

Low-Dose Olanzapine Plus Granisetron and Dexamethasone for Carboplatin-Induced Nausea and Vomiting in Patients with Thoracic Malignancies: A Prospective Multicenter Phase II Trial

CHIZURU SAKAI,^a MOTOTSUGU SHIMOKAWA,^{b,c} HIROTOSHI IIHARA^{d,e}, YUKIYOSHI FUJITA,^f SHINNOSUKE IKEMURA,^{g,h} CHIEMI HIROSE,^d MIE KOTAKE,ⁱ NORIHIKO FUNAGUCHI,^j TAKENOBU GOMYO,^a HISAO IMAI,^{i,k} JUN HAKAMATA,^l DAIZO KAITO,^a KOICHI MINATO,ⁱ TAKAHIRO ARAI,^f HITOSHI KAWAZOE,^m AKIO SUZUKI,^{d,e} YASUSHI OHNO,^a HIROYUKI OKURA^a

^aDepartment of Cardiology and Respiratory Medicine, Gifu University Graduate School of Medicine, Gifu, Gifu, Japan; ^bDepartment of Biostatistics, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan; ^cCancer Biostatistics Laboratory, Clinical Research Institute, National Hospital Organization Kyushu Cancer Center, Minami-ku, Fukuoka, Japan; ^dDepartment of Pharmacy, Gifu University Hospital, Gifu, Gifu, Japan; ^eLaboratory of Pharmacy Practice and Social Science, Gifu Pharmaceutical University, Gifu, Gifu, Japan; ^fDivision of Pharmacy, Gunma Prefectural Cancer Center, Ohta, Gunma, Japan; ^gDivision of Pulmonary Medicine, Department of Medicine, Keio University, School of Medicine, Shinjuku-ku, Tokyo, Japan; ^hKeio Cancer Center, Keio University, School of Medicine, Shinjuku-ku, Tokyo, Japan; ⁱDivision of Respiratory Medicine, Gunma Prefectural Cancer Center, Ohta, Gunma, Japan; ^jDepartment of Respiratory, Asahi University Hospital, Gifu, Gifu, Japan; ^kDepartment of Respiratory Medicine, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, Hidaka, Saitama, Japan (present address); ^lDepartment of Pharmacy, Keio University Hospital, Shinjuku-ku, Tokyo, Japan; ^mDivision of Pharmaceutical Care Sciences, Center for Social Pharmacy and Pharmaceutical Care Sciences, Keio University Faculty of Pharmacy, Minato-ku, Tokyo, Japan

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Thoracic malignancies • Olanzapine • Carboplatin • Nausea • Vomiting

ABSTRACT

Background. Olanzapine is an inexpensive and durable agent for the treatment of chemotherapy-induced nausea and vomiting and is also superior to neurokinin-1 receptor antagonists in the control of nausea. This study aimed to investigate the efficacy and safety of a low dose of 5 mg olanzapine plus granisetron and dexamethasone for treatment of carboplatin (CBDCA)-induced nausea and vomiting in patients with thoracic malignancies.

Materials and Methods. We conducted a prospective, open-label, single-arm, multicenter, phase II trial in four centers in Japan. Registered patients were scheduled to receive area under the curve (AUC) ≥ 5 mg/mL per minute of CBDCA and had never received moderately to highly emetogenic chemotherapy. Patients received olanzapine 5 mg/day orally after supper for 4 days, in combination with granisetron and dexamethasone. Primary endpoint

was complete response (CR; no emesis and no use of rescue medication) rate during the overall phase (0–120 hours).

Results. Between February 2018 and June 2020, 51 patients were enrolled, and 50 patients were evaluated. The CR rates in the overall (0–120 hours), acute (0–24 hours), and delayed phases (24–120 hours) were 94.0%, 100%, and 94.0%, respectively. No grade 3 or higher adverse effects of olanzapine were observed.

Conclusion. Prophylactic antiemetic therapy with a low dose of 5 mg olanzapine plus granisetron and dexamethasone showed durable efficacy with an acceptable safety profile. This three-drug combination appears to be a reasonable treatment approach in patients with thoracic malignancies receiving an AUC ≥ 5 mg/mL per minute of CBDCA-based regimen. *Clinical trial identification number:* UMIN000031267. *The Oncologist* 2021;26:e1066–e1072

Implications for Practice: The results of this phase II trial indicated that the prophylactic administration of low-dose of 5 mg olanzapine combined with granisetron and dexamethasone has promising activity with acceptable safety profile in patients with thoracic malignancy receiving high-dose carboplatin chemotherapy.

