# Olanzapine Plus Triple Antiemetic Therapy for the Prevention of Carboplatin-Induced Nausea and Vomiting: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial

# Olanzapine Plus Triple Antiemetic Therapy for the Prevention of Carboplatin-Induced Nausea and Vomiting: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial

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## ABSTRACT

**PURPOSE** We evaluated the efficacy and safety of antiemetic therapy with olanzapine, a neurokinin-1 receptor antagonist (RA), a 5-hydroxytryptamine-3 (5-$HT_3$) RA, and dexamethasone for preventing chemotherapy-induced nausea and vomiting in patients receiving carboplatin-containing chemotherapy.

**PATIENTS AND METHODS** Chemotherapy-naïve patients scheduled to receive carboplatin (AUC ≥5) were randomly assigned to receive either olanzapine 5 mg once daily (olanzapine group) or placebo (placebo group) in combination with aprepitant, a 5-$HT_3$ RA, and dexamethasone. The primary end point was the complete response (CR; no vomiting and no rescue therapy) rate in the overall phase (0-120 hours). Secondary end points included the proportion of patients free of nausea and safety.

**RESULTS** In total, 355 patients (78.6% male, median age 72 years, 100% thoracic cancer), including 175 and 180 patients in the olanzapine and placebo groups, respectively, were evaluated. The overall CR rate was 86.9% in the olanzapine group versus 80.6% in the placebo group. The intergroup difference in the overall CR rate was 6.3% (95% CI, −1.3 to 13.9). The proportions of patients free of chemotherapy-induced nausea in the overall (88.6% in the olanzapine group *v* 75.0% in the placebo group) and delayed (89.7% *v* 75.6%, respectively) phases were significantly higher in the olanzapine group than in the placebo group (both $P < .001$). Somnolence was observed in 43 (24.6%) and 41 (22.9%) patients in the olanzapine and placebo groups, respectively, and no events were grade ≥3 in severity.

**CONCLUSION** The addition of olanzapine was not associated with a significant increase in the overall CR rate. Regarding the prevention of nausea, adding olanzapine provided better control in patients receiving carboplatin-containing chemotherapy, which needs further exploration.

ACCOMPANYING CONTENT

Appendix

Protocol

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## INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is among the most frequent and distressing adverse events.[1-4] The prevention of CINV using optimal antiemetic treatment is important to achieve treatment success.[5] Although supportive care with prophylactic antiemetic drugs has improved the control of emesis, CINV remains a significant challenge in cancer supportive care.[2-4,6-8]

Carboplatin can induce acute and delayed emesis.[2,3,6] Previously, carboplatin had been classified as a moderately emetogenic chemotherapy (MEC) agent that necessitated double antiemetic therapy with a 5-hydroxytryptamine-3 (5-$HT_3$) receptor antagonist (RA) and dexamethasone.[2,9,10] Currently, carboplatin is managed independently from MEC, and antiemetic guidelines recommend the prophylactic administration of a neurokinin-1 ($NK_1$) RA, a 5-$HT_3$ RA, and dexamethasone.[4,6,11] This triple antiemetic therapy for carboplatin-containing chemotherapy provided a 60%-80% complete response (CR; no vomiting and no use of rescue medication) rate in the overall phase.[12-16] However, the control of CINV, especially nausea, remains suboptimal despite prophylactic treatment with these antiemetic agents.

## CONTEXT

**Key Objective**

Can adding olanzapine to triple antiemetic therapy improve chemotherapy-induced nausea and vomiting in patients receiving carboplatin?

**Knowledge Generated**

The overall complete response rate was excellent, 86.9%, albeit without significance. Olanzapine significantly prevented carboplatin-induced nausea in the delayed and overall phases.

**Relevance *(C. Zimmermann)***

Further trials are warranted that evaluate adding a 10 mg dose of olanzapine to triple antiemetic therapy, and that assess olanzapine in samples including non-thoracic cancers and a greater proportion of younger, female patients.*

*Relevance section written by *JCO* Associate Editor Camilla Zimmermann, MD, PhD, FRCPC.



Olanzapine is an antipsychotic drug that inhibits signaling via multiple neurotransmitter receptors.[17-20] Because these multiple receptors, particularly the dopaminergic $D_2$, 5-$HT_{2c}$, and 5-$HT_3$ receptors, are considered to be involved in vomiting and nausea, the effect of olanzapine on these receptors provides a pharmacologic rationale for its use in CINV prevention.[17,18]

Several studies demonstrated that adding olanzapine to triple therapy consisting of an $NK_1$ RA, a 5-$HT_3$ RA, and dexamethasone in highly emetogenic chemotherapy (HEC) regimens improved CINV control.[21] Navari et al[22] conducted a randomized phase III study of patients receiving cisplatin-based or cyclophosphamide and anthracycline regimens, and reported that olanzapine (10 mg) in combination with aprepitant or fosaprepitant, a 5-$HT_3$ RA, and dexamethasone improved the CR rate in the acute, delayed, and overall phases. A randomized, Japanese trial revealed that olanzapine 5 mg improved the delayed CR rate in patients receiving cisplatin-based chemotherapy.[23] Zhao et al[24] reported that adding olanzapine improved antiemetic efficacy even in patients receiving multiday chemotherapy. At present, guidelines recommend a four-drug combination therapy with olanzapine for cisplatin-based or cyclophosphamide and anthracycline regimens.[4,6,11]

As observed in antiemetic therapy for HEC regimens, we hypothesized that adding olanzapine would be useful for patients receiving carboplatin-containing chemotherapy. We previously conducted a pilot phase II study to evaluate antiemetic therapy with olanzapine 5 mg, aprepitant, 5-$HT_3$ RA, and dexamethasone in patients who received carboplatin.[25] The overall CR rate was 93.3% (95% CI, 80.4 to 98.3). At present, triple therapy is standardized for carboplatin-containing chemotherapy, and a placebo-controlled comparative study between triple therapy and olanzapine-added therapy is warranted. In this phase III study, we examined the efficacy and safety of adding olanzapine 5 mg once daily to triple antiemetic therapy for CINV prevention in patients receiving carboplatin-containing chemotherapy.

