OXFORD UNIVERSITY PRESS | Japanese Journal of Clinical Oncology

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Journal:	*Japanese Journal of Clinical Oncology*
Manuscript ID	JJCO-17-0189.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Nakashima, Kazuhisa Murakami, Haruyasu Yokoyama, Kouichi Omori, Shouta Wakuda, Kazushige Ono, Akira Kenmotsu, Hirotsugu Naito, Tateaki Nishiyama, Fumie Kikugawa, Mami Kaneko, Masayo Iwamoto, Yumiko Koizumi, Satomi Mori, Keita Isobe, Takeshi Takahashi, Toshiaki
Sub-category:	Palliative and supportive care
Keywords:	Supportive care, Lung Medicine, Clinical Trials

A phase II study of palonosetron, aprepitant, dexamethasone, and olanzapine for the prevention of cisplatin-based chemotherapy-induced nausea and vomiting in patients with thoracic malignancy

Authors:

Kazuhisa Nakashima[1], Haruyasu Murakami[1], Kouichi Yokoyama[2], Shota Omori[1], Kazushige Wakuda[1], Akira Ono[1], Hirotsugu Kenmotsu[1], Tateaki Naito[1], Fumie Nishiyama[2], Mami Kikugawa[2], Masayo Kaneko[2], Yumiko Iwamoto[2], et al.

Affiliations:

[1]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan

[2]Nursing Department, Shizuoka Cancer Center, Shizuoka, Japan

Corresponding Author: Kazuhisa Nakashima, MD

Division of Thoracic Oncology, Shizuoka Cancer Center, 1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan

Telephone: +81-55-989-5222

Fax: +81-55-989-5783

19 E-mail: ka.nakashima@scchr.jp

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21 **Running head:** Olanzapine for the prevention of CINV

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Abstract

Background: The three-drug combination of a 5-hydroxytryptamine type 3 receptor antagonist, a neurokinin 1 receptor antagonist, and dexamethasone is recommended for patients receiving highly emetogenic chemotherapy. However, standard antiemetic therapy is not completely effective in all patients.

Methods: We conducted an open-label, single-center, single-arm phase II study to evaluate the efficacy of olanzapine in combination with standard antiemetic therapy in preventing chemotherapy-induced nausea and vomiting in patients with thoracic malignancy receiving their first cycle of cisplatin-based chemotherapy. Patients received 5 mg oral olanzapine on days 1–5 in combination with standard antiemetic therapy. The primary endpoint was complete response (no vomiting and no use of rescue therapy) during the overall phase (0–120 h post-chemotherapy).

Results: Twenty-three men and seven women were enrolled between May and October 2015. The median age was 64 years (range: 36–75 years). The most common chemotherapy regimen was 75 mg/m^2 cisplatin and 500 mg/m^2 pemetrexed, which was administered to 14 patients. Complete response rates in acute (0–24 h post-chemotherapy), delayed (24–120 h post-chemotherapy), and

overall phases were 100%, 83%, and 83% (90% confidence interval: 70–92%; 95% confidence interval: 66–93%), respectively. There were no grade 3 or grade 4 adverse events. Although four patients (13%) experienced grade 1 somnolence, no patients discontinued olanzapine.

Conclusions: The addition of 5 mg oral olanzapine to standard antiemetic therapy demonstrates promising efficacy in preventing cisplatin-based chemotherapy-induced nausea and vomiting and an acceptable safety profile in patients with thoracic malignancy.

A mini-abstract: The addition of 5 mg oral olanzapine to standard antiemetic therapy demonstrates promising efficacy in preventing cisplatin-based chemotherapy-induced nausea and vomiting in patients with thoracic malignancy.

Keywords: Chemotherapy-induced nausea and vomiting, Highly emetogenic chemotherapy, Cisplatin, Olanzapine

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a distressing symptom that reduces patient quality of life [1]. Cisplatin combination therapy, which is classified as a highly emetogenic chemotherapy (HEC), is a standard treatment for advanced lung cancer. Prophylactic antiemetic therapy is important for HEC. The three-drug combination of a 5-hydroxytryptamine type 3 receptor antagonist, a neurokinin 1 receptor antagonist, and dexamethasone is recommended for patients receiving HEC [2, 3]. Previous phase III studies have reported that the complete response (CR; no vomiting and no rescue therapy) rate with this three-drug therapy in patients receiving HEC is approximately 60–70% in the overall phase (0–120 h post-chemotherapy) [4–7], suggesting that there is room for improvement with standard antiemetic therapy.

