Effects of adding a neurokinin-1 receptor antagonist to 5 mg olanzapine, a 5-hydroxytryptamine-3 receptor antagonist, and dexamethasone for preventing carboplatin-induced nausea and vomiting: a propensity score-matched analysis

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Abstract

Background: Olanzapine has been reported to be an effective antiemetic in patients receiving carboplatin-based chemotherapy. However, the efficacy of a neurokinin-1 receptor antagonist (NK1RA) added to olanzapine, a 5-hydroxytryptamine-3 receptor antagonist (5-HT3RA), and dexamethasone (DEX) has not been proven. This study aimed to assess the efficacy and safety of NK1RA, in combination with three-drug antiemetic regimens containing olanzapine, in preventing nausea and vomiting induced by carboplatin-based chemotherapy.

Methods: Data were pooled for 140 patients receiving carboplatin-based chemotherapy from three multicenter, prospective, single-arm, open-label phase II studies that evaluated the efficacy and safety of olanzapine for chemotherapy-induced nausea and vomiting. The propensity score of the co-administration of NK1RA was estimated for each patient using a logistic regression model that included age, sex, and carboplatin dose. We analyzed a total of 62 patients, who were treated without NK1RA (non-NK1RA group: 31 patients) and with NK1RA (NK1RA group: 31 patients). The patients were selected using propensity score matching.

Results: The complete response rate (without emetic episodes or with no administration of rescue medication) in the overall period (0–120 h post carboplatin administration) was 93.5% in the non-NK1RA group and 96.8% in the NK1RA group, with a difference of -3.2% (95% confidence interval, -18.7% to 10.9%; P = 1.000). In terms of safety, there

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Background

Carboplatin is classified as a moderate-emetic-risk chemotherapy (MEC) or high-emetic-risk chemotherapy (HEC) [1–4]. Jordan et al. conducted a systematic review and meta-analysis of randomized controlled trials that assessed the effects of adding a neurokinin-1 receptor antagonist (NK₁RA) to a 5-hydroxytryptamine-3 receptor antagonist (5-HT₃RA) and dexamethasone (DEX) in MEC [5]. In this study, a total of 1790 patients from seven trials were analyzed, and the results of 1538 patients for whom complete response (CR) rate could be assessed supported the NK₁RA combined regimen for carboplatin-based chemotherapy with an absolute risk difference of 15% and an odds ratio of 1.96 (95% confidence interval [CI]: 1.57–2.45; \( p < 0.001 \)). Currently, international antiemetic guidelines consistently recommend a three-drug antiemetic prophylaxis with NK₁RA, 5-HT₃RA, and DEX in patients receiving carboplatin-based chemotherapy [1–4].

Olanzapine is an antipsychotic drug that is classified as a multi-acting, receptor-targeted agent. It has been reported to be a highly effective antiemetic drug in patients receiving MEC and/or HEC [6–12]. Three high-quality phase II studies have reported the efficacy and safety of 5 mg olanzapine for antiemetic prophylaxis in patients receiving carboplatin-based chemotherapy [13–15]. Two of these studies evaluated the antiemetic effects of a four-drug combination consisting of olanzapine, NK₁RA, 5-HT₃RA, and DEX, and one evaluated a three-drug combination consisting of olanzapine, 5-HT₃RA, and DEX. To the best of our knowledge, there are no phase III studies evaluating the efficacy and safety of olanzapine for the management of nausea and vomiting in cancer patients receiving carboplatin-based chemotherapy. Therefore, we integrated these three phase II studies and reported the efficacy and safety of olanzapine in patients receiving carboplatin-based chemotherapy and the risk factors associated with carboplatin-induced nausea and vomiting [16].

The results showed that olanzapine had an antiemetic effect with a CR rate (defined as no emetic episodes and no administration of rescue medication for nausea and vomiting) of 87.9% in the overall period (0–120 h). In the analysis of risk factors affecting carboplatin-induced nausea and vomiting, co-administration of NK₁RA was not significantly associated with carboplatin-induced nausea and vomiting. This integrated analysis is the only study that analyzes the effect of NK₁RA, when added to an olanzapine-containing antiemetic regimen, on carboplatin-induced nausea and vomiting. However, the efficacy of NK₁RA in combination with an olanzapine-containing antiemetic regimen remains to be demonstrated. Therefore, the present study aimed to evaluate the efficacy and safety of the combination of NK₁RA, olanzapine, 5-HT₃RA, and DEX in preventing carboplatin-induced nausea and vomiting in a propensity score-matched analysis.

