·4) p<0·0001. ‡Average difference, 8·4% (95% CI 4·9–12·0) p<0·0001. §For total control, the difference for each day was estimated because treatment by time was considered almost significant. Day 1: 5·2% (95% CI −0·3 to 10·8); day 2: 10·4% (3·9 to 17·0); day 3: 10·1% (3·5 to 16·8); day 4: 13·3% (6·7 to 19·8); day 5: 7·0% (0·3 to 13·8).

Table 2: **Proportion of patients in the efficacy analysis set achieving a complete response, complete control, and total control from day 1 to day 5**

Analyses were done with SAS software (version 9.4). Japan Supportive, Palliative and Psychological Oncology Group monitored safety data. This study is registered with the University Hospital Medical Information Network Clinical Trials Registry, number UMIN000024676.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 9, 2017 and July 13, 2018, 710 patients were enrolled (figure 1). The patients were randomly assigned to receive olanzapine (356 patients) or placebo (354 patients). Four patients did not receive the antiemetic treatment; thus, 706 patients (355 in the olanzapine group and 351 in the placebo group) were analysed for safety. All 706 patients were given the triplet-combination therapy as scheduled. Moreover, one patient discontinued treatment on day 1 because of hyperammonemia; therefore, data regarding nausea and vomiting in the delayed phase were not obtained for this patient. Consequently, the patient was excluded from the efficacy analysis population.

No obvious differences in baseline characteristics were observed between the two groups (table 1). All patients who received cisplatin were followed up for 120 h after treatment initiation. 43 (12%) of 354 patients in the olanzapine group and 83 (24%) of 351 in the placebo group had vomiting, required additional treatment with antiemetics, or both.

After adjusting for allocation adjustment factors, the proportion of patients who achieved a complete response in the delayed phase was significantly higher in the olanzapine group than in the placebo group (280 [79%; 95% CI 75–83] of 354 patients *vs* 231 [66%; 61–71] of 351 patients; p<0·0001). In the acute phase, 336 (95%; 95% CI 93–97) patients in the olanzapine group and 311 (89%; 85–92) patients in the placebo group achieved a complete response (p=0·0021). In the overall period, 276 (78%; 95% CI 74–82) patients in the olanzapine group versus 223 (64%; 59–69) patients in the placebo group achieved a complete response (p<0·0001).

Additionally, the proportion of patients achieving complete control and the proportion of those achieving total control were higher in the olanzapine group than in the placebo group (appendix p 1). In the delayed phase, 276 (78%; 95% CI 74–82) of 354 patients in the olanzapine

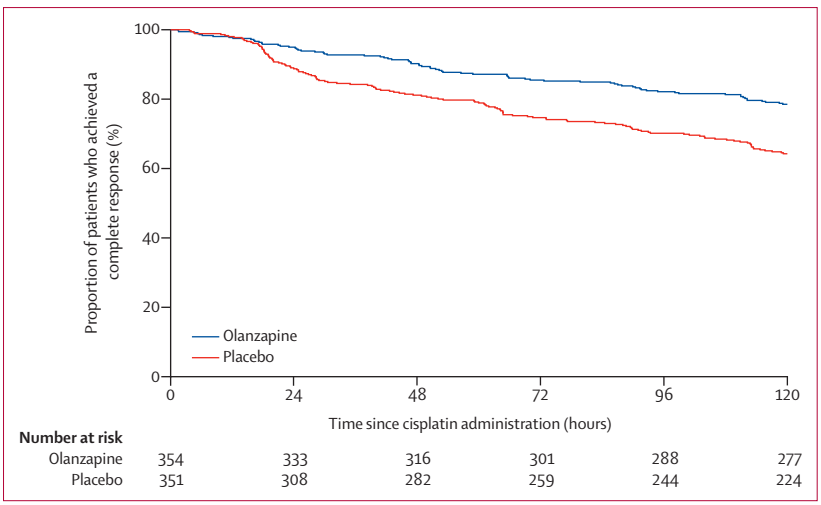

Figure 2: **Kaplan-Meier plot showing time to treatment failure for olanzapine and placebo**

	Olanzapine (n=355)			Placebo (n=351)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Constipation	32 (9%)	19 (5%)	1 (<1%)	21 (6%)	16 (5%)	0
Hiccups	31 (9%)	4 (1%)	0	19 (5%)	2 (1%)	0
Somnolence	137 (39%)	15 (4%)	1 (<1%)	103 (29%)	13 (4%)	0
Insomnia	15 (4%)	2 (1%)	0	22 (6%)	4 (1%)	0
Dizziness	28 (8%)	1 (<1%)	0	11 (3%)	0	0
Dry mouth	73 (21%)	1 (<1%)	0	32 (9%)	0	0

Table 3: **Treatment-related adverse events in the safety population**

group versus 223 (64%; 59–67) of 351 patients in the placebo group achieved complete control (p<0·0001) and 213 (60%; 55–65) versus 176 (50%; 45–55) achieved total control (p=0·0071). In the overall period, 270 (76%; 95% CI 72–81) patients in the olanzapine group versus 214 (61%; 56–66) in the placebo group achieved complete control (p<0·0001) and 208 (59%; 54–64) versus 169 (48%; 43–53) achieved total control (p<0·0049). In the acute phase, 333 (94%; 95% CI 92–97) patients in the olanzapine group versus 309 (88%; 85–91) patients in the placebo group achieved complete control (p=0·0042) and 304 (86%; 82–90) versus 283 (81%; 77–85) achieved total control (p=0·055). Changes in the proportion of patients achieving a complete response, complete control, and total control over time (every 24 h) are presented in table 2.