Olanzapine is an atypical antipsychotic drug. It inhibits neurotransmitter pathways known to be involved in nausea and vomiting, including serotonergic, dopaminergic, alpha-1 adrenergic, histaminic, and muscarinic receptors. Several studies have reported the efficacy of olanzapine for CINV. Phase III trials demonstrated that the antiemetic efficacy of olanzapine in patients treated with

HEC was higher than that of dexamethasone and equal to that of aprepitant [8, 9]. Navari et al. [10] reported that the efficacy of olanzapine was higher than that of metoclopramide as a rescue therapy for standard antiemetic therapy–refractory CINV. Abe et al. [11] administered 5 mg olanzapine in combination with standard antiemetic therapy as a preventive therapy to patients treated with cisplatin who experienced grade 3 nausea (Common Terminology Criteria for Adverse Events ver. 4.0) despite receiving standard antiemetic therapy. The researchers retrospectively evaluated control of nausea and found that olanzapine improved the nausea control rate from 0% to 90% in the overall phase. Previous studies reported no grade 3 or grade 4 adverse events related to olanzapine.

To evaluate the efficacy of olanzapine in combination with standard antiemetic therapy for the prevention of CINV, we conducted an open-label, single-center, single-arm phase II study in patients with thoracic malignancy receiving cisplatin-based chemotherapy.

Patients and methods

Patient selection

Eligible patients were 20 years of age or older with histologically or cytologically confirmed thoracic malignant disease who were scheduled to receive first-course cisplatin (≥ 60 mg/m^2) combination therapy. For inclusion in the study, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 and adequate organ function (alanine aminotransferase < 100 IU/L, aspartate aminotransferase < 100 IU/L, total bilirubin concentration < 2.0 mg/dL, and creatinine clearance ≥ 60 mL/min).

Patients were excluded if they had a history of severe hypersensitivity to aprepitant, palonosetron, corticosteroids, or olanzapine; had severe complications; were pregnant or breastfeeding; were receiving abdominal or pelvic radiation therapy during the period between 6 days before and 6 days after the date of first chemotherapy; had diabetes mellitus or a history of diabetes mellitus; had abnormal glucose tolerance (hemoglobin A1c ≥ 6.5 and fasting blood glucose ≥ 126 mg/dL or non-fasting blood glucose ≥ 200 mg/dL); had emetic episodes requiring administration of antiemetics prior to chemotherapy; had a personal or familial history of malignant syndrome; had creatine phosphokinase levels greater than 2.5 times the institutional upper normal limit; had active infection; could not stop smoking during this study; had a

body mass index ≥ 35; or took an antiemetic medicine regularly.

Study treatment

Enrolled patients received standard antiemetic therapy and olanzapine. Palonosetron was intravenously administered at a dose of 0.75 mg 30–60 min prior to chemotherapy administration on day 1. Aprepitant was orally administered at a dose of 125 mg 60–90 min prior to chemotherapy administration on day 1 and at a dose of 80 mg on days 2 and 3. Dexamethasone was intravenously administered at a dose of 9.9 mg 30–60 min prior to chemotherapy administration on day 1 and was then orally administered at a dose of 8 mg on days 2–4. Olanzapine was orally administered at a dose of 5 mg once per day at night on days 1–5. Patients were permitted to receive a rescue therapy of the treating investigator's choice for nausea or emesis based on clinical circumstances. Patients were not allowed to take prophylactic antiemetic therapy other than the study treatment before breakthrough emesis.

Outcome measures

The enrolled patients were hospitalised for treatment from the day prior to and up

to day 6 of chemotherapy. Episodes of nausea and vomiting were recorded in a patient diary for the acute phase (0–24 h post-chemotherapy) and the delayed phase (24–120 h post-chemotherapy). The degree of nausea was evaluated by each patient using an 11-point (0–10) numeric rating scale (NRS).

