

RESEARCH

Open Access



# 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

Senri Yamamoto<sup>1</sup>, Hirotoshi Iihara<sup>1,2\*</sup>, Ryuji Uozumi<sup>3</sup>, Hitoshi Kawazoe<sup>4,5</sup>, Kazuki Tanaka<sup>6</sup>, Yuki Yoshi Fujita<sup>7</sup>, Masakazu Abe<sup>8,9</sup>, Hisao Imai<sup>10,11</sup>, Masato Karayama<sup>6,12</sup>, Yoh Hayasaki<sup>13</sup>, Chiemi Hirose<sup>1</sup>, Takafumi Suda<sup>6</sup>, Kazuto Nakamura<sup>14</sup>, Akio Suzuki<sup>1,2</sup>, Yasushi Ohno<sup>15</sup>, Ken-ichirou Morishige<sup>13</sup> and Naoki Inui<sup>6,16\*</sup>

## 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 (NK<sub>1</sub>RA) added to olanzapine, a 5-hydroxytryptamine-3 receptor antagonist (5-HT<sub>3</sub>RA), and dexamethasone (DEX) has not been proven. This study aimed to assess the efficacy and safety of NK<sub>1</sub>RA, 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 NK<sub>1</sub>RA 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 NK<sub>1</sub>RA (non-NK<sub>1</sub>RA group: 31 patients) and with NK<sub>1</sub>RA (NK<sub>1</sub>RA 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-NK<sub>1</sub>RA group and 96.8% in the NK<sub>1</sub>RA group, with a difference of -3.2% (95% confidence interval, -18.7% to 10.9%;  $P = 1.000$ ). In terms of safety, there

\*Correspondence: dai0920@gifu-u.ac.jp; inui@hama-med.ac.jp

<sup>1</sup> Department of Pharmacy, Gifu University Hospital, 1-1 Yanagido, Gifu 501-1194, Japan

<sup>6</sup> Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, Shizuoka 431-3192, Japan

Full list of author information is available at the end of the article



was no significant difference between the groups in daytime sleepiness and concentration impairment, which are the most worrisome adverse events induced by olanzapine.

**Conclusions:** The findings suggest that antiemetic regimens consisting of olanzapine, 5HT<sub>3</sub>RA, and DEX without NK<sub>1</sub>RA 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

## 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 (NK<sub>1</sub>RA) to a 5-hydroxytryptamine-3 receptor antagonist (5-HT<sub>3</sub>RA) 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 NK<sub>1</sub>RA 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 NK<sub>1</sub>RA, 5-HT<sub>3</sub>RA, 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, NK<sub>1</sub>RA, 5-HT<sub>3</sub>RA, and DEX, and one evaluated a three-drug combination consisting of olanzapine, 5-HT<sub>3</sub>RA, 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 NK<sub>1</sub>RA was not significantly associated with carboplatin-induced nausea and vomiting. This integrated analysis is the only study that analyzes the effect of NK<sub>1</sub>RA, when added to an olanzapine-containing antiemetic regimen, on carboplatin-induced nausea and vomiting. However, the efficacy of NK<sub>1</sub>RA 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 NK<sub>1</sub>RA, olanzapine, 5-HT<sub>3</sub>RA, and DEX in preventing carboplatin-induced nausea and vomiting in a propensity score-matched analysis.

## Methods

### Study design

We analyzed 62 patients, treated without NK<sub>1</sub>RA (non-NK<sub>1</sub>RA group, 31 patients) and with NK<sub>1</sub>RA (NK<sub>1</sub>RA 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-HT<sub>3</sub>RA (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/orally: 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].

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).

