

Optimizing antiemetic support in anthracycline-based chemotherapy for early breast cancer: A protocol for a prospective observational study of four-drug antiemetic therapy including fosnetupitant and olanzapine

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Optimizing antiemetic support in anthracycline-based chemotherapy for early breast cancer: A protocol for a prospective observational study of four-drug antiemetic therapy including fosnetupitant and olanzapine

Ayako Higuchi¹ MSc; Yumiko Koi² MD, PhD; Tomoaki Eto^{3, 1} MSc; Yuka Maeda¹; Wakako Tajiri² MD; Junji Kawasaki² MD; Sayuri Akiyoshi² MD, PhD; Hideki Ijichi² MD, PhD; Yoshiaki Nakamura² MD, PhD; Chinami Koga² MD; Mototsugu Shimokawa⁴ PhD; Hiroaki Shimizu^{1, 5}; Toshihiro Matsumoto¹; Eriko Tokunaga² MD, PhD

¹Department of Pharmacy National Hospital Organization Kyushu Cancer Center Fukuoka JP

²Department of Breast Oncology National Hospital Organization Kyushu Cancer Center Fukuoka JP

³Department of Pharmacy National Hospital Organization Kokura Medical Center Kitakyushu JP

⁴Department of Biostatistics Yamaguchi University Yamaguchi JP

⁵Department of Pharmacy National Sanatorium Kikuchi Keifuen Koshi JP

Corresponding Author:

Eriko Tokunaga MD, PhD

Department of Breast Oncology

National Hospital Organization Kyushu Cancer Center

3-1-1 Notame Minami-ku

Fukuoka

JP

Abstract

Background: Prophylaxis for chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC) is essential. Four-drug antiemetic therapy, consisting of a neurokinin-1 receptor antagonist (NK1RA), a 5-hydroxytryptamine type 3 receptor antagonist (5-HT3RA), dexamethasone (DEX), and olanzapine (OLZ), is currently recommended for HEC. However, the efficacy, optimal dosing schedule, and appropriate dosage of OLZ remain unclear when combined with a highly selective NK1RA, fosnetupitant (FosNTP).

Objective: To evaluate the efficacy and safety of a four-drug antiemetic regimen including FosNTP and OLZ for prophylaxis of CINV in patients receiving anthracycline-based (neo)adjuvant chemotherapy for early breast cancer (EBC) and to explore outcomes with OLZ dose adjustments in the second course.

Methods: This single-institution, prospective observational study will receive 100 patients with EBC who undergoes HEC. All patients will receive a four-drug antiemetic regimen consisting of FosNTP, 5-HT3RA, DEX, and the guideline-recommended dose of OLZ administered orally from days -1 to 4. During the second course of treatment, OLZ dosing may be adjusted based on tolerability and patient preference. The primary endpoint is the proportion of patients who experienced no nausea during the overall phase (0–120 h) of the first course, as assessed using the daily visual analog scale. A sample size of 86 was calculated to assess the efficacy of the four-drug antiemetic regimen, including OLZ, assuming an expected no nausea rate of 42%, a threshold no nausea rate of 27% based on historical data, 90% power, and a 1-sided significance level of 5.0%. A single-sample z-test with a normal approximation will be used for the analyses.

Results: This study was approved by the Ethics Committee in March 2024, and participant recruitment and data collection commenced in May 2024. As of September 2025, approximately 70 participants have been recruited. Data collection is expected to continue until April 2026, and both data collection and analyses are anticipated to be completed in 2027.

Conclusions: This study will provide real-world evidence on the effectiveness and safety of a four-drug antiemetic regimen, including FosNTP and OLZ, in patients receiving anthracycline-based HEC and may inform optimal OLZ dosing strategies. Clinical Trial: UMIN-CTR UMIN000054250; <https://www.umin.ac.jp/ctr/>

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Original Manuscript

Research Protocol

Optimizing antiemetic support in anthracycline-based chemotherapy for early breast cancer: A protocol for a prospective observational study of four-drug antiemetic therapy including fosnetupitant and olanzapine

Ayako Higuchi¹, MSc; Yumiko Koi², MD, PhD; Tomoaki Eto^{1,3}, MSc; Yuka Maeda¹; Wakako Tajiri², MD; Junji Kawasaki², MD; Sayuri Akiyoshi², MD, PhD; Hideki Ijichi², MD, PhD; Yoshiaki Nakamura², MD, PhD; Chinami Koga², MD; Mototsugu Shimokawa⁴, PhD; Hiroaki Shimizu^{1,5}; Toshihiro Matsumoto¹; Eriko Tokunaga², MD, PhD

¹Department of Pharmacy, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

²Department of Breast Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

³Department of Pharmacy, National Hospital Organization Kokura Medical Center, Kitakyushu, Japan

⁴Department of Biostatistics, Graduate School of Medicine, Yamaguchi University, Yamaguchi, Japan

⁵Department of Pharmacy, National Sanatorium Kikuchi Keifuen, Koshi, Japan

Corresponding Author:
Eriko Tokunaga, MD, PhD.