Methods

Study design

We analyzed 62 patients, treated without NK₁RA (non-NK₁RA group, 31 patients) and with NK₁RA (NK₁RA group: 31 patients), using a propensity score-matched sample from the pooled data of 140 patients receiving carboplatin-based chemotherapy. The data were from three multicenter, prospective, single-arm, open-label, phase II studies.

The results of these three phase II studies and the integrated analysis of the pooled data of 140 patients have been published previously [13–16]. Study 1 reported the efficacy of a four-drug combination consisting of olanzapine (orally: 5 mg on days 1–4), aprepitant (orally: 125 mg on day 1 and 80 mg on days 2 and 3), 5-HT₃RA (intravenously: granisetron 1 mg, granisetron 3 mg, palonosetron 0.75 mg, or ramosetron 0.3 mg on day 1), and DEX (intravenously: 4.95 mg on day 1) in 33 patients with lung cancer [13]. Study 2 reported the efficacy of a four-drug combination consisting of olanzapine (orally: 5 mg on day 1 to 4), aprepiant (orally: 125 mg on day 1 and 80 mg on days 2 and 3), 5-HT₃RA (intravenously: granisetron 1 mg, granisetron 3 mg, palonosetron 0.75 mg, or ramosetron 0.3 mg on day 1), and DEX (intravenously: 4.95 mg on day 1) in 33 patients with lung cancer [13]. Study 2 reported the efficacy of a four-drug combination consisting of olanzapine (orally: 5 mg on day 1 to 4), aprepitant (orally: 125 mg on day 1 and 80 mg on days 2 and 3), granisetron (intravenously: 1 mg on day 1), and DEX (intravenously: 9.9 mg on day 1) in 57 patients with gynecological cancer [14]. Study 3 reported the efficacy of a three-drug combination consisting of olanzapine (orally: 5 mg on day 1 to 4), granisetron (intravenously: 1 mg on day 1), and DEX (intravenously: 9.9 mg/12 mg on day 1 and 6.6 mg/8 mg on days 2 and 3) in 50 patients with thoracic malignancies [15].

Conclusions:
The findings suggest that antiemetic regimens consisting of olanzapine, 5HT₃RA, and DEX without NK₁RA may be a treatment option for patients receiving carboplatin-based chemotherapy.

Keywords: Antiemetics, Carboplatin, Dexamethasone, Nausea, Neurokinin-1 receptor antagonist, Olanzapine, Vomiting, 5-hydroxytryptamine-3 receptor antagonists
The patient enrollment flowchart for the present study is shown in Fig. 1.

Data collection
Data were collected from self-reported diaries. Patients reported nausea, decreased appetite, somnolence, and decreased concentration severity using a four-point scale (none, mild, moderate, and severe), as well as frequency of vomiting, and the use of rescue medication. The daily diary began from the initiation of carboplatin treatment on day 1, and entries were made over a 5-day period (Studies 1 and 3) and a 7-day period (Study 2).

Outcome
The primary endpoints for efficacy were CR rate, defined as the proportion of patients without emetic episodes or administration of rescue medication; complete control (CC) rate, defined as the proportion of patients with CR and no more than mild nausea; and total control (TC) rate, defined as the proportion of patients with CR and no nausea. The assessment periods for carboplatin-induced nausea and vomiting were 0–120 h post carboplatin administration (overall period), 0–24 h post carboplatin administration (acute period), and 24–120 h post carboplatin administration (delayed period). Additionally, the secondary endpoints for efficacy were incidences of nausea, vomiting, and decreased appetite for 5 days after the initiation of carboplatin treatment on day 1.

The endpoints for safety were incidences of somnolence and decreased concentration for 5 days after the initiation of carboplatin treatment on day 1.

Statistical analysis
Patient characteristics, rate of carboplatin-induced nausea and vomiting control, and treatment-related adverse events were summarized using descriptive statistics or reported in terms of frequencies and proportions of total patients. The propensity score of the co-administration of NK₁RA was estimated for each patient using a logistic regression model that included age, sex, and carboplatin dose which most potentially affect the occurrence of chemotherapy-induced nausea and vomiting (CINV) in patients [17–20]. In the propensity score matching, 1:1 nearest neighbor matching algorithm without replacement was employed with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score [21]. The difference in the primary endpoints between the NK₁RA and non-NK₁RA groups was shown with a two-sided exact CI [22] and compared using Fisher’s exact test. All statistical analyses were performed using JMP 15.0.0 and SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). All P-values were two-sided, and statistical significance was set at P<0.05.
Results
Study patients
A total of 62 patients were included in the analysis. Of these patients, 31 were in the non-NK,R group and 31 in the NK,R group. Baseline patient characteristics are presented in Table 1. The median ages of patients in the non-NK,R group and those in the NK,R group were 71 years (range, 25th and 75th percentiles,