Patient-reported severity of nausea was significantly higher in the placebo group than in the olanzapine group on days 2–4, but not on days 1 and 5 (appendix p 2). Patient-reported severity of vomiting and use of rescue medication are in the appendix (p 2) Time to treatment failure was significantly longer in the olanzapine group than in the placebo group (hazard ratio [HR] 0·544 [95% CI 0·410–0·723]; p<0·0001; figure 2). Median time to treatment failure was not reached in either group (95% CI not reached).

The proportion of patients who graded their severity of sleepiness in the daytime as "very much" was significantly higher in the olanzapine group than in the placebo group on day 1, but was similar between the groups on all other days (appendix p 4). The proportion of patients who reported sleepiness during daytime in their symptom diary changed over time in each group and is presented in the appendix (p 5). The proportion of patients who reported good quality of sleep was higher in the olanzapine group than in the placebo group throughout the study period (appendix p 6). The incidence of concentration impairment due to sleepiness was higher in the placebo group than in the olanzapine group on days 4 and 5 (appendix p 7). The proportion of patients who reported appetite loss was significantly lower in the olanzapine group than in the placebo group on days 2–5 (appendix p 8).

Regarding the level of satisfaction with the treatment, the proportion of patients who reported that they were "very satisfied" and "satisfied" was significantly higher in the olanzapine group than in the placebo group (appendix p 3).

Grade 3 constipation (n=1) and somnolence (n=1) related to treatment were reported in two patients in the olanzapine group (table 3).

Discussion

To our knowledge, this was the first randomised, double-blind, placebo-controlled, phase 3 study to show a significant improvement in complete response in the delayed phase for patients who received olanzapine 5 mg plus triplet-combination therapy versus those who received placebo plus triplet-combination therapy during treatment with cisplatin. Consistent with the results of a previous study, the proportion of patients achieving a complete response in the acute phase was also significantly higher in the olanzapine group versus the placebo group.[11] In a study that replaced aprepitant in the standard triplet-combination therapy with olanzapine 10 mg, the proportion of patients achieving complete response was 87% in the aprepitant group and 97% in the olanzapine group.[10] Addition of olanzapine to the standard triplet-combination therapy exerted a satisfactory antiemetic effect throughout the entire observation period, including in the acute phase of highly emetogenic chemotherapy treatment.

The observed differences in proportions of patients achieving a complete response between the olanzapine and placebo groups was 6 percentage points for the acute phase, 13 percentage points for the delayed phase, and 14 percentage points for the overall phase. Of note, the proportion differences reported in a previous study were 21 for the acute phase, 15 for the delayed phase, and 23 for the overall phase.[11] The differences observed in the proportion of patients who achieved a complete response between the studies could be attributed to differences in the target

populations, but not to differences in the dose of olanzapine because patients included in the previous study were treated with cisplatin and anthracycline and cyclophosphamide.[11] In another clinical study investigating triplet-combination therapy in patients treated with anthracycline and cyclophosphamide, the outcome in the acute phase was poorer in patients treated with anthracycline and cyclophosphamide than in those treated with cisplatin.[17] Therefore, these two populations should not be deemed identical. In a study examining the sparing of dexamethasone from the triplet-combination therapy in patients who received anthracycline and cyclophosphamide or cisplatin, non-inferiority was not demonstrated in the group treated with cisplatin.[18] Therefore, the effect of antiemetic therapy against highly emetogenic chemotherapy in patients treated with anthracycline and cyclophosphamide and those treated with cisplatin should be independently evaluated.

The present four-drug combination therapy containing olanzapine 5 mg sufficiently controls nausea and vomiting at a lower dose compared with the olanzapine 10 mg recommended by several guidelines. The necessity to confirm the usability of olanzapine at doses less than 10 mg was also emphasised in the study that provided evidence for the use of olanzapine 10 mg.[11]

Sleepiness is one of the most inconvenient adverse events associated with olanzapine. However, in the present study, no differences were found between the two groups in the incidence of daytime sleepiness and degree of associated difficulty experienced in daily life. This observed reduction compared wth the previous study in the incidence of sleepiness might be linked to the lower olanzapine dose (5 mg *vs* 10 mg), and the time of administration (after dinner). The time to maximum blood concentration of olanzapine is 3–5 h. Therefore, when administered after dinner, the concentration of olanzapine in the blood reaches its peak while patients are sleeping. The incidence of sleepiness was higher than the baseline on day 2 and decreased thereafter. Notably, a similar effect was observed in previous studies.[11,14]

Additionally, the incidence of insomnia and appetite loss was significantly lower in the olanzapine group than in the placebo group. The decreased appetite loss is inconsistent with the results of a previous study,[11] which did not report a difference in appetite loss between the olanzapine and placebo groups.