Correspondence: Hirotoshi Iihara, Ph.D., 1-1 Yanagido, Gifu, Gifu, 501-1194, Japan. Telephone: 81-58-230-7088; e-mail: dai0920@gifu-u.ac.jp
Received October 30, 2020; accepted for publication March 12, 2021; published Online First on May 4, 2021. <http://dx.doi.org/10.1002/onco.13772>

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INTRODUCTION

Carboplatin (CBDCA) is a key drug for the treatment of patients with thoracic malignancies [1–8]. However, CBDCA is well known to have a higher emetic risk among moderately emetogenic chemotherapy (MEC) and/or highly emetogenic chemotherapy (HEC). Chemotherapy-induced nausea and vomiting (CINV) deteriorates patients' quality of life (QOL), impairs compliance to medications, decreases the efficacy of therapy, and reduces the likelihood of therapeutic success [9]. Therefore, the maximum prevention of CINV is vital for maintaining the patients' QOL and continuing chemotherapy. In the latest international antiemetic guidelines, for patients with thoracic malignancies receiving CBDCA-based regimens, standard antiemetic prophylaxis for CINV is a three-drug combination comprising 5-hydroxytryptamine type-3 receptor antagonist (5-HT₃ RA), dexamethasone (DEX), and neurokinin-1 receptor antagonist (NK₁ RA) [10–12]. Emetogenicity is not only dependent on the type of anticancer agents but also has associated patient-related risk factors [13–16]. In particular, female sex and younger age have repeatedly been associated with an increased risk of CINV. In contrast, older age, which is in majority of the patients with thoracic malignancies, decreases the risk for CINV. In CBDCA-based chemotherapy, the complete response (CR), which was defined as the absence of emetic episodes and no administration of rescue medication for CINV, rate of treatment with first-generation 5-HT₃ RA, and DEX was approximately 50% and 65% in patients with gynecological [17, 18] and thoracic [19, 20] malignancies, respectively. Moreover, the CR rate of a standard three-drug combination treatment containing aprepitant (APR) is as high as 80%–90% in patients with lung cancer [19, 21–23].

Olanzapine (OLZ) is an antipsychotic drug classified as a multiacting, receptor-targeted agent and is a highly effective, inexpensive, and easily available antiemetic agent. Several pivotal randomized trials demonstrated that prophylactic administration of 10 mg of OLZ improved nausea prevention and the CR rate in patients who received MEC and/or HEC [24–28].

Navari et al. reported a head-to-head comparison of the effect of APR versus 10 mg of OLZ when combined with palonosetron (PALO), a second-generation 5-HT₃ RA, plus DEX for HEC regimen in a phase III trial [24]. The study demonstrated that the CR rate of OLZ is comparable to that of APR. In contrast, treatment with 10 mg of OLZ showed excellent control of nausea in the delayed and overall periods than APR. This finding was also confirmed in a network meta-analysis of HEC regimens [29]. There are studies using 10 mg of OLZ for CBDCA-induced CINV, although they included fewer patients receiving CBDCA as a part of various MEC regimens [25, 30]. Moreover, patient sedation due to 10 mg of OLZ therapy may be a concern [24]. Guidelines suggest that reducing the dose of OLZ to 5 mg should be considered for patients with a risk of excessive sedation while receiving 10 mg of OLZ [10–12]. A phase II trial indicated that treatment with 5 mg and 10 mg of OLZ showed a comparable CR rate, but 5 mg of OLZ was less sedative in patients who received cisplatin-based regimens [31]. The

cost per treatment cycle of 5 mg of OLZ (\$7.03, \$1 = ¥104.34 [October 29, 2020]) is less than that of APR (\$111.54) and fosaprepitant (\$139.40). We believe that OLZ can replace NK₁ RA, because NK₁ RA has high cost and clinically significant pharmacokinetic drug-drug interactions via inhibition of cytochrome P450 3A4 [32]. However, the efficacy and safety of treatment with OLZ, especially at a low dose of 5 mg, against CBDCA-induced CINV in patients with thoracic malignancies, has not been demonstrated.