| Table 1 Baseline patient characteristics |
|------------------------------------------|
|                                          |
| **Non-NK,R group**                      |
| **NK,R group**                          |
| (n = 31)                                 |
| (n = 31)                                 |
| Age, years                               |
| Median (interquartile range)             |
| 71 (67–76)                               |
| 71 (65–77)                               |
| < 60 years                               |
| 2 (6.5%)                                 |
| 2 (6.5%)                                 |
| ≥ 60 years                               |
| 29 (93.5%)                               |
| 29 (93.5%)                               |
| Sex                                       |
| Male                                      |
| 18 (58.1%)                               |
| 18 (58.1%)                               |
| Female                                    |
| 13 (41.9%)                               |
| 13 (41.9%)                               |
| ECOG performance status                  |
| 0                                         |
| 14 (45.2%)                               |
| 28 (90.3%)                               |
| 1                                         |
| 12 (38.7%)                               |
| 2 (6.5%)                                 |
| 2                                         |
| 5 (16.1%)                                |
| 1 (3.2%)                                 |
| Cancer type                              |
| Small-cell lung cancer                   |
| 9 (29.0%)                                |
| 8 (25.8%)                                |
| Non-small-cell lung cancer               |
| 17 (54.8%)                               |
| 14 (45.2%)                               |
| Thymoma / thymic carcinoma               |
| 5 (16.1%)                                |
| 0 (0.0%)                                 |
| Ovarian cancer                           |
| 0 (0.0%)                                 |
| 4 (12.9%)                                |
| Endometrial cancer                       |
| 0 (0.0%)                                 |
| 4 (12.9%)                                |
| Peritoneal cancer                        |
| 0 (0.0%)                                 |
| 1 (3.2%)                                 |
| Planned carboplatin dose                 |
| AUC 5 mg/mL/min                          |
| 21 (67.7%)                               |
| 21 (67.7%)                               |
| AUC 6 mg/mL/min                          |
| 10 (32.3%)                               |
| 10 (32.3%)                               |
| Additional anticancer drugs              |
| Paclitaxel                                |
| 3 (9.7%)                                 |
| 9 (29.0%)                                |
| Paclitaxel + Pembrolizumab               |
| 1 (3.2%)                                 |
| 0 (0.0%)                                 |
| Paclitaxel + Bevacizumab                 |
| 0 (0.0%)                                 |
| 1 (3.2%)                                 |
| Paclitaxel + Bevacizumab + Atezolizumab  |
| 2 (6.5%)                                 |
| 0 (0.0%)                                 |
| Nab-Paclitaxel                           |
| 0 (0.0%)                                 |
| 3 (9.7%)                                 |
| Nab-Paclitaxel + Pembrolizumab           |
| 3 (9.7%)                                 |
| 0 (0.0%)                                 |
| Pemetrexed                               |
| 7 (22.6%)                                |
| 6 (19.4%)                                |
| Pemetrexed + Pembrolizumab               |
| 2 (6.5%)                                 |
| 0 (0.0%)                                 |
| Pemetrexed + Bevacizumab                 |
| 0 (0.0%)                                 |
| 2 (6.5%)                                 |
| Etoposide                                |
| 8 (25.8%)                                |
| 8 (25.8%)                                |
| Etoposide + Atezolizumab                 |
| 2 (6.5%)                                 |
| 0 (0.0%)                                 |
| Vinorelbine                              |
| 2 (6.5%)                                 |
| 0 (0.0%)                                 |
| S-1                                      |
| 1 (3.2%)                                 |
| 2 (6.5%)                                 |
| Risk factor                              |
| Habitual alcohol consumption             |
| 19 (61.3%)                               |
| 10 (32.3%)                               |
| Motion sickness                          |
| 25 (80.6%)                               |
| 2 (6.5%)                                 |
| Morning sickness                         |
| 3 (9.7%)                                 |
| 7 (22.6%)                                |

Data are n (%)  
ECOG Eastern Cooperative Oncology Group  
AUC Area under the curve  
S-1 tegafur plus gimeracil plus oteracil potassium
67–76 years) and 71 years (range, 25th and 75th percentiles, 65–77 years), respectively. The proportion of males (58.1%) to females (41.9%) was similar in both groups.

**Efficacy**

The primary endpoints of efficacy are shown in Table 2. As shown in the table, CR rates for the overall, delayed, and acute periods in the non-NK_{1}RA and NK_{1}RA groups did not show any statistically significant difference. Likewise, the CC and TC rates in the non-NK_{1}RA group, during each period, were not significantly different from those in the NK_{1}RA group.