Department of Breast Oncology, NHO Kyushu Cancer Center

Address: 3-1-1 Notame Minami-ku Fukuoka city Fukuoka, 811-1395, Japan

Tel: +810925413231

E-mail: erikotokunaga.nkcc@gmail.com

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Abstract

Background: Prophylaxis for chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC) is essential. Four-drug antiemetic therapy, consisting of a neurokinin-1 receptor antagonist (NK1RA), a 5-hydroxytryptamine type 3 receptor antagonist (5-HT3RA), dexamethasone (DEX), and olanzapine (OLZ), is currently recommended for HEC. However, the efficacy, optimal dosing schedule, and appropriate dosage of OLZ remain unclear when combined with a highly selective NK1RA, fosnetupitant (FosNTP).

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Conclusions: This study will provide real-world evidence on the effectiveness and safety of a four-drug antiemetic regimen, including FosNTP and OLZ, in patients receiving anthracycline-based HEC and may inform optimal OLZ dosing strategies.

Trial registration

UMIN-CTR UMIN000054250; <https://www.umin.ac.jp/ctr/>

Keywords: Antiemetics, Olanzapine, Neurokinin-1 Receptor Antagonists, Patient Reported Outcome Measures, Breast Neoplasms

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and distressing side effects of cancer treatment, significantly impairing patients' quality of life (QOL), especially due to nausea [1–3]. For highly emetogenic chemotherapy (HEC), international and Japanese guidelines currently recommend a four-drug antiemetic therapy consisting of a neurokinin-1 (NK1) receptor antagonist, 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist, dexamethasone (DEX), and olanzapine (OLZ) [4–7].

OLZ, a multi-receptor antipsychotic, exerts its antiemetic effects partly via 5-HT_{2B/2C} receptor antagonism and enhancement of ghrelin signaling [8]. However, owing to its broad receptor activity, OLZ frequently causes daily somnolence, particularly at the standard dose of 10 mg (73.0%). Based on previous studies demonstrating equivalent efficacy and favorable tolerability of 5 mg OLZ relative to the standard 10 mg dose [9–12], a daily dose of 5 mg has become the recommended initial dose in Japan [7]. Even at a dose of 5 mg, 20.3% of patients required dose reduction, and 6.2% discontinued OLZ [3,13]. A phase III randomized trial demonstrated that a 2.5 mg dose of OLZ was non-inferior to 10 mg for CINV prevention, with significantly less somnolence [14].

Fosnetupitant (FosNTP), a relatively new NK1 receptor antagonist, has been shown to be non-inferior to fosaprepitant in two domestic phase III trials (CONSOLE [15] and CONSOLE-BC [16]), but its combination with OLZ has not been evaluated.

This study will evaluate the real-world efficacy and safety of a four-drug regimen (FosNTP, palonosetron [PALO], DEX, and OLZ) for CINV prophylaxis in patients receiving (neo)adjuvant anthracycline-based chemotherapy (HEC) for early breast cancer. We also aim to explore the outcomes of patients requiring OLZ dose adjustments after the first course.

Methods

Study setting

This prospective, single-institution, observational cohort study will be conducted at the National Hospital Organization Kyushu Cancer Center, Japan. We aim to enroll 100 participants over a 2-year period from May 2024 to April 2026. The first participant was enrolled on May 7, 2024.

Study participants

- Inclusion criteria

Patients eligible for this study must meet all the following criteria:

1. Female patients 20–74 years old who were able to understand and provide their written informed consent.
2. A diagnosis of early-stage or locally advanced breast cancer (stages I–III) in a patient scheduled to receive (neo)adjuvant chemotherapy.
3. No prior chemotherapy.
4. A plan was made to receive either EC (epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks) or dose-dense EC (epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² every 2 weeks).
5. An Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
6. A preserved major organ function within 8 days prior to enrollment (defined as AST <100 IU/L, ALT <100 IU/L, and total bilirubin <2.0 mg/dL).
7. Able to understand and report patient-reported outcomes.
8. Clinical data available for analyses.

- Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. A history of allergy to any of the study drugs or related compounds.