Therefore, this study aimed to investigate the efficacy and safety of a three-drug combination of low dose OLZ of 5 mg combined with granisetron (GRN) and DEX in treatment of CBDCA-induced CINV in Japanese patients with thoracic malignancies.

MATERIALS AND METHODS

Study Design

This prospective study was an open-label, single-arm, multicenter, phase II trial conducted in four centers (Gifu University Hospital, Gunma Prefectural Cancer Center, Keio University Hospital, and Asahi University Hospital) in Japan, and in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies. The study was approved by the institutional review board at each participating center. This study was registered with the University Hospital Medical Information Network (umin.ac.jp/ctr/index/htm), number UMIN000031267 (principal investigators: H.I., Y.O.; primary statistician: M.S.).

Patients' Selection

Patients with thoracic malignancies, who were scheduled to receive CBDCA (area under the curve [AUC] ≥5)-based chemotherapy, were registered in this study. Other eligibility criteria were age ≥ 20 years and < 80 years and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2; no symptomatic brain metastasis and carcinomatosis; no history of administration of moderately-to-highly emetogenic chemotherapy; no current use of any drugs with antiemetic activity or somnolence, such as 5-HT₃ RA, NK₁ RA, corticosteroids, antidopamine agonists, phenothiazine tranquilizers, antihistamine drugs (premedication at paclitaxel administration was allowed), benzodiazepine agents, and so on; meeting the following standard values in general clinical tests: aspartate aminotransferase and alanine aminotransferase ≤100 U/L and total bilirubin ≤2.0 mg/dL; and provided written informed consent.

Patients were ineligible based on the following criteria: history of hypersensitivity or allergy for study drugs or similar compounds; requirement of antiemetics at enrollment; administration of opioids within 48 hours prior to enrollment; unstable angina, ischemic heart disease, cerebral hemorrhage or apoplexy, and active gastric or duodenal ulcer within 6 months prior to enrollment; having convulsive disorders requiring anticonvulsant therapy; ascites effusion requiring paracentesis; gastrointestinal obstruction; breastfeeding or expecting women or who do not wish to use contraception; having psychosis or psychiatric symptoms that interfere

Table 1. Patients' characteristics

Characteristics	All Patients
Total number of patients	50
Age, yr	
Median (range)	71 (34–79)
Gender, <i>n</i> (%)	
Male	35 (70.0)
Female	15 (30.0)
ECOG PS, <i>n</i> (%)	
0	26 (52.0)
1	18 (36.0)
2	6 (12.0)
Thoracic malignancy, <i>n</i> (%)	
Small cell lung cancer	11 (22.0)
Non-small cell lung cancer	33 (66.0)
Thymoma/thymic carcinoma	5 (10.0)
Others	1 (2.0)
Carboplatin dose, <i>n</i> (%)	
AUC 5 mg/mL/min	40 (80.0)
AUC 6 mg/mL/min	10 (20.0)
Additional anticancer drugs, <i>n</i> (%)	
Pemetrexed	10 (20.0)
Pemetrexed+bevacizumab	3 (6.0)
Pemetrexed+pembrolizumab	4 (8.0)
Paclitaxel	3 (6.0)
Paclitaxel+bevacizumab+atezorizumab	2 (4.0)
paclitaxel+pembrolizumab	2 (4.0)
Nab-paclitaxel	2 (4.0)
Nab-paclitaxel+pembrolizumab	4 (8.0)
Etoposide	10 (20.0)
Etoposide+atezorizumab	2 (4.0)
Vinorelbine	5 (10.0)
Tegafur/gimeracil/oteracil	3 (6.0)
Habitual alcohol consumption, <i>n</i> (%)	
Yes	25 (50.0)
No	25 (50.0)
Motion sickness, <i>n</i> (%)	
Yes	7 (14.0)
No	43 (86.0)
Morning sickness, <i>n</i> (%)	
Yes	9 (18.0)
No	6 (12.0)
No experience, <i>n</i> (%)	19 (38.0)
Unknown	16 (32.0)

Abbreviations: AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group performance status.

with daily life; having received abdominal or pelvic irradiation within 6 days prior to enrollment; having had diabetes mellitus; habitual smoker at enrollment; and other patients who were judged to be inappropriate for the study by the investigator.