The primary endpoint was the CR (no vomiting and no use of rescue therapy) rate during the overall phase. Secondary endpoints were CR rates in the acute and delayed phases and rates of complete control (CC; no vomiting, no rescue, no significant nausea [NRS score of 0–2]), total control (TC: no vomiting, no rescue, no nausea [NRS score of 0]), and adverse events in the acute, delayed, and overall phases.

Statistical methods

In a phase III trial, the overall phase CR rate for the three-drug combination of palonosetron, aprepitant, and dexamethasone was 65.7% [7]. Therefore, we set the threshold overall CR rate at 65% and the expected CR rate at 85% for the present study. To reach 5% (one-sided) significance and 80% statistical power, we calculated that a minimum sample size of 28 patients was required [12]. Assuming a 10% exclusion rate, the planned sample size was 30 patients.

Ethics

Our institutional review board approved the design of this study. All enrolled patients provided written informed consent.

Results

Patient characteristics

Thirty patients with thoracic malignancy were enrolled from May 2015 through October 2015. Patient characteristics are listed in Table 1. The most common type of thoracic malignancy in this study was non-small cell lung cancer. Nineteen patients received systemic chemotherapy, with the rest receiving chemoradiation therapy or postoperative adjuvant therapy. Cisplatin was administered at a dose of 60–80 mg/m^2, and pemetrexed (14 patients), etoposide (seven patients), vinorelbine (four patients), irinotecan (two patients), S-1 (two patients), or gemcitabine (one patient) were administered as the combination anticancer drug.

Efficacy

Antiemetic effects are shown in Table 2. Although outcome measures were evaluated based on the diary submitted by each patient, there were no missing data. The overall phase CR rate (primary endpoint) was 83% (90% confidence interval: 70–92%; 95% confidence interval: 66–93%). CR rates for the acute and delayed phases were 100% and 83%, respectively. In the acute, delayed, and overall phases, CC rates were 93%, 73%, and 70%, respectively, and TC rates were 77%, 70%, and 63%, respectively. No vomiting was reported in 100% of patients in the acute phase and in 90% of patients in both the delayed and overall phases. Likewise, rates of no rescue therapy were 100%, 90%, and 90% for the acute, delayed, and overall phases, respectively. In the acute, delayed, and overall phases, no significant nausea was reported in 93%, 77%, and 73% of patients, respectively, while no nausea was reported in 77%, 70%, and 63% of patients, respectively.

Safety

There were no grade 3 or grade 4 adverse events during treatment. Grade 1 constipation was observed in 20 patients (67%). Grade 1 hiccupping was observed in 16 patients (53%), and grade 2 hiccupping was observed in one

patient (3%). Although four patients (13%) experienced grade 1 somnolence, which is an adverse event thought to be caused by olanzapine, no patients discontinued olanzapine. We conducted blood tests on days 6–8. Grade 1 elevated levels of alanine aminotransferase were observed in 11 patients (37%). There was no incidence of hyperglycemia or increase in creatine phosphokinase.

Discussion

The 83% CR rate observed during the overall phase met the primary endpoint, and the lower limit of the 90% confidence interval for the overall phase CR rate was 70%, suggesting that the addition of 5 mg oral olanzapine to standard antiemetics may reduce CINV in patients with thoracic malignancy receiving cisplatin-based chemotherapy. The secondary endpoints and safety profiles were also favorable in this study. The results of the present study are consistent with a recently published phase II study that investigated the efficacy and safety of the addition of 5 mg oral olanzapine to standard antiemetics for the prevention of CINV in patients with gynecological cancer (n = 40) receiving HEC [13]. CR rates during the overall phase were reported in 37 (92.5%) of the 40 patients with

gynecological cancer. Although all patients were female and the cisplatin dose was 50 mg/m^2 in most of the patients included in the previous study, our study demonstrated the efficacy of this treatment in a patient group that was mostly male and receiving a higher cisplatin dose (60–80 mg/m^2).