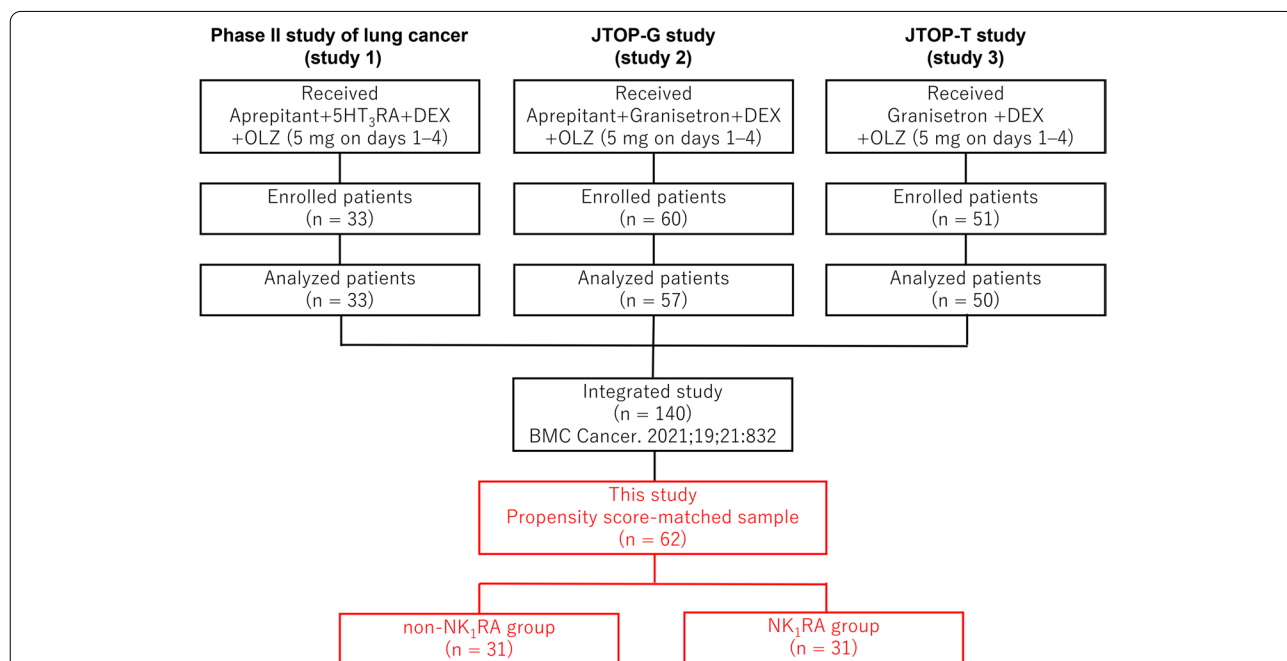
**Outcome**

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 NK<sub>1</sub>RA 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 NK<sub>1</sub>RA and non-NK<sub>1</sub>RA 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.



**Fig. 1** Patient enrollment flowchart. In all, 62 patients were selected using the propensity score-matched sample from three multicenter, prospective, single-arm, open-label, phase II studies. 5-HT<sub>3</sub>RA, 5-hydroxytryptamine-3 receptor antagonists; DEX, dexamethasone; OLZ, olanzapine

## Results

### Study patients

A total of 62 patients were included in the analysis. Of these patients, 31 were in the non-NK<sub>1</sub>RA group and

31 in the NK<sub>1</sub>RA group. Baseline patient characteristics are presented in Table 1. The median ages of patients in the non-NK<sub>1</sub>RA group and those in the NK<sub>1</sub>RA group were 71 years (range, 25th and 75th percentiles,

**Table 1** Baseline patient characteristics

	Non-NK <sub>1</sub> RA group (n = 31)	NK <sub>1</sub> RA group (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<sub>1</sub>RA and NK<sub>1</sub>RA groups did not show any statistically significant difference. Likewise, the CC and TC rates in the non-NK<sub>1</sub>RA group, during each period, were not significantly different from those in the NK<sub>1</sub>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<sub>1</sub>RA group and 16.1% in the NK<sub>1</sub>RA group ( $P=1.000$ ), that of vomiting was 6.5% in the non-NK<sub>1</sub>RA group and 3.2% in the NK<sub>1</sub>RA group ( $P=1.000$ ), and that of decreased appetite was 58.1% in the non-NK<sub>1</sub>RA group and 61.3% in the NK<sub>1</sub>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<sub>1</sub>RA group and 80.6% in the NK<sub>1</sub>RA group. However, moderate or severe somnolence was 6.5% in the non-NK<sub>1</sub>RA group and 0% in the NK<sub>1</sub>RA group. The incidence of decreased concentration was 48.4% in the non-NK<sub>1</sub>RA group and 48.4% in the NK<sub>1</sub>RA group. However, moderate or severe decreased concentration was 3.2% in the non-NK<sub>1</sub>RA group and 0% in the NK<sub>1</sub>RA group. The

peak incidence of somnolence and decreased concentration was observed on day 4 in both groups.