Treatment Regimen

GRN of 1 mg was intravenously administered to patients 30 minutes before chemotherapy on day 1. DEX (9.9 mg intravenous infusion or 12 mg oral) was administered 30 minutes before chemotherapy on day 1. DEX (6.6 mg intravenous infusion or 8 mg oral) was also administered on days 2 and 3. OLZ (5 mg oral) was administered after supper for 4 days from the initial administration of CBDCA-based regimens. When paclitaxel was used as a combination of chemotherapy, the dose of DEX was increased to 19.8 mg intravenously or 20 mg orally on day 1 to prevent infusion-related hypersensitivity reactions.

Assessment Procedures

In the prestudy period, all patients' demographic characteristics and medical data were recorded. Data were collected from patient diaries. Patients filled out the diary every 24 hours from the start of CBDCA to 120 hour periods, in which they daily reported the presence or absence of nausea, decreased appetite, somnolence, decreased concentration, and insomnia using a four-point Likert scale (none, mild, moderate, and severe). Vomiting was reported using a five-item scale (none, 1–2 times, 3–5 times, 6 times or more, and almost always), and the use of rescue medication was reported using a four-item scale (none, 1 time, 2 times, and 3 times or more). After the overall assessment period (0–120 hours), patient-reported study diaries were collected. Patients were also assessed before the initiation of chemotherapy to record baseline parameters. Overall patient satisfaction with antiemetic therapy was measured on a seven-point Likert scale (very satisfied, satisfied, somewhat satisfied, rather satisfied, rather dissatisfied, dissatisfied, and very dissatisfied) after the overall assessment period (0–120 hours).

Outcomes

The primary endpoint was CR rate, which was defined as no emetic episodes and no administration of rescue medication for CINV in the overall assessment period (0–120 hours) after initiation of CBDCA-based regimen.

Secondary endpoints were CR rate in the acute period (0–24 hours), CR rate in the delayed period (24–120 hours), and complete control (CC) rate, which was defined as no emetic episodes, no use of rescue medication, and no significant nausea in the overall, acute, and delayed period. Significant nausea was defined as “moderate” and “severe” categories; a total control (TC) rate, which was defined as no emetic episodes, no use of rescue medication, and no nausea in the overall, acute, and delayed period; a time to treatment failure, which was defined as time to first emetic episode or use of rescue medication; and patient satisfaction with antiemetic therapy.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical Analysis

This study hypothesized that the CR rate for 5 mg OLZ combined with GRN and DEX for AUC ≥ 5 mg/mL per minute of CBDCA-based regimens would be significantly higher than that

Table 2. Rate of complete response, complete control, and total control during acute, delayed, and overall treatment period

Endpoint	Overall phase			Acute phase No. (%)	Delayed phase No. (%)
	No. (%)	80% CI	<i>p</i> value		
Complete response	47 (94.0)	(87.1–97.8)	<.0001	50 (100.0)	47 (94.0)
Complete control	47 (94.0)			50 (100.0)	47 (94.0)
Total control	43 (86.0)			50 (100.0)	43 (86.0)

Abbreviation: CI, confidence interval.

of the CR rate for standard antiemetic doublet therapy. Other trials have shown CR rates of approximately 65% [19, 20]. An improvement of the treatment effect has to be >10% to amend the guidelines of the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology 2016 [10] based on previous studies in which the CR ratio of antiemetic treatment with PALO, DEX, and APR was 80.5%–92% [19, 21–23]. We believe that an improvement of >15% in the CR rate can be clinically meaningful.

Therefore, assuming the null hypothesis of the CR rate to be ≤65% and an alternative hypothesis to be 80%, we calculated that a minimum of 48 patients were required to achieve a one-sided type I error of 0.1 and 80% of power, based on the exact binomial distribution. As some study dropouts were expected, we set the target sample size to 50 patients.

Patients' characteristics, rate of CINV control, and treatment-related adverse events were summarized by descriptive statistics or reported as the frequency and proportion of total patients. The 80% confidence interval [CI] for the CR rate was calculated by the Clopper–Pearson exact method.