## PATIENTS AND METHODS

### Study Design

This multicenter, prospective, randomized, double-blind, placebo-controlled phase III trial was conducted at 16 hospitals in Japan.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the institutional review board (approval No.: 19-120). Written informed consent was obtained from all participants included in this study. The trial was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN ID 000037749).

### Patients

Patients with pathologically confirmed malignant solid tumors who had not received previous chemotherapy and who were scheduled to receive the first course of carboplatin-containing chemotherapy (AUC ≥5) were eligible for inclusion. Additional eligibility criteria included age 20 years and older; adequate hematopoietic, renal, and liver functions; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. The exclusion criteria included nausea and vomiting within 24 hours before chemotherapy administration for any reason, the use of any antiemetic agents within 48 hours before carboplatin administration, and the use of pimozide or anticonvulsants (because of contraindication or caution against combined use). Patients

with diabetes mellitus or symptomatic brain metastasis were excluded. Patients who received concurrent chest and abdominal radiotherapy were excluded from this study.

### Randomization and Masking

Eligible patients were randomly assigned 1:1 to receive olanzapine 5 mg once daily or matching placebo orally in addition to triple antiemetic therapy. Registration was performed by the investigators via an interactive entry system. Randomization was undertaken centrally using a computer program. Unblinded pharmacists were mandatorily required to maintain the blinding procedures to ensure the double blinding of the study. Regarding the study drugs, olanzapine or maltose (placebo) was added to the capsules to achieve effective masking. Patients, medical professionals, and investigators who handled the data were blinded to treatment assignment.

### Treatment Schedule

Olanzapine or a matching placebo was administered orally on days 1-4 after the evening meal once daily. All patients received the guideline-directed prophylactic antiemetic therapy and dosage, including a 5-$HT_3$ RA on day 1, dexamethasone (4.95 mg intravenously) on day 1, and aprepitant (125 mg on day 1 and 80 mg on days 2-3) once daily. A 5-$HT_3$ RA (palonosetron intravenously at a dose of 0.75 mg or granisetron intravenously at a dose of 4 $\mu$g/kg body weight or orally at a dose of 2 mg) was selected according to the discretion of the attending physician and the package insert in Japan. When patients received paclitaxel, they received prophylactic dexamethasone and $H_1$ and $H_2$ blockers according to the package insert in Japan. Additional antiemetic agents and other supportive treatments were administered at the discretion of the treating physicians. The carboplatin dose was calculated according to the Calvert formula. The glomerular filtration rate was estimated using the Cockcroft-Gault formula. Bevacizumab or immune checkpoint inhibitors were added for some eligible patients.

### Assessments

Efficacy assessments during 0-120 hours in the first course of the first chemotherapy cycle were performed during hospitalization. Patients were asked to complete a daily questionnaire regarding the frequency of vomiting, the presence and severity of nausea, and appetite loss according to a four-point Likert scale (0, none; 1, mild; 2, moderate; 3, severe) every 24 hours. In assessing the number of emetic events that occurred, one episode was counted as one occurrence. Medical staff recorded the use of additional rescue antiemetic therapies during the study period.

### Outcomes

The primary end point was the CR rate in the overall phase (the first 120 hours after the start of chemotherapy). Secondary end points included the CR rates in the acute (0-24 hours) and delayed phases (24-120 hours); the proportion of patients free of nausea (where nausea is considered a subjective sick or queasy sensation[17] and defined as a score of 0 on the basis of a four-point scale); the complete control (CC) rate (no vomiting, no rescue therapy, and no or mild nausea); the total control (TC) rate (no vomiting, no rescue therapy, and no nausea); the proportions of patients without appetite loss in the overall, acute, and delayed phases; and safety. Adverse events were graded according to the terminology and grading categories defined in the Common Toxicity Criteria for Adverse Events, version 5.0.

### Statistical Analysis

For the CR rate, no nausea rate, CC rate, TC rate, and prevalence of appetite loss, intergroup differences were calculated, and their 95% CIs were estimated. The primary and secondary end points between the groups were compared using Fisher's exact test. The proportion of patients achieving a CR, CC, or TC, and those with nausea and appetite loss were analyzed every 24 hours. Subgroup analyses of the overall CR rate were conducted to assess the efficacy of adding olanzapine across demographic characteristics. The overall CR rate for triple antiemetic therapy in patients receiving carboplatin-containing chemotherapy was assumed to be 80% on the basis of the results of a phase II study.[12] Because a >10% improvement upon the addition of a new agent to standard treatment is considered clinically significant in the design of a superiority trial,[26] the sample size was calculated to be 354 patients to achieve 80% statistical power with a two-sided $\alpha$ error of .05. The planned number of patients for enrollment was set at 380 after considering dropouts or withdrawals. Efficacy analyses were based on the full analysis set, which comprised randomly assigned patients who satisfied the eligibility criteria, received carboplatin-containing chemotherapy, and used at least one study drug. All data were analyzed using JMP (version 13.2) and EZR statistical software (version 1.41). The significance level in the two-sided test was set at 5%.