### Discussion

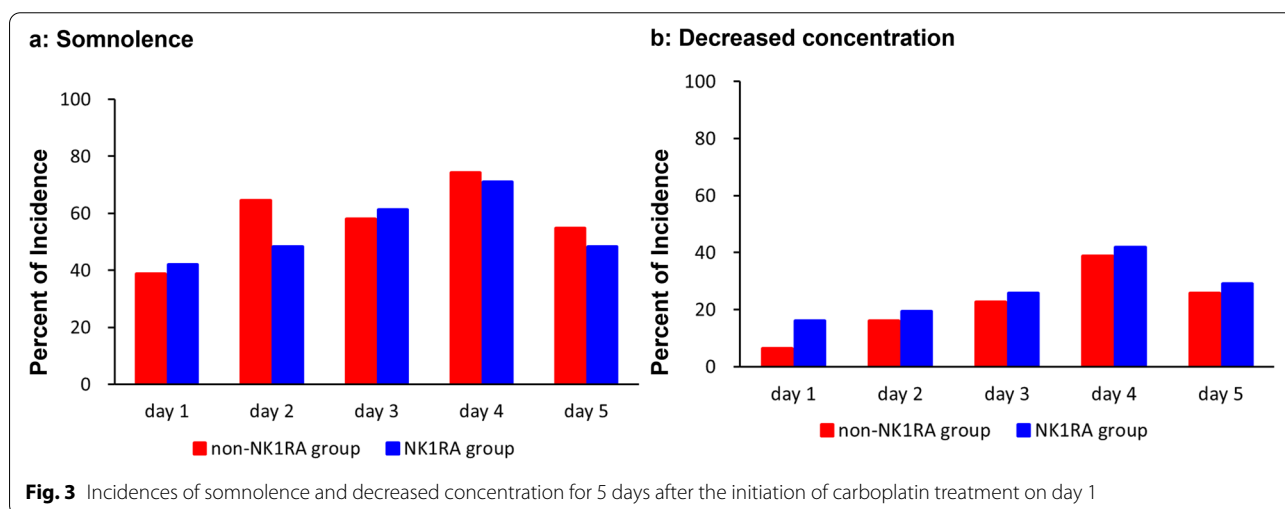
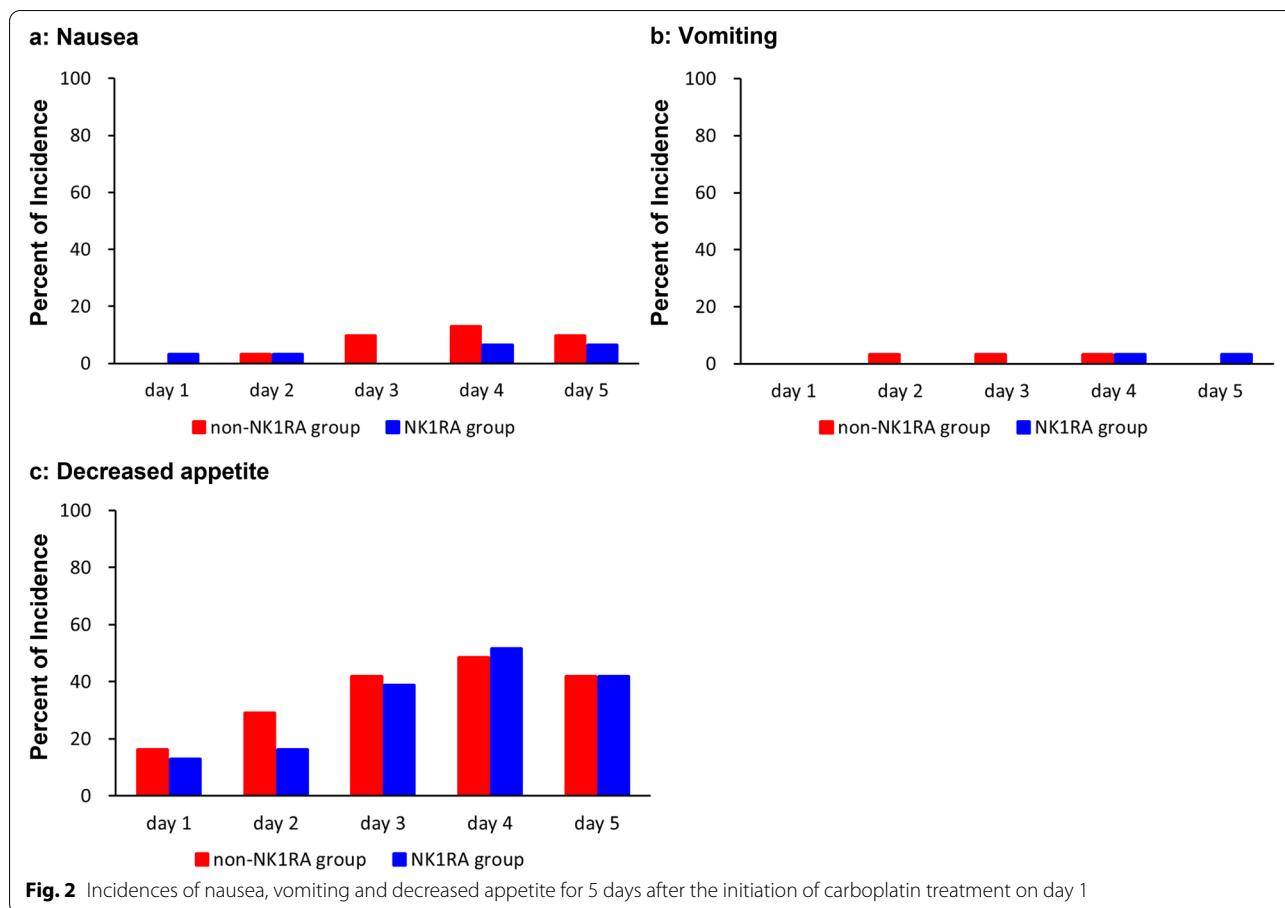
To the best of our knowledge, there are no studies that have evaluated the efficacy of adding NK<sub>1</sub>RA to antiemetic therapy consisting of olanzapine, 5HT<sub>3</sub>RA, and DEX in MEC and HEC. In the present study, the prophylactic antiemetic combination regimen of olanzapine, 5-HT<sub>3</sub>RA, and DEX showed no statistical difference between groups treated with or without NK<sub>1</sub>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<sub>1</sub>RA administration. The incidences of moderate and severe daytime sleepiness and concentration impairment were rare.