Univariate and multivariate logistic regression analyses with the backward elimination method were performed to determine the risk factors associated with CINV in the overall period. All potential explanatory variables reported in several previous studies were included as independent variables. These were patient-related risk factors, such as age, sex, ECOG PS, habitual alcohol consumption, and motion sickness [13–16]. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). All *p* values were two-sided, and *p* < .05 was considered statistically significant.

RESULTS

Study Patients

Between February 2018 and June 2020, 51 patients were enrolled in this study. One patient was excluded from the

Table 3. The incidence of nausea and vomiting over time (every 24 hours) for 5 days

Day	Nausea	Vomiting
Day 1	0 (0)	0 (0)
Day 2	1 (2.0)	1 (2.0)
Day 3	6 (12.0)	2 (4.0)
Day 4	7 (14.0)	2 (4.0)
Day 5	3 (6.0)	0 (0)

Data are *n* (%).

analysis as the patient failed to receive chemotherapy because of an angina attack. Thus, 50 patients were evaluated for efficacy and safety analysis. Demographic data and patient characteristics are shown in Table 1.

Efficacy

As shown in Table 2, the CR rates in the overall, acute, and delayed phases were 94.0% (80% CI, 87.1–97.8; *p* < .0001), 100%, and 94.0%, respectively. The incidences of nausea and vomiting over time (every 24 hours) for 5 days are presented in Table 3. The incidence of nausea and vomiting was higher on days 3–4 than on other days.

Safety

The prevalence of major adverse events upon treatment with OLZ is shown in Table 4. In the CTCAE version 4.0, there were no grade 3 or higher adverse events. In the patient diaries, the highest incidences of somnolence and decreased concentration were noted on day 4 compared with other days, with incidence rates of 76.0% and 40.0%, respectively (Fig. 1). The rates of severe symptoms were as low as 4% for somnolence and 2% for decreased concentration.

Patient Factors Affecting CINV Control

There were no risk factors associated with non-CR, CC, or vomiting. The results of univariate logistic analyses are shown in Table 5. The multivariate logistic analyses showed that only incidence of motion sickness remained the most strongly associated factor with TC and no nausea in the overall phase (odds ratio, 0.14; 95% CI, 0.022–0.841; *p* = .0318; and odds ratio, 0.14; 95% CI, 0.022–0.841; *p* = .0318, respectively), but the values were similar to the results of the univariate logistic analysis.

Patient Satisfaction

Patient satisfaction with the antiemetic therapy was rated as follows: very satisfied (38.0%), satisfied (44.0%), somewhat satisfied (8.0%), rather satisfied (8.0%), and dissatisfied (2.0%).

Table 4. Treatment-related adverse events

Symptom term	Grade 1	Grade 2	Any grade
Dry mouth	31 (62.0)	1 (2.0)	32 (64.0)
Hiccups	20 (40.0)	5 (10.0)	25 (50.0)
Constipation	20 (40.0)	16 (32.0)	36 (72.0)
Insomnia	25 (50.0)	3 (6.0)	28 (56.0)
Somnolence	36 (72.0)	2 (4.0)	38 (76.0)
Dizziness	19 (38.0)	0 (0.0)	19 (38.0)

Data are *n* (%).