## RESULTS

### Patients

Between August 15, 2019, and June 30, 2023, 378 patients with cancer were enrolled and randomly assigned to receive olanzapine (188 patients) or placebo (190 patients; Fig 1). After random assignment, 13 patients in the olanzapine group and nine patients in the placebo group did not receive chemotherapy because of protocol deviation, worsening general condition, or consent withdrawal. Moreover, one patient in the placebo group discontinued treatment on day 1 because of an anaphylactic reaction to an anticancer agent; therefore, this patient was excluded from the analysis. Patient characteristics are listed in Table 1. The median age was 72 years (range, 38-85 years), and 279 patients (78.6%) were male. Most patients had a good performance status, and 11

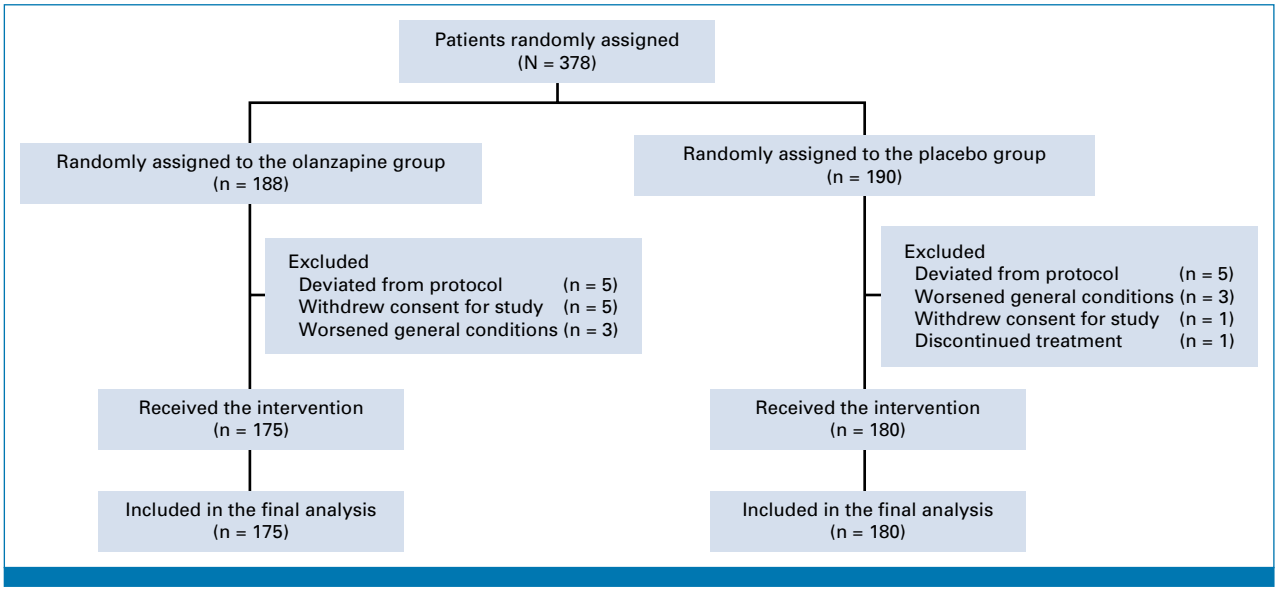


**FIG 1.** CONSORT diagram.

**TABLE 1.** Patient Characteristics

| Characteristic | Olanzapine (n = 175) | Placebo (n = 180) |
|---|---|---|
| Age, years | | |
| Median (range) | 72 (38-85) | 72 (49-85) |
| Sex, No. (%) | | |
| Male | 139 (79.4) | 140 (77.8) |
| Female | 36 (20.6) | 40 (22.2) |
| Performance status,[a] No. (%) | | |
| 0 | 134 (76.6) | 133 (73.9) |
| 1 | 35 (20.0) | 42 (23.3) |
| 2 | 6 (3.4) | 5 (2.8) |
| Cancer type, No. (%) | | |
| Lung adenocarcinoma | 82 (46.9) | 95 (52.8) |
| Squamous cell lung carcinoma | 33 (18.9) | 33 (18.3) |
| Small cell lung cancer | 38 (21.7) | 33 (18.3) |
| Others[b] | 22 (12.5) | 19 (10.6) |
| Carboplatin-containing chemotherapy regimen, No. (%) | | |
| Pemetrexed ± bevacizumab ± ICI | 49 (28.0) | 63 (35.0) |
| Nab-paclitaxel ± ICI | 52 (29.7) | 52 (28.9) |
| Paclitaxel ± ICI | 33 (18.9) | 26 (14.4) |
| S-1 | 0 (0.0) | 1 (1.0) |
| Etoposide ± ICI | 41 (23.4) | 38 (21.1) |
| 5-hydroxytryptamine-3 receptor antagonist, No. (%) | | |
| Granisetron | 34 (19.4) | 41 (22.8) |
| Palonosetron | 141 (80.6) | 139 (77.2) |
| Drinking habits, No. (%) | 73 (41.7) | 59 (32.8) |

Abbreviation: ICI, immune checkpoint inhibitor.
[a]Performance status was determined according to the Eastern Cooperative Oncology Group scale.
[b]Others include large cell lung carcinoma, non–small cell lung carcinoma not otherwise specified, pleomorphic lung carcinoma, thymic carcinoma, and pleural mesothelioma.