In the present study, prophylactic antiemetic treatment without NK<sub>1</sub>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<sub>1</sub>RA group was also very low (12.9%). A head-to-head comparison of the antiemetic effects of olanzapine and NK<sub>1</sub>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<sub>1</sub>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<sub>1</sub>RA regimen. It has been reported that when 5-HT released by anticancer drugs acts on 5-HT<sub>2b</sub> and 5-HT<sub>2c</sub> receptors, the secretion of

**Table 2** Primary endpoint for efficacy

Outcome	Non-NK <sub>1</sub> RA group (n = 31)	NK <sub>1</sub> 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%	
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%	
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<sub>2b</sub> and 5-HT<sub>2c</sub> 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-NK<sub>1</sub>RA group and 71 years (range, 25th and 75th percentiles, 65–77 years) in the NK<sub>1</sub>RA 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 NK<sub>1</sub>RA 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 NK<sub>1</sub>RA. 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-HT<sub>3</sub>RA, and DEX, with or without NK<sub>1</sub>RA in patients receiving carboplatin-based chemotherapy is warranted.

## Conclusion

These findings suggest that antiemetic combination regimens of olanzapine, 5-HT<sub>3</sub>RA, and DEX without NK<sub>1</sub>RA may be a treatment option for patients treated with carboplatin-based combination chemotherapy with an area under the curve of  $\geq 5$  mg/mL/min.

## Abbreviations

5-HT<sub>3</sub>RA: 5-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; NK<sub>1</sub>RA: Neurokinin-1 receptor antagonist; TC: Total control.

## Acknowledgements

We are grateful to all the patients and their families for participating in this study. We would like to thank Editage ([www.editage.com](http://www.editage.com)) for English language editing.

## 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., K.T., Y.F., M.A., H.I., M.K., Y.H., C.H., T.S., K.N., A.S., and N.I. 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., Y.O., K.M., and N.I. critically revised the manuscript. All authors reviewed the manuscript. The author(s) read and approved the final manuscript.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## 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 (16–296). 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.

### Author details

<sup>1</sup>Department of Pharmacy, Gifu University Hospital, 1-1 Yanagido, Gifu 501-1194, Japan. <sup>2</sup>Laboratory of Pharmacy Practice and Social Science, Gifu Pharmaceutical University, 1-25-4 Daigakunishi, Gifu 501-1196, Japan. <sup>3</sup>Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. <sup>4</sup>Division of Pharmaceutical Care Sciences, Center for Social Pharmacy and Pharmaceutical Care Sciences, Keio University Faculty of Pharmacy, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan. <sup>5</sup>Division of Pharmaceutical Care Sciences, Keio University Graduate School of Pharmaceutical Sciences, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan. <sup>6</sup>Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, Shizuoka 431-3192, Japan. <sup>7</sup>Division of Pharmacy, Gunma Prefectural Cancer Center, 617-1 Takahayashi-nishi, Ohta, Gunma 373-8550, Japan. <sup>8</sup>Division of Gynecology, Shizuoka Cancer

Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan. <sup>9</sup>Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, Shizuoka 431-3192, Japan. <sup>10</sup>Division of Respiratory Medicine, Gunma Prefectural Cancer Center, 617-1, Takahayashi-nishi, Ohta, Gunma 373-8550, Japan. <sup>11</sup>Department of Respiratory Medicine, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan. <sup>12</sup>Department of Clinical Oncology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, Shizuoka 431-3192, Japan. <sup>13</sup>Department of Obstetrics and Gynecology, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan. <sup>14</sup>Department of Gynecology, Gunma Prefectural Cancer Center, 617-1 Takahayashi-nishi, Ohta, Gunma 373-8550, Japan. <sup>15</sup>Department of Cardiology and Respiratory Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan. <sup>16</sup>Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, Shizuoka 431-3192, Japan.