2. Vomiting or nausea within one day prior to enrollment.
3. Use of antiemetic drugs within two days prior to enrollment.
4. A history of or patient who is scheduled to undergo surgery or radiation therapy within seven days prior to enrollment or during the observation period.
5. Regular use of medications that may affect antiemetic efficacy, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin-dopamine antagonists, multireceptor-targeted antipsychotics, corticosteroids, histamine H₁ receptor antagonists, phenothiazine antipsychotics, dopamine receptor antagonists, and benzodiazepines.
6. Initiation of opioid analgesics within 14 days prior to enrollment.
7. Seizure disorders requiring anticonvulsant treatment.
8. Gastrointestinal obstruction, including pyloric stenosis or intestinal obstruction.
9. Pregnant or lactating women or women of childbearing potential unwilling to use effective contraception.
10. A history of diabetes requiring treatment with insulin or oral hypoglycemic agents.
11. Concurrent participation in another interventional clinical trial.
12. Any condition that, in the opinion of the attending physician, would render the patient unsuitable for participation in the study.

Procedure and treatment

The study consisted of a screening period prior to the initiation of EC, followed by a treatment period of 7 days (168 h), beginning at the start of EC administration. Written informed consent will be obtained prior to enrollment after confirming that the patients meet all the inclusion criteria and do not meet any exclusion criteria.

All patient information will be handled in a re-identifiable anonymized format, with the linkage key strictly controlled and never shared externally. Data will be appropriately managed

within the institution and securely stored for at least five years after study completion or three years after publication, whichever is longer.

Treatment

All enrolled patients will receive PALO (day 1: 0.75 mg intravenously, 30 min before chemotherapy), FosNTP (day 1: 235 mg intravenously, 30 min before chemotherapy), DEX (day 1: 9.9 mg intravenously, 30 min before chemotherapy) and OLZ 5 mg. In this study, OLZ will be administered orally and post-prandially from day -1 to day 4, rather than initiating administration on the evening of day 1 as is conventional [9]. This earlier initiation was adopted based on the higher incidence of acute-phase CINV on days 1–2 reported for HEC [17].

For the second course, the OLZ dose may be adjusted based on patient preference and physician discretion. Patients may choose to continue with 5 mg/day, reduce the dose to 2.5 mg/day, increase it to 10 mg/day, or discontinue OLZ.

If nausea or vomiting occurs and the physician deems it necessary, or if the patient requests additional antiemetic therapy, rescue medications not included in the study protocol may be administered. These include metoclopramide, domperidone, alprazolam, and other drugs, as appropriate.

Follow-up

During the seven-day treatment period, all patients will record symptoms in a diary, including nausea, vomiting, use of rescue medications (additional antiemetics), daytime somnolence, and its impact on daily activities. Nausea, somnolence, and the impact of somnolence on daily activities will be assessed using a visual analog scale (VAS).

At the end of the observation period, patients will retrospectively assess the adverse events they experienced over a seven-day period using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [18]. They will also assess their

satisfaction with antiemetic therapy using a seven-point Likert scale: very satisfied, satisfied, somewhat satisfied, slightly satisfied, slightly dissatisfied, dissatisfied, or very dissatisfied. Figure 1 illustrates the timeline for participant enrolment, intervention, and assessment.

Endpoints

- Primary endpoint

The primary endpoint is no nausea during the overall phase (0–120 h after the start of epirubicin administration) in the first course.

- Secondary endpoints

The secondary endpoints include no nausea during phases other than the overall phase of the first course, complete response (CR) rate, complete control (CC) rate, total control (TC) rate, time to treatment failure, degree of daytime somnolence, impact of somnolence on daily activities, no nausea during the second course, rate of OLZ dose modification, incidence of adverse events, and patient satisfaction with antiemetic therapy.

Observation periods

The observation periods will be classified into five phases: acute (0–24 h after the start of epirubicin administration), delayed (24–120 h), overall (0–120 h), extended delayed (24–168 h), and extended overall (0–168 h).

Definitions of key endpoints

No nausea is defined as a VAS score of <5 mm [19]. The CR rate is defined as not an emetic event and no rescue medication will be administered. The CC rate showed no emetic event, no rescue medication, and no significant nausea (VAS score <25 mm). The TC rate is defined as no emetic events, rescue medication, or nausea. Time to treatment failure was defined as the time from the start

of epirubicin administration to the earliest occurrence of either the first episode of vomiting or first use of rescue medication.

Patient and public involvement

The patients and public were not involved in the development of the research question, study design, outcome measures, or recruitment plans.