**TABLE 2.** Proportion of Patients Achieving CINV Control

| End Point | Olanzapine (n = 175), % (95% CI) | Placebo (n = 180), % (95% CI) | Difference, % (95% CI) | *P* |
|---|---|---|---|---|
| CR rate | | | | |
| Overall (0-120 hours) | 86.9 (80.9 to 91.5) | 80.6 (74.0 to 86.1) | 6.3 (−1.3 to 13.9) | .116 |
| Acute (0-24 hours) | 98.9 (95.9 to 99.9) | 97.8 (94.4 to 99.4) | 1.1 (−1.6 to 3.7) | .685 |
| Delayed (24-120 hours) | 87.4 (81.6 to 92.0) | 80.6 (74.0 to 86.1) | 6.8 (−0.7 to 14.5) | .084 |
| Complete control rate | | | | |
| Overall (0-120 hours) | 85.1 (78.8 to 90.1) | 77.8 (71.0 to 83.7) | 7.3 (−0.9 to 15.4) | .097 |
| Acute (0-24 hours) | 98.2 (95.0 to 99.6) | 97.7 (94.3 to 99.4) | 0.5 (−2.4 to 3.4) | 1.000 |
| Delayed (24-120 hours) | 86.9 (80.8 to 91.6) | 77.8 (71.0 to 83.7) | 9.1 (1.1 to 17.0) | .034 |
| TC rate | | | | |
| Overall (0-120 hours) | 83.9 (77.5 to 89.1) | 74.4 (67.3 to 80.7) | 9.5 (1.0 to 18.0) | .034 |
| Acute (0-24 hours) | 98.2 (95.0 to 99.6) | 97.2 (93.5 to 99.1) | 1.0 (−2.1 to 4.2) | .724 |
| Delayed (24-120 hours) | 85.7 (79.5 to 90.6) | 75.0 (67.9 to 81.2) | 10.7 (2.4 to 19.0) | .015 |
| No nausea | | | | |
| Overall (0-120 hours) | 88.6 (82.9 to 92.9) | 75.0 (68.0 to 81.1) | 13.6 (5.7 to 21.5) | <.001 |
| Acute (0-24 hours) | 98.9 (95.9 to 99.9) | 97.8 (94.4 to 99.4) | 1.1 (−1.6 to 3.7) | .685 |
| Delayed (24-120 hours) | 89.7 (84.2 to 93.8) | 75.6 (68.6 to 81.6) | 14.2 (6.4 to 21.9) | <.001 |
| No appetite loss | | | | |
| Overall (0-120 hours) | 42.3 (34.9 to 50.0) | 22.2 (16.4 to 29.0) | 20.1 (10.6 to 29.6) | <.001 |
| Acute (0-24 hours) | 80.0 (73.3 to 85.7) | 68.3 (61.0 to 75.1) | 11.7 (2.6 to 20.7) | .015 |
| Delayed (24-120 hours) | 45.7 (38.2 to 53.4) | 23.3 (17.4 to 30.2) | 22.4 (12.8 to 32.0) | <.001 |

NOTE. *P* values were calculated using the Fisher's exact test. CR was defined as the absence of vomiting and rescue therapy use. Complete protection was defined as the absence of vomiting, no use of rescue therapy, and no or mild nausea. TC was defined as no vomiting, no rescue therapy use, and no nausea. The occurrence of nausea and appetite loss was evaluated using patient questionnaires. No nausea was defined as a score of 0 on the basis of a four-point scale.
Abbreviations: CINV, chemotherapy-induced nausea and vomiting; CR, complete response; TC, total control.



patients with small cell lung carcinoma had a performance status of 2. Baseline characteristics were generally balanced between groups, and there were no significant differences in terms of age, sex, stage, ECOG performance status, cancer type, histology, and the chemotherapy regimen and 5-$HT_3$ RA administered.

## Efficacy

The overall CR rate was 86.9% (95% CI, 80.9 to 91.5) in the olanzapine group versus 80.6% (95% CI, 74.0 to 86.1) in the placebo group (Table 2). The intergroup difference in the overall CR rate was 6.3% (95% CI, −1.3 to 13.9; $P = .116$; Appendix Fig A1, online only). The delayed CR tended to be better in the olanzapine group than in the placebo group, albeit without significance (153 patients [87.4%] *v* 145 patients [80.6%], respectively; $P = .084$). The proportion of patients achieving CC in the delayed phase was significantly higher in the olanzapine group (86.9% *v* 77.8%; $P = .034$; Table 2). The TC rate was significantly higher in the olanzapine group in the overall and delayed phases. When analyzed at 24-hour intervals, the CC and TC rates were higher at 48 hours after chemotherapy initiation (Table 3). The benefit of olanzapine regarding the CR rate was observed in almost all subgroups, albeit without significance (Appendix Fig A2). The occurrence of nausea was evaluated using patient questionnaires. The proportions of patients free of nausea in the overall (88.6% *v* 75.0%) and delayed (89.7% *v* 75.6%) phases were significantly higher in the olanzapine group (both $P < .001$; Table 2). In the assessment of 24-hour intervals, the proportions of patients free of nausea were higher in the olanzapine group at all time points after the first 24 hours of chemotherapy (Fig 2 and Table 3). The proportions of patients who reported no nausea and no appetite loss were significantly higher in the olanzapine group on days 2-5 and 1-5, respectively (Appendix Table A1).

## Safety

The prevalence of major adverse events is presented in Table 4. Constipation, hiccups, and insomnia were observed in ≥5% of patients in both groups. Somnolence was observed in 43 and 41 patients in the olanzapine and placebo groups, respectively, and no events were of grade ≥3 severity. There were no serious and irreversible toxicities or adverse events leading to olanzapine discontinuation.