Navari et al. [14] reported the results of a phase III trial that evaluated the additional efficacy of 10 mg oral olanzapine for the prevention of CINV in patients receiving their first course of HEC. In that study, 380 patients were randomised at a 1:1 ratio for treatment with either olanzapine and standard triplet antiemetic therapy (n = 192) or placebo and standard triplet antiemetic therapy (n = 188). The proportion of patients who reported no nausea and the CR rates were significantly higher in the olanzapine arm compared with the placebo arm. However, sedation was observed more frequently in patients receiving olanzapine compared with those receiving placebo. Hashimoto et al. conducted a randomised phase II study to compare the efficacy and safety of administering 10 mg versus 5 mg oral olanzapine for the prevention of CINV in patients receiving HEC [15]. Somnolence was higher in the 10 mg arm than in the 5 mg arm. In our study, only four patients (13%) experienced grade 1 somnolence. Five milligrams of olanzapine may result in less somnolence than 10 mg.

Thus, three phase II studies, including the present study, have shown the efficacy of adding 5 mg olanzapine to standard antiemetic therapy for HEC [13, 15]. Although Navari et al. demonstrated the efficacy of 10 mg oral olanzapine plus standard antiemetics in a phase III study [14], the optimal dose of olanzapine for CINV may be 5 mg, considering efficacy and safety. In addition, Navari et al.'s phase III study had some limitations. First, the majority of subjects were female (72%), had breast cancer (63%), and received anthracycline and cyclophosphamide therapy as chemotherapy (63%). The findings cannot be generalised to all patients who receive HEC. Second, the CR rate in the placebo arm (41%) was lower than that in standard three-drug therapy in other previous phase III studies [4–7]. This is also open to interpretation. The efficacy of additional olanzapine in standard antiemetic therapy for CINV should be investigated further.

The present study has several limitations. First, it was a small single-arm study (n = 30) conducted at a single institution. Second, this study was conducted only in subjects with thoracic malignancy. Third, the majority of subjects were male; olanzapine clearance is known to be higher in men than in women [16]. Therefore, a phase III study to verify the efficacy and safety of 5 mg oral

olanzapine with standard triplet antiemetic therapy is under contemplation (UMIN000024676).

In conclusion, the addition of 5 mg oral olanzapine to standard antiemetic therapy demonstrates promising efficacy for the prevention of CINV and provides an acceptable safety profile in patients with thoracic malignancy.

Conflict of interest

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

Haruyasu Murakami and Hirotsugu Kenmotsu received remuneration from Eli Lilly Japan. Toshiaki Takahashi received remuneration from Eli Lilly Japan and ONO PHARMACEUTICAL CO., LTD. Other authors declare no conflicts of interest.

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310 **Appendix**

311 **The other authors:** Satomi Koizumi[2], Keita Mori[3], Takeshi Isobe[4], Toshiaki

312 Takahashi[1]

313

314 [1]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan

315 [2]Nursing Department, Shizuoka Cancer Center, Shizuoka, Japan

316 [3]Clinical Research Center, Shizuoka Cancer Center, Shizuoka, Japan

317 [4]Division of Medical Oncology and Respiratory Medicine, Shimane University

318 Faculty of Medicine, Shimane, Japan

Table 1. Patient characteristics.

		n = 30
Median age (range)		64 years (36–75 years)
Sex	Male	23
	Female	7
ECOG Performance Status	0	22
	1	8
Thoracic malignancy	Non-small cell lung cancer	19
	Small cell lung cancer	8
	Malignant pleural mesothelioma	2
	Thymoma	1
Purpose of chemotherapy	Systemic chemotherapy	19
	Chemoradiation therapy	9
	Postoperative adjuvant therapy	2
Combination anticancer drug	Pemetrexed	14
	Etoposide	7

	Vinorelbine	4
	Irinotecan	2
	S-1	2
	Gemcitabine	1
	60 mg/m^2	4
Cisplatin dose	75 mg/m^2	14
	80 mg/m^2	12

ECOG, Eastern Cooperative Oncology Group.

Table 2. Antiemetic effects.

	Study phase	Rate (%)	90% CI (%)	95% CI (%)
Complete response	Acute	100	92–100	89–100
	Delayed	83	70–92	66–93
	Overall	83	70–92	66–93
Complete control	Acute	93	82–98	79–98
	Delayed	73	59–84	56–86
	Overall	70	55–82	52–83
Total control	Acute	77	62–87	59–88
	Delayed	70	55–82	52–83
	Overall	63	48–76	46–78

CI, confidence interval.