Less than 7 h sleep is an established risk factor for nausea.[19] A low incidence of insomnia might exert a favourable effect on nausea. Finally, the level of satisfaction with the antiemetic therapy was higher in the olanzapine group than the placebo group.

A limitation of this study was that patients treated with anthracycline and cyclophosphamide were excluded. This study was done in patients treated exclusively with a regimen containing cisplatin. A study of antiemetic therapy in patients treated with anthracycline and cyclophosphamide reported that dexamethasone could be omitted after day 2.[20] By contrast, another study reported that the use of dexamethasone on days 2 and 3 is effective.[17] Therefore, patients treated with anthracycline and cyclophosphamide were excluded from the present study, because treatment with dexamethasone on days 2 and 4 is an essential component of standard antiemetic therapy.

In conclusion, olanzapine 5 mg combined with aprepitant, palonosetron, and dexamethasone could be a new standard antiemetic therapy option in patients undergoing cisplatin-based chemotherapy.

Contributors

HH, MA, TYT, SI, SZ, and NY contributed to trial conception and design. YH contributed to data management. TY did the statistical analysis. HH and MA contributed to the initial draft of the manuscript and are responsible for the decision to submit the manuscript for publication. The first author (HH) and statistician (TY) had full access to the data, and take responsibility for the integrity of the data and adherence to the study protocol. All authors contributed to data collection and interpretation, and revision of the manuscript for important content.

Declaration of interests

TY reports grants from AC Medical, A2 Healthcare Corporation, FMD K&L Japan KK, Japan Media Corporation, Luminary Medical KK, Kyowa Hakko Kirin, Otsuka Pharmaceutical, Eisai, Medrio, intellim Corporation, Welby, 3H Medi Solution, Nobori, Puravida Technologies LLC, and Baseconnect; grants and personal fees from CAC Croit Corporation, Japan Tobacco, Medidata Solutions, Ono Pharmaceutical, Tsumura & Co, Daiichi Sankyo Company, Asahi Sahi Intecc, 3H Clinical Trial, Nipro Corporation; and personal fees from Kowa Company, Chugai Pharmaceutical, and Asahi Kasei Pharma Corporation, outside of the submitted work. SZ reports personal fees from Merck Serono, outside of the submitted work. SI reports grants from Japan Agency for Medical Research and Development, during the conduct of the study; grants and personal fees from Eli Lily; personal fees from Taiho, Chugai and Ono Pharmaceutical; and grants from Novartis, Merck-Serono, Daiichi-Sankyo, Bristol-Myers Squibb, Bayer, and Eisai, outside of the submitted work. NY reports grants from Chugai, Taiho, and Eisai, Lilly, Quintiles, Astellas, BMS, Novartis, Daiichi-Sankyo, Pfizer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Bayer, Ono Pharmaceutical, Takeda, Janssen Pharma, MSD, and Merck; and personal fees from Ono Pharmaceutical, Taiho, Chugai, AstraZeneca, Pfizer, Lilly, BMS, Eisai, Otsuka, Takeda, Boehringer Ingelheim, and Cimic, outside of the submitted work. YU reports grants from Japan Agency for Medical Research and Development, during the conduct of the study. YO reports grants from Kissei, Dainippon-Sumitomo, Ignyta, and ROXO; grants and personal fees from AstraZeneca, Taiho, Chugai, Lilly, Ono Pharmaceutical, BMS, Pfizer, MSD, Kyorin, Takeda, and Novartis; and personal fees from Celltrion, Amgen, and Boehringer Ingelheim, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual participant data that underlie the results reported in this article, after deidentification, will be shared with investigators whose proposed use of the data has been approved by the investigators from the data monitoring committee of the Japan Supportive, Palliative and Psychological Oncology Group. The study protocol, statistical analysis plan, informed consent forms, and ethics committee approval are available. Proposals should be directed to hhashimo@ncc.go.jp.

Acknowledgments

This was an investigator-initiated study, supported by the Japan Supportive, Palliative and Psychosocial Oncology Group, and funded

by the Japan Agency for Medical Research and Development.
We thank the patients and the study teams for their participation in this study. We are also grateful to the members of the National Cancer Center Hospital Data Management Section for their support in data management (Kaoru Koike, Mikio Mori), and oversight of the study management (Haruhiko Fukuda). The study was supported in part by the Japan Supportive, Palliative and Psychosocial Oncology Group and funded by the Japan Agency for Medical Research and Development, grant number JP18ck0106214.

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