**TABLE 3.** Proportion of Patients Achieving CINV Control in 24-Hour Intervals

| End Point | Olanzapine (n = 175) | Placebo (n = 180) | Difference | *P* |
|---|---|---|---|---|
| CR rate | | | | |
| 0-24 hours | 98.9 (95.9 to 99.9) | 97.8 (94.4 to 99.4) | 1.1 (−1.6 to 3.7) | .685 |
| 24-48 hours | 97.7 (94.3 to 99.4) | 95.0 (90.7 to 97.7) | 2.7 (−1.2 to 6.6) | .258 |
| 48-72 hours | 94.3 (89.7 to 97.2) | 88.9 (83.4 to 93.1) | 5.4 (−0.3 to 11.1) | .086 |
| 72-96 hours | 94.9 (90.5 to 97.6) | 86.1 (80.2 to 90.8) | 8.8 (2.7 to 14.8) | .006 |
| 96-120 hours | 92.6 (87.6 to 96.0) | 87.2 (81.4 to 91.7) | 5.4 (−0.9 to 11.6) | .114 |
| Complete control rate | | | | |
| 0-24 hours | 98.2 (95.0 to 99.6) | 97.7 (94.3 to 99.4) | 0.5 (−2.4 to 3.4) | 1.000 |
| 24-48 hours | 97.6 (94.1 to 99.4) | 94.3 (89.8 to 97.2) | 3.3 (−0.8 to 7.4) | .172 |
| 48-72 hours | 93.5 (88.7 to 96.7) | 84.3 (78.1 to 89.3) | 9.2 (2.8 to 15.8) | .007 |
| 72-96 hours | 92.4 (87.4 to 95.9) | 84.8 (78.7 to 89.8) | 7.6 (1.0 to 14.2) | .029 |
| 96-120 hours | 91.8 (86.6 to 95.4) | 84.8 (78.7 to 89.8) | 7.0 (0.2 to 13.6) | .048 |
| TC rate | | | | |
| 0-24 hours | 98.2 (95.0 to 99.6) | 97.2 (93.5 to 99.1) | 1.0 (−2.1 to 4.2) | .724 |
| 24-48 hours | 96.5 (92.6 to 98.7) | 91.5 (86.4 to 95.2) | 5.0 (−0.2 to 10.0) | .070 |
| 48-72 hours | 93.1 (88.2 to 96.4) | 80.4 (73.9 to 86.0) | 12.7 (5.7 to 19.6) | <.001 |
| 72-96 hours | 91.4 (86.2 to 95.1) | 81.6 (75.1 to 87.0) | 9.8 (2.8 to 16.9) | .005 |
| 96-120 hours | 90.2 (84.7 to 94.2) | 80.6 (74.0 to 86.1) | 9.6 (2.3 to 16.9) | .016 |
| No nausea | | | | |
| 0-24 hours | 98.9 (95.9 to 99.9) | 97.8 (94.4 to 99.4) | 1.1 (−1.6 to 3.7) | .335 |
| 24-48 hours | 98.3 (95.0 to 99.6) | 91.0 (85.8 to 94.8) | 7.3 (2.6 to 11.9) | .015 |
| 48-72 hours | 95.4 (91.1 to 98.0) | 80.6 (74.0 to 86.1) | 14.8 (8.2 to 21.4) | <.001 |
| 72-96 hours | 93.1 (88.3 to 96.4) | 82.7 (76.3 to 87.9) | 10.4 (3.7 to 17.1) | .009 |
| 96-120 hours | 91.9 (86.8 to 95.5) | 81.7 (75.2 to 87.0) | 10.2 (3.3 to 17.2) | .008 |
| No appetite loss | | | | |
| 0-24 hours | 80.0 (73.3 to 85.7) | 68.3 (61.0 to 75.1) | 11.7 (2.6 to 20.7) | .034 |
| 24-48 hours | 79.9 (73.2 to 85.6) | 58.3 (50.8 to 65.6) | 21.6 (12.2 to 30.9) | <.001 |
| 48-72 hours | 70.3 (62.9 to 76.9) | 39.7 (32.4 to 47.2) | 30.6 (20.8 to 40.5) | <.001 |
| 72-96 hours | 56.0 (48.3 to 63.5) | 33.5 (26.7 to 40.9) | 22.5 (12.4 to 32.6) | <.001 |
| 96-120 hours | 56.3 (48.6 to 63.8) | 33.0 (26.1 to 40.4) | 23.3 (13.3 to 33.4) | <.001 |

NOTE. *P* values were calculated using the Fisher's exact test. CR was defined as the absence of vomiting and rescue therapy use. Complete protection was defined as the absence of vomiting, no use of rescue therapy, and no or mild nausea. TC was defined as no vomiting, no rescue therapy use, and no nausea. The occurrence of nausea and appetite loss was evaluated using patient questionnaires. No nausea was defined as a score of 0 on the basis of a four-point scale.

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; CR, complete response; TC, total control.



## DISCUSSION

In this study, we assessed the efficacy and safety of adding olanzapine to standard triple antiemetic therapy with aprepitant, a 5-$HT_3$ RA, and dexamethasone in patients who received carboplatin-containing chemotherapy. The CR rate in the overall phase was excellent, and it tended to be higher in the olanzapine group (86.9%), albeit without significance. However, olanzapine significantly improved nausea prevention in the overall and delayed phases in patients who received carboplatin. The addition of olanzapine did not cause any serious adverse events.

Previous studies assessed the efficacy of olanzapine in patients receiving non-HEC regimens.[21] Navari et al[27] added olanzapine to palonosetron and dexamethasone in patients receiving MEC regimens and recorded an overall CR rate of 72%. However, few patients received carboplatin-containing chemotherapy. Tan et al[28] assessed the efficacy of adding olanzapine to a 5-$HT_3$ RA and dexamethasone, but the effectiveness of olanzapine for carboplatin regimens was not determined. In several phase II studies, the efficacy of adding olanzapine to triple antiemetic therapy was evaluated. We found that olanzapine provided excellent CINV control in patients receiving carboplatin.[25] The overall CR rate was 93.3%. Strikingly, the TC rate in the overall phase was 81.8%, and nausea was markedly decreased. Regarding oxaliplatin, adding olanzapine to triple therapy resulted in a CR rate of 86.1%.[29] Iihara et al[30] reported a CR rate of 78.9% in the overall phase when assessing the efficacy of adding