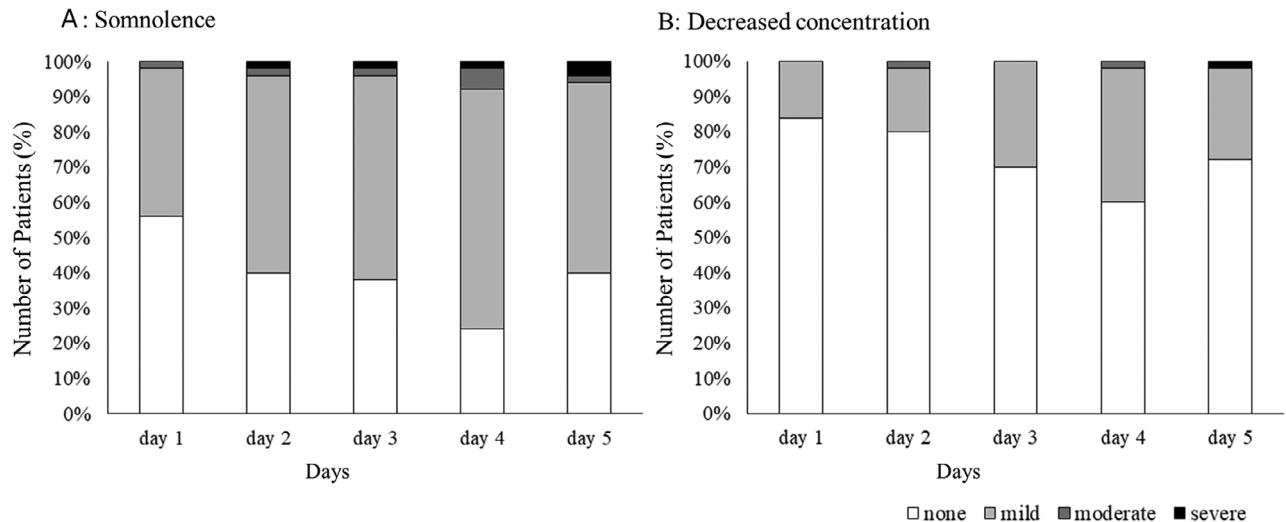


Figure 1. Distribution of somnolence severity and decreased concentration for 5 days after initiation of chemotherapy in patients with thoracic malignancy.

No patients reported feeling rather dissatisfied and very dissatisfied.

DISCUSSION

This well-designed phase II study demonstrated for the first time that a low dose of 5 mg OLZ with the addition of first-generation 5-HT₃ RA and DEX for the treatment of CBDCA-induced CINV appeared to have a beneficial effect with an acceptable safety profile in patients with thoracic malignancies.

Jordan et al. conducted a meta-analysis to evaluate the efficacy of the addition of NK₁ RA to 5-HT₃ RA and DEX combination therapy for MEC [33]. The study demonstrated that the absolute risk difference for the overall CR rate was 15%, corroborating the addition of NK₁ RA in CBDCA-based chemotherapy. In the present study, we hypothesized that 5 mg of OLZ would improve CR rate by 15% than a two-drug combination. The CR rate was 94.0%, which was 29% higher than the null hypothesis and greater than our alternative hypothesis of 80%. Thus, 5 mg of OLZ might be more effective than adding NK₁ RA because of a high CR rate of 94.0%. We also found that the highest incidence of nausea and vomiting was on days 3–4, consistent with a previous report

of two- or three-drug combinations for CBDCA [34]. Therefore, it is necessary to closely monitor the onset of nausea and vomiting on days 3–4, despite administration of OLZ.

Tanaka et al. reported the efficacy of a four-drug combination consisting of OLZ (5 mg), APR, 5-HT₃ RA (GRA or PALO), and DEX for CINV induced in response to CBDCA-based chemotherapy in 33 patients with lung cancer [35]. They reported that the rates of CR, CC, and TC during the overall period were 93.9%, 90.9%, and 81.8%, respectively. The antiemetic efficacy of the present study was consistent with that of a previous study, although there were a few differences in patient characteristics (age and sex), APR, and 5-HT₃ RA (GRA or PALO). In that report, patients had average age of 75 years, and 87.9% were male. Thus, the present study had younger patients, a higher population of female sex, a three-drug combination, and administered first-generation 5-HT₃ RA in comparison with the previous study. The outcomes of the present study were comparable, although the risk of developing CINV was higher.

We previously reported the efficacy of a four-drug combination using first-generation 5-HT₃ RA in 57 patients with gynecological cancer who were treated with CBDCA-based chemotherapy [36]. The rates of CR, CC, and TC during the overall period were 78.9%, 77.2%, and 56.1%, respectively. However, these results were worse than those of the present study and that by Tanaka et al. The difference in antiemetic effects may be not due to the differences in the anticancer agents used in combination with CBDCA; for instance, paclitaxel, which was used in 96.5% of the patients with gynecological cancer, is known to have a lower emetic risk than pemetrexed, which is more commonly used in the treatment of lung cancer [37]. The risk analysis in this study failed to reveal any differences based on sex or age, but female sex and younger age have proven to be well-known patient-related risk factors [13–16]. In our previous study, all patients with gynecological cancer had a median age of 58 years. Nevertheless, somnolence and decreased concentration were found to be comparable with that in younger patients, and OLZ was considered safe for use in the elderly.