The secondary endpoints for efficacy are shown in Fig. 2. Patient-reported nausea, vomiting, and decreased appetite in the overall period were not significantly different between the two groups. The incidence of nausea was 12.9% in the non-NK_{1}RA group and 16.1% in the NK_{1}RA group ($P = 1.000$), that of vomiting was 6.5% in the non-NK_{1}RA group and 3.2% in the NK_{1}RA group ($P = 1.000$), and that of decreased appetite was 58.1% in the non-NK_{1}RA group and 61.3% in the NK_{1}RA group ($P = 1.000$).

**Safety**

Data on somnolence and decreased concentration assessed by the patients’ self-reported diaries are shown in Fig. 3. The incidence of somnolence was 83.9% in the non-NK_{1}RA group and 80.6% in the NK_{1}RA group. However, moderate or severe somnolence was 6.5% in the non-NK_{1}RA group and 0% in the NK_{1}RA group. The incidence of decreased concentration was 48.4% in the non-NK_{1}RA group and 48.4% in the NK_{1}RA group. However, moderate or severe decreased concentration was 3.2% in the non-NK_{1}RA group and 0% in the NK_{1}RA group. The peak incidence of somnolence and decreased concentration was observed on day 4 in both groups.

**Discussion**

To the best of our knowledge, there are no studies that have evaluated the efficacy of adding NK_{1}RA to antiemetic therapy consisting of olanzapine, 5HT_{3}RA, and DEX in MEC and HEC. In the present study, the prophylactic antiemetic combination regimen of olanzapine, 5-HT_{3}RA, and DEX showed no statistical difference between groups treated with or without NK_{1}RA for CINV control, as demonstrated by the endpoints of CR, CC, and TC rates during the overall, acute, and delayed periods. Moreover, daytime sleepiness and concentration impairment, the most worrisome adverse events associated with olanzapine administration, were unaffected by NK_{1}RA administration. The incidences of moderate and severe daytime sleepiness and concentration impairment were rare.

In the present study, prophylactic antiemetic treatment without NK_{1}RA had a high CR rate of 93.5%, CC rate of 93.5%, and TC rate of 87.1%. The incidence of nausea in the non-NK_{1}RA group was also very low (12.9%). A head-to-head comparison of the antiemetic effects of olanzapine and NK_{1}RA, each combined with palonosetron and DEX, has been reported for patients receiving HEC. [6, 7]. In these studies, the CR rates of the olanzapine and NK_{1}RA regimens were comparable in the overall, acute, and delayed periods. Nevertheless, antiemetic prophylaxis with the olanzapine regimen resulted in a significantly higher control of nausea in the delayed and overall periods than that with the NK_{1}RA regimen. It has been reported that when 5-HT released by anticancer drugs acts on 5-HT_{2b} and 5-HT_{2e} receptors, the secretion of

### Table 2  Primary endpoint for efficacy

| Outcome | Non-NK_{1}RA group ($n = 31$) | NK_{1}RA group ($n = 31$) | Risk Difference (95% CI) | $P$ value |
|---------|-------------------------------|---------------------------|--------------------------|-----------|
| CR      |                               |                           |                          |           |
| Overall | 29 (93.5%)                    | 30 (96.8%)                | -3.2% (-18.7 to 10.9)    | 1.000     |
| Acute   | 31 (100%)                     | 31 (100%)                 | 0%                       | 1.000     |
| Delayed | 29 (93.5%)                    | 30 (96.8%)                | -3.2% (-18.7 to 10.9)    | 1.000     |
| CC      |                               |                           |                          |           |
| Overall | 29 (93.5%)                    | 29 (93.5%)                | 0% (-16.6 to 16.6)       | 1.000     |
| Acute   | 31 (100%)                     | 31 (100%)                 | 0%                       | 1.000     |
| Delayed | 29 (93.5%)                    | 29 (93.5%)                | 0% (-16.6 to 16.6)       | 1.000     |
| TC      |                               |                           |                          |           |
| Overall | 27 (87.1%)                    | 26 (83.9%)                | 3.2% (-16.6 to 22.9)     | 1.000     |
| Acute   | 31 (100%)                     | 30 (96.8%)                | 3.2% (-8.4 to 16.7)      | 1.000     |
| Delayed | 27 (87.1%)                    | 27 (87.1%)                | 0% (-19.0 to 19.0)       | 1.000     |

CR Complete response, CC Complete control, TC Total control, CI Confidence interval
Ghrelin, an appetite-stimulating hormone, is decreased, inducing anorexia and nausea [23]. Olanzapine is an antipsychotic drug classified as a multi-acting, receptor-targeted agent that is known to antagonize 5-HT at the 5-HT\(_{2b}\) and 5-HT\(_{2c}\) receptors [24]. These mechanisms may account for the excellent nausea-suppressing effects of olanzapine.