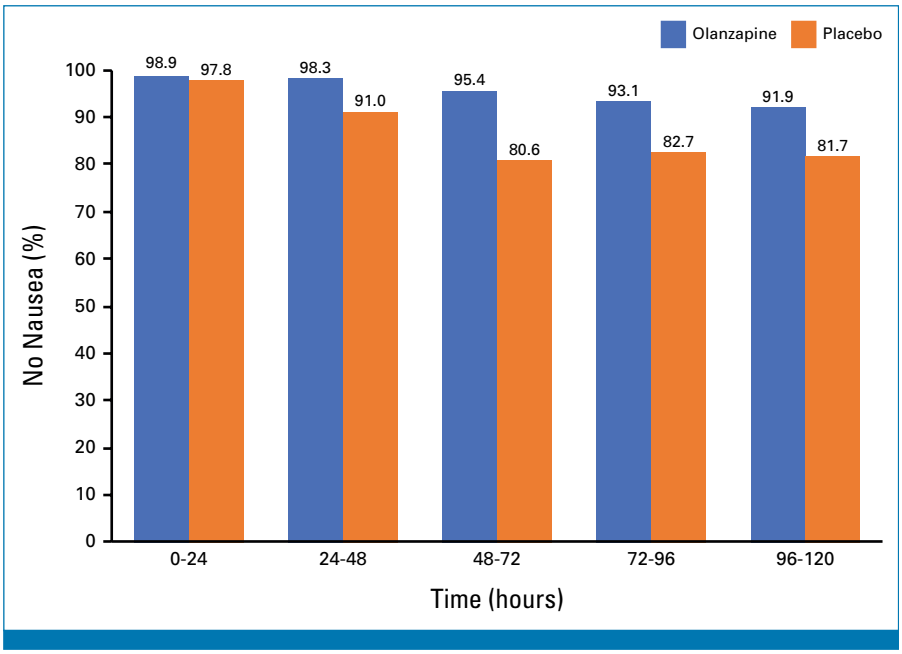


**FIG 2.** Time course of proportions of patients free of nausea.

olanzapine in patients receiving carboplatin for gynecologic cancer. Sakai et al[31] reported a CR rate of 94.0% in patients with thoracic malignancies, in line with our study of patients with lung cancer. Olanzapine can provide good CINV control, but these were single-arm pilot studies. An et al[32] performed a randomized controlled trial of patients receiving carboplatin-containing chemotherapy. However, they assessed the efficacy of adding olanzapine to double therapy with dexamethasone and a 5-$HT_3$ RA, which is not the standard antiemetic therapy for carboplatin.

In this trial, we assessed the CR rate, which is used as the primary end point in most clinical trials assessing antiemetic therapy, as well as nausea prevention. The overall CR rate in the olanzapine group was 86.9%, which was excellent, but the difference between the groups did not reach clinical relevance. Several reasons might explain this finding. First, antiemetic control in carboplatin regimens is already reasonable with triple antiemetic therapy. In our previous trial assessing adding aprepitant to a 5-$HT_3$ RA and dexamethasone, the overall CR rate was 80.3%,[12] consistent with that in the placebo group in this trial. Although we expected that adding olanzapine would increase the CR rate in patients receiving carboplatin, it might have been difficult to increase the CR rate by >10% because of the already high control rate of the triple antiemetic therapy. Conversely, the CR rate in the placebo group was approximately 60% in patients receiving HEC regimens, indicating room for improvement.[22-24] Second,

**TABLE 4.** Treatment-Related Adverse Events

| | Olanzapine (n = 175), No. (%) | | | | Placebo (n = 180), No. (%) | | | |
|---|---|---|---|---|---|---|---|---|
| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Hematologic toxicity | | | | | | | | |
| Leukopenia | 17 (9.7) | 36 (20.6) | 40 (22.9) | 16 (9.1) | 11 (6.1) | 32 (17.9) | 49 (27.4) | 12 (6.7) |
| Neutropenia | 15 (8.6) | 20 (11.4) | 31 (17.7) | 42 (24.0) | 12 (6.7) | 23 (12.8) | 37 (20.7) | 33 (18.4) |
| Anemia | 81 (46.3) | 23 (13.1) | 8 (4.6) | 1 (5.7) | 77 (43.0) | 31 (17.3) | 9 (5.0) | 0 |
| Thrombocytopenia | 26 (14.9) | 9 (5.1) | 9 (5.1) | 4 (2.3) | 36 (20.1) | 11 (6.1) | 15 (8.4) | 3 (1.7) |
| Nonhematologic toxicity | | | | | | | | |
| Hepatotoxicity | 71 (40.6) | 16 (9.1) | 9 (5.1) | 0 | 74 (41.3) | 16 (8.9) | 8 (4.5) | 0 |
| Nephrotoxicity | 19 (10.9) | 5 (2.9) | 1 (0.6) | 0 | 25 (14.0) | 6 (3.4) | 0 | 0 |
| Constipation | 54 (30.9) | 23 (13.1) | 0 | 0 | 61 (34.1) | 18 (10.1) | 0 | 0 |
| Hiccup | 8 (4.6) | 3 (1.7) | 0 | 0 | 13 (7.3) | 6 (3.4) | 0 | 0 |
| Somnolence | 40 (22.9) | 3 (1.7) | 0 | 0 | 36 (20.1) | 5 (2.8) | 0 | 0 |
| Insomnia | 27 (15.4) | 0 | 0 | 0 | 27 (15.1) | 10 (5.6) | 0 | 0 |

most patients received palonosetron in this study. Compared with palonosetron which has a longer half-life, greater binding affinity, and superior antiemetic control in patients receiving HEC regimens,[33] the addition of olanzapine had a greater effect in patients treated with the first-generation 5-$HT_3$ RA granisetron (the intergroup difference in the overall CR rate was 14.1%; Appendix Fig A2). Third, we did not exclude paclitaxel-containing regimens, whose package insert highlights the need for prophylactic dexamethasone, because we wanted to confirm the implications of adding olanzapine in a real-world setting. When patients who received paclitaxel-containing regimens were excluded, the addition of olanzapine tended to yield favorable antiemetic control (the intergroup difference in the overall CR rate was 7.3%). Fourth, we targeted patients with malignancy without limiting the primary site of disease, but all study participants had thoracic tumors. This study included more male and older patients, who are considered less likely to have CINV, than female and younger patients,[2,3] which might have weakened the effect of adding olanzapine. Indeed, subgroup analysis demonstrated that adding olanzapine had a favorable CR in female patients and patients younger than 70 years.