Received: 28 October 2021 Accepted: 10 March 2022

Published online: 23 March 2022

## References

- Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016;27:v119–33.
- Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, et al. Antiemetics: ASCO guideline update. *J Clin Oncol*. 2020;38:2782–97.
- NCCN Clinical Practice Guidelines in Oncology: Antiemesis. version 1.2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/antiemesis.pdf](https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf). Accessed 11 Apr 2021.
- Aogi K, Takeuchi H, Saeki T, Aiba K, Tamura K, Iino K, et al. Optimizing antiemetic treatment for chemotherapy-induced nausea and vomiting in Japan: update summary of the 2015 Japan society of clinical oncology clinical practice guidelines for antiemesis. *Int J Clin Oncol*. 2021;26:1–17.
- Jordan K, Blättermann L, Hinke A, Müller-Tidow C, Jahn F. Is the addition of a neurokinin-1 receptor antagonist beneficial in moderately emetogenic chemotherapy?—a systematic review and meta-analysis. *Support Care Cancer*. 2018;26:21–32.
- Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. *J Support Oncol*. 2011;9:188–95.
- Navari RM, Nagy CK, Le-Rademacher J, Loprinzi CL. Olanzapine versus fosaprepitant for the prevention of concurrent chemotherapy radiotherapy-induced nausea and vomiting. *J Community Support Oncol*. 2016;14:141–7.
- Tan L, Liu J, Liu X, Chen J, Yan Z, Yang H, et al. Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting. *J Exp Clin Cancer Res*. 2009;28:131.
- Babu G, Saldanha SC, Kuntegowdanahalli Chinnagiriappa L, Jacob LA, Mallekavu SB, Dasappa L, et al. The efficacy, safety, and cost benefit of olanzapine versus aprepitant in highly emetogenic chemotherapy: a pilot study from South India. *Chemother Res Pract*. 2016;2016:3439707.
- Wang X, Wang L, Wang H, Zhang H. Effectiveness of olanzapine combined with ondansetron in prevention of chemotherapy-induced nausea and vomiting of non-small cell lung cancer. *Cell Biochem Biophys*. 2015;72:471–3.
- Navari RM, Qin R, Ruddy KJ, Liu H, Powell SF, Bajaj M, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2016;375:134–42.
- Hashimoto H, Abe M, Tokuyama O, Mizutani H, Uchitomi Y, Yamaguchi T, et al. 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. *Lancet Oncol*. 2020;21:242–9.
- Tanaka K, Inui N, Karayama M, Yasui H, Hozumi H, Suzuki Y, et al. Olanzapine-containing antiemetic therapy for the prevention of carboplatin-induced nausea and vomiting. *Cancer Chemother Pharmacol*. 2019;84:147–53.
- Iihara H, Shimokawa M, Hayasaki Y, Fujita Y, Abe M, Takenaka M, et al. Efficacy and safety of 5 mg olanzapine combined with aprepitant, granisetron and dexamethasone to prevent carboplatin-induced nausea and vomiting in patients with gynecologic cancer: a multi-institution phase II study. *Gynecol Oncol*. 2020;156:629–35.
- Sakai C, Shimokawa M, Iihara H, Fujita Y, Ikemura S, Hirose C, et al. Low-dose olanzapine plus granisetron and dexamethasone for carboplatin-induced nausea and vomiting in patients with thoracic malignancies: a prospective multicenter phase II trial. *Oncologist*. 2021;26:e1066-72-e1072.
- Yamamoto S, Iihara H, Uozumi R, Kawazoe H, Tanaka K, Fujita Y, et al. Efficacy and safety of 5 mg olanzapine for nausea and vomiting management in cancer patients receiving carboplatin: integrated study of three prospective multicenter phase II trials. *BMC Cancer*. 2021;21:832.
- Hesketh PJ, Aapro M, Street JC, Carides AD. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. *Support Care Cancer*. 2010;18:1171–7.
- Warr DG, Street JC, Carides AD. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of phase 3 trial of aprepitant in patients receiving adriamycin-cyclophosphamide-based chemotherapy. *Support Care Cancer*. 2011;19:807–13.
- Hilarius DL, Kloeg PH, van der Wall E, van den Heuvel JJ, Gundy CM, Aaronson NK. Chemotherapy-induced nausea and vomiting in daily clinical practice: A community hospital-based study. *Support Care Cancer*. 2012;20:107–17.
- Sekine I, Segawa Y, Kubota K, Saeki T. Risk factors of chemotherapy-induced nausea and vomiting: index for personalized antiemetic prophylaxis. *Cancer Sci*. 2013;104:711–7.
- Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10:150–61.
- Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics*. 1999;55:1202–9.
- Takeda H, Sadakane C, Hattori T, Katsurada T, Ohkawara T, Nagai K, et al. Rikkunshito, an herbal medicine, suppresses cisplatin-induced anorexia in rats via 5-HT<sub>2</sub> receptor antagonism. *Gastroenterology*. 2008;134:2004–13.
- Shahid M, Walker GB, Zorn SH, Wong EH. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. *J Psychopharmacol*. 2009;23:65–73.
- Iihara H, Shimokawa M, Hayashi T, Kawazoe H, Saeki T, Aiba K, et al. A nationwide, multicenter registry study of antiemesis for carboplatin-based chemotherapy-induced nausea and vomiting in Japan. *Oncologist*. 2020;25:e373–80.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