Table 5. Risk analysis for total control and no nausea in overall phase

Prognostic factors	Univariate analysis		
	OR	95% CI	p value
Female	0.26	(0.050–1.337)	.1066
Age	0.98	(0.866–1.101)	.6951
ECOG PS	1.27	(0.254–6.380)	.7694
Habitual alcohol consumption	1.40	(0.279–7.001)	.6845
Motion sickness	0.14	(0.022–0.841)	.0318

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio.

These results suggest that triplet therapy of first-generation 5-HT₃ RA, DEX, and OLZ could be an effective, low-cost, standard treatment in elderly and/or male patients with thoracic malignancies with AUC \geq 5 mg/mL per minute of CBDCA-based combination chemotherapy. Moreover, patients in limited-resource countries would be benefitted with this therapy.

There were several limitations in the phase II study, despite the valuable results obtained. First, this study had an open-label and single-arm design. Second, the results were obtained only in the Japanese population and, thus, cannot be extrapolated to patients globally. Finally, patients with thoracic malignancies were predominantly elderly, although enrollment in the study was restricted to those aged less than 80 years.

CONCLUSION

This study demonstrated that the administration of a low dose of 5 mg of OLZ combined with GRN and DEX showed promising activity with manageable safety, suggesting that this combination appears to be a reasonable treatment approach for patients with thoracic malignancies with AUC \geq 5 mg/mL per minute of CBDCA-based combination therapy. Future investigations are warranted to compare the efficacy of 5 mg of OLZ regimen to triplet standard therapy, which includes NK₁ RA in a phase III trial.

ACKNOWLEDGMENTS

We express our gratitude to all the patients and their families for participating in this study. We thank the members of the independent data monitoring committee: Prof. Shigehira Saji (Fukushima Medical University), Dr. Toru Mukohara (National Cancer Center Hospital East), Dr. Hideki Hayashi (Gifu Pharmaceutical University); and the independent alliance data center:

Mami Matsumaru (Gifu University Hospital). We are very grateful to Yukari Ohtsuka (Gifu University Hospital) for the assistance in this study. We would like to thank Editage (www.editage.com) for English language editing and reviewing. This study was self-funded by the Department of Cardiology and Respiratory Medicine, Gifu University Graduate School of Medicine.

This trial protocol was presented at the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology Annual Meeting 2018, Vienna, Austria, June 28–30, 2018. The protocol has been published as the following: Iihara H, Shimokawa M, Gomyo T et al. Clinical trial protocol of doublet therapy and olanzapine for carboplatin-induced nausea and vomiting in patients with thoracic cancer: a multicenter phase II trial. *BMJ Open* 2019;9:e028056.

AUTHOR CONTRIBUTIONS

Conception/design: Hirotohi Iihara, Mototsugu Shimokawa, Yukiyoshi Fujita, Takenobu Gomyo, Yasushi Ohno

Acquisition of data: Chiemi Hirose, Takahiro Arai, Mie Kotake, Hisao Imai, Chizuru Sakai, Daizo Kaito, Jun Hakamata, Norihiko Funaguchi

Analysis and interpretation of data: Hirotohi Iihara, Mototsugu Shimokawa, Yukiyoshi Fujita, Hitoshi Kawazoe, Chizuru Sakai, Takenobu Gomyo, Yasushi Ohno

Drafting the article or revising it critically for important intellectual content: Chizuru Sakai, Hirotohi Iihara, Mototsugu Shimokawa, Hitoshi Kawazoe, Takenobu Gomyo, Shinnosuke Ikemura, Koichi Minato, Akio Suzuki, Yasushi Ohno, Hiroyuki Okura

Final approval of manuscript: Chizuru Sakai, Hirotohi Iihara, Mototsugu Shimokawa, Yukiyoshi Fujita, Shinnosuke Ikemura, Chiemi Hirose, Mie Kotake, Norihiko Funaguchi, Takenobu Gomyo, Hisao Imai, Jun Hakamata, Daizo Kaito, Koichi Minato, Takahiro Arai, Hitoshi Kawazoe, Akio Suzuki, Yasushi Ohno, Hiroyuki Okura

DISCLOSURES

The authors indicated no financial relationships.

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