Importantly, olanzapine decreased nausea in both overall and delayed phases. In addition, olanzapine increased the TC rate, which strongly reflects the control of nausea. Chemotherapy-induced nausea is a subjective symptom with an etiology independent of chemotherapy-induced vomiting.[1-3,34] In a prospective observational study of 1,910 patients with cancer, up to 50% of the patients experienced nausea even with prophylactic antiemetic therapy, which reduced the rate of vomiting to 16%.[35] In a cohort of patients treated with carboplatin, the rate of no vomiting was 81.3%, but that of no nausea was only 55.6%.[36] Control of nausea is difficult despite the use of triple antiemetic therapy, and this represents an unmet and crucial goal in CINV control.[1-3,7,8,35] In a phase III trial, Navari et al[22] found that olanzapine prevented nausea in patients treated with cisplatin or cyclophosphamide-doxorubicin. Their study differed from our trial in several points. In their study, 35% of patients received cisplatin and 65% received cyclophosphamide-doxorubicin. In addition, the main site of primary disease was the breast. The overall CR rate in the placebo arm was 40.6%, which was much lower than that in our trial targeting patients who received carboplatin. In this trial, adding olanzapine to triple therapy significantly reduced the onset of nausea in patients receiving carboplatin. Although the primary end point was not met in this study, we found the addition of olanzapine was a valuable option for nausea prevention, a challenge that remains, even in patients receiving carboplatin-containing chemotherapy.

Somnolence is a significant problem that requires attention. Patients who received 10 mg of olanzapine once daily more commonly experienced drowsiness, particularly on day 2.[22] Hashimoto et al[23] used olanzapine 5 mg administered after the evening meal. The incidence of daytime sleepiness and the degree of associated difficulty experienced in daily life did not differ between the olanzapine and placebo arms. The incidence of somnolence was 24.6%, and no patient had grade ≥3 somnolence in this study. The time to the maximum concentration of olanzapine is 4.8 hours, and administration after an evening meal might cause olanzapine levels to peak during sleep.

This study had several limitations. First, we used 5 mg olanzapine once daily to limit adverse events. There is a possibility that a higher dose of olanzapine, such as 10 mg once daily, might improve CINV control further. Second, all patients in this study had thoracic cancer. Olanzapine might have greater benefits in patients with other cancers such as gynecologic cancer.

In conclusion, the addition of olanzapine 5 mg once daily to standard triple therapy with aprepitant, a 5-$HT_3$ RA, and dexamethasone did not significantly improve the CR rate in patients receiving carboplatin-containing chemotherapy. However, the addition of olanzapine improved the control of nausea in patients treated with carboplatin, and this might represent an effective and feasible prophylactic strategy for nausea. Further comparative studies are warranted to determine the benefits of this strategy.

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## DATA SHARING STATEMENT

Data collected for the study can be requested from the investigators on reasonable request and approval of the institutional review board of Hamamatsu University School of Medicine. The data are not publicly available because of privacy or ethical restrictions.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Olanzapine Plus Triple Antiemetic Therapy for the Prevention of Carboplatin-Induced Nausea and Vomiting: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial**

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## APPENDIX

**TABLE A1.** Severity of Nausea and Appetite Loss in 24-Hour Intervals

| | Olanzapine, % | | | | Placebo, % | | | | |
|---|---|---|---|---|---|---|---|---|---|
| End Point | None | Mild | Moderate | Severe | None | Mild | Moderate | Severe | *P* |
| Nausea | | | | | | | | | |
| 0-24 hours | 98.9 | 0.0 | 0.0 | 1.1 | 97.8 | 1.7 | 0.0 | 0.5 | .335 |
| 24-48 hours | 98.3 | 1.1 | 0.0 | 0.6 | 91.0 | 5.1 | 1.7 | 2.2 | .015 |
| 48-72 hours | 95.4 | 1.7 | 2.3 | 0.6 | 80.6 | 9.4 | 6.1 | 3.9 | <.001 |
| 72-96 hours | 93.1 | 1.7 | 3.5 | 1.7 | 82.7 | 8.4 | 6.7 | 2.2 | .009 |
| 96-120 hours | 91.9 | 5.2 | 0.6 | 2.3 | 81.7 | 8.9 | 6.1 | 3.3 | .008 |
| Appetite loss | | | | | | | | | |
| 0-24 hours | 80.0 | 17.7 | 2.3 | 0.0 | 68.3 | 28.9 | 2.2 | 0.6 | .034 |
| 24-48 hours | 79.9 | 15.5 | 4.6 | 0.0 | 58.3 | 35.0 | 5.0 | 1.7 | <.001 |
| 48-72 hours | 70.3 | 20.0 | 7.4 | 2.3 | 39.7 | 39.7 | 15.6 | 5.0 | <.001 |
| 72-96 hours | 56.0 | 33.7 | 7.4 | 2.9 | 33.5 | 36.9 | 25.7 | 3.9 | <.001 |
| 96-120 hours | 56.4 | 31.0 | 8.0 | 4.6 | 33.0 | 41.3 | 17.9 | 7.8 | <.001 |

NOTE. The occurrence and severity of nausea and appetite loss were evaluated using patient questionnaires.