The incidence of nausea, vomiting, and decreased appetite mainly peaked on day 4 in both groups, which is consistent with a recent report by Iihara et al. showing...
that CINV associated with carboplatin occurs on day 4 [25].

Younger age is a well-known patient-related risk factor for CINV [17–20]. In our previous study, which evaluated the efficacy of olanzapine for carboplatin-induced nausea and vomiting in younger patients, the cut-off value for age was set to 60 years, and was significantly associated with an increased risk of non-TC in the overall study period [16]. The median patient age in the present study was 71 years (range, 25th and 75th percentiles, 67–76 years) in the non-NK1RA group and 71 years (range, 25th and 75th percentiles, 65–77 years) in the NK1RA group, which had relatively older patients. Only two patients under the age of 60 years were included in both groups. Therefore, caution should be exercised when extrapolating the results of this study to younger patients, especially those aged below 60 years. We suggest that these findings should be confirmed with a randomized comparison of older and younger patients in future research.

Undesired patient sedation with 10 mg olanzapine is a problem in its antiemetic use for elderly or oversedated patients [1, 3, 11]. The J-FORCE study, which evaluated 5 mg olanzapine in patients receiving high-dose cisplatin, suggested that 5 mg olanzapine therapy does not have a significant effect on daytime somnolence and decreased concentration [12]. Our previously reported integrated analysis evaluating 5 mg of olanzapine in patients receiving carboplatin was consistent with this result [16]. This was not affected by the presence or absence of the NK1RA combination.

The present study has some limitations. First, this study had an open-label, single-arm design. Second, data was small number from three studies. But we used a propensity score-matched analysis which is a popular methodology for a retrospective study design. Third, the results of this study are not a direct comparison between patients treated with or without NK1RA. Furthermore, due to the older age of the patients included in this analysis, the results may not be applicable to younger patients. Finally, the results were obtained only in the Japanese population. In the future, a phase III trial comprising a direct comparison of the efficacy and safety of an antiemetic combination regimen of olanzapine, 5-HT3RA, and DEX, with or without NK1RA in patients receiving carboplatin-based chemotherapy is warranted.

Conclusion
These findings suggest that antiemetic combination regimens of olanzapine, 5-HT3RA, and DEX without NK1RA may be a treatment option for patients treated with carboplatin-based combination chemotherapy with an area under the curve of ≥ 5 mg/mL/min.

Abbreviations
S-HT3RA: S-Hydroxytryptamine-3 receptor antagonist; CC: Complete control; CI: Confidence interval; CINV: Chemotherapy-induced nausea and vomiting; CR: Complete response; DEX: Dexamethasone; ECOG-PS: Eastern Cooperative Oncology Group performance status; HEC: High-emetic-risk chemotherapy; MEC: Moderate-emetic-risk chemotherapy; NK1RA: Neurokinin-1 receptor antagonist; TC: Total control.

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Authors’ contributions
S.Y., H.I., R.U., H.K., and N.I. conceived the study. S.Y., H.I., R.U., H.K., and N.I. conducted the claims data analysis. R. U. performed the statistical analyses. Y.O. and K.M. provided technical support. S.Y., H.I., R.U., H.K., XT, YF, MA, H.I., MK, YH, CH, TS, KN, AS, and NI. contributed to the interpretation of data and assisted in the preparation of the manuscript. S.Y., H.I., R.U., and H.K. drafted the manuscript. S.Y., H.I., R.U., H.K. A. S., YO., K.M., and N.I. critically revised the manuscript. All authors reviewed the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the study groups, but restrictions apply to the availability of these data, which were used under license for the current study; therefore, the data are not publicly available. However, data are available from the corresponding authors upon reasonable request and with permission from the study groups.

Declarations

Ethics approval and consent to participate
Study 1 was approved by the Medical Review Board of the Hamamatsu University Graduate School of Medicine (16–290). Written informed consent was obtained from all patients. Study 1 was an opt-out study for the secondary use of data with approval (20–335). Studies 2 and 3 were approved by the Medical Review Board of Gifu University Graduate School of Medicine (30–002, 2018–19). Written informed consent was obtained from all patients. In studies 2 and 3, written informed consent was obtained for the secondary use of data. These studies were conducted in accordance with the Declaration of Helsinki and ethical guidelines for clinical studies.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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