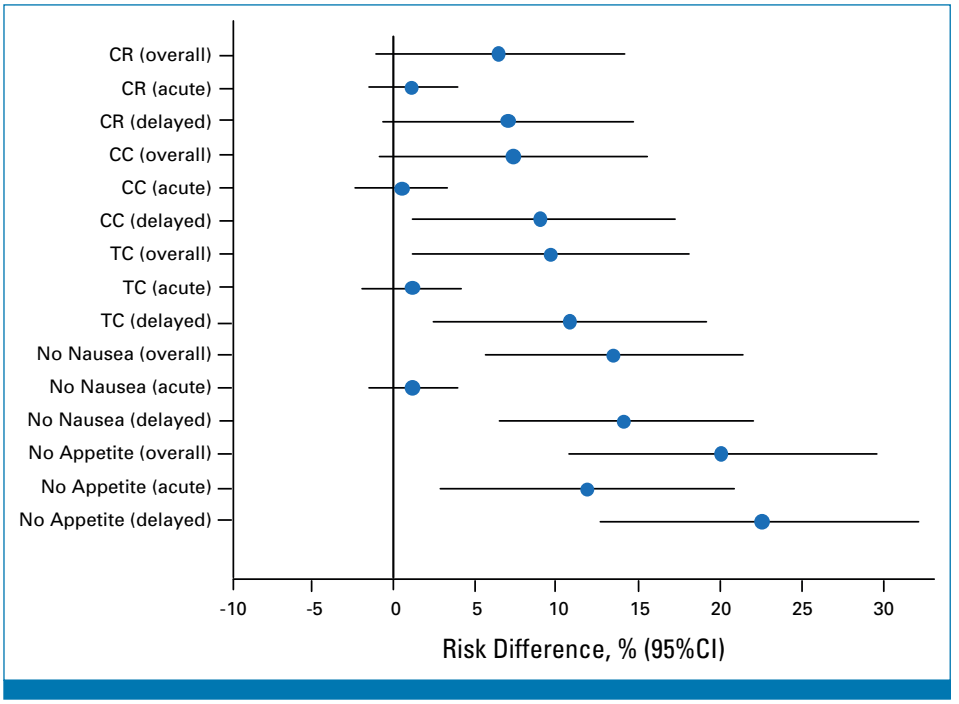


**FIG A1.** Risk difference between the olanzapine and placebo groups. The solid line indicates a risk difference of 0. The right region of the solid line corresponds to values in favor of olanzapine. Acute, acute phase (0-24 hours); CC, complete control; CR, complete response; Delayed, delayed phase (24-120 hours); Overall, overall phase (0-120 hours); TC, total control.

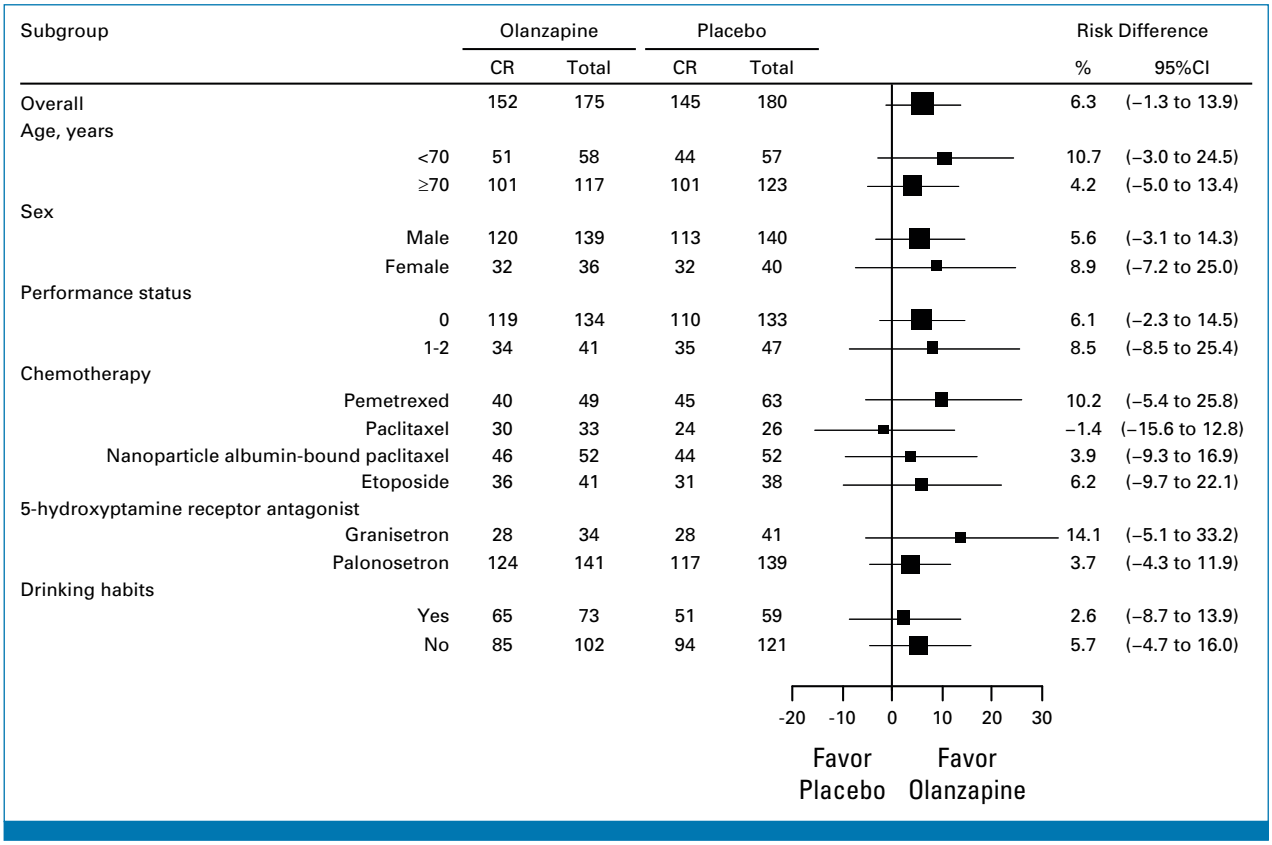


**FIG A2.** Subgroup analysis of the CR rate in the overall phase. Performance status was determined according to the Eastern Cooperative Oncology Group scale. The different sizes of the boxes represent the number of patients. CR, complete response; Overall, overall phase (0-120 hours).