Sample size

Previous studies have reported varying rates of no nausea during the overall phase depending on the antiemetic therapy used. A 3-drug combination of FosNTP, PALO, and DEX reportedly achieved no nausea rate of 27.5% in patients receiving HEC [20], and this value was used as the historical control threshold in the current study. In addition, a phase 3 randomized control trial by Navari et al. showed that adding 10 mg of OLZ to a 3-drug combination of aprepitant, PALO (5-HT₃RA), and DEX improved the rate of nausea by 15.4% compared to the antiemetic regimen without OLZ [21]. Based on this evidence, a threshold no-nausea rate of 27% was defined for this study, especially in the context of using a lower and potentially more tolerable dose of OLZ (5 mg). The required sample size was calculated using an expected no-nausea rate of 42%, minimum acceptance rate of 27%, one-sided significance level of 5.0%, and power of 90%. Based on these assumptions, the required number of participants was 86. The target sample size was set at 100 patients considering the anticipated consent and valid response rates.

Statistical analyses

The primary analysis will be conducted on the full analysis set, defined as patients who have undergone at least one efficacy assessment. Patients who were retrospectively deemed ineligible or registered in violation of the protocol will be excluded from this set in accordance with the predefined criteria. The analysis will be based on point estimates with corresponding 95%

confidence intervals and will be conducted using a normal approximation z-test. All statistical analyses will be performed using R version 4.4.2.

Ethical considerations

This study was approved by the Ethics Committee of the National Hospital Organization Kyushu Cancer Center (approval number: [2023-41]). Written informed consent will be obtained from all the participants prior to enrollment. The study will be conducted in accordance with the Declaration of Helsinki and applicable national regulations. The results will be disseminated through presentations at academic conferences and publications in peer-reviewed journals. No personally identifiable information is disclosed.

This study has been registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) under the identifier UMIN000054250.

No ancillary or post-trial care is required, as the study involves routine chemotherapy and antiemetic treatment without additional risks beyond usual care.

Results

This study was approved by the Ethics Committee in March 2024, and participant recruitment and data collection commenced in May 2024. As of September 2025, approximately 70 participants had been recruited. Data collection is expected to continue until April 2026, and both data collection and analyses are anticipated to be completed in 2027.



Discussion

This prospective study was designed to comprehensively evaluate the primary preventive efficacy and tolerability of antiemetic therapy for CINV, incorporating patient-reported outcomes as a direct measure of symptom burden. Despite adherence to current guideline-recommended regimens, approximately 70% of patients with breast cancer continue to experience insufficient control of nausea [5, 22], underscoring a substantial unmet need in supportive care. Effective CINV prevention is essential for maintaining treatment adherence and enabling successful completion of (neo)adjuvant chemotherapy. Among patients receiving HEC, anthracycline-based chemotherapy is associated with an increased incidence of acute-phase CINV on days 1 and 2 when OLZ is not included in antiemetic therapy, highlighting the importance of earlier intervention [17]. In the present study, OLZ was administered from day -1 to day 4, a novel schedule that differs from the conventional initiation on the evening of day 1 and, to our knowledge, has not been previously evaluated in this population.

By assessing the real-world effectiveness of a four-drug antiemetic therapy incorporating FosNTP and OLZ, this study will generate clinically relevant data beyond those available from conventional approaches. Furthermore, evaluating the tolerability of guideline-recommended OLZ dosing and exploring dose adjustments in subsequent cycles may inform individualized antiemetic strategies that balance efficacy and safety.

These findings are expected to refine antiemetic practice by providing real-world evidence on optimized four-drug therapy, improving supportive care standards, and enhancing the quality of life and treatment adherence for patients with early breast cancer receiving anthracycline-based chemotherapy.

Funding

This study received no specific grants from any funding agency in the public, commercial, or not-for-profit sector.

Conflicts of Interests

None declared.

Data Availability

No datasets were generated or analyzed for this protocol. Deidentified data arising from the completed study will be made available upon reasonable request after publication of the main results in accordance with institutional policies.

Authors' Contributions

All the authors contributed to the conception and design of the study protocol. The protocol was initially drafted by AH, YK, TE and ET. MS provided statistical expertise. AH and YK wrote the manuscript. YM, WT, JK, SA, HI, YN, CK, MS, HS and ET critically reviewed the manuscript. All authors have read and approved the final version of the manuscript.

Abbreviations

5-HT3: 5-hydroxytryptamine type 3

CC: complete control

CINV: chemotherapy-induced nausea and vomiting

CR: complete response

DEX: dexamethasone

EBC: early breast cancer

EC: epirubicin and cyclophosphamide

ECOG PS: Eastern Cooperative Oncology Group performance status

HEC: highly emetogenic chemotherapy

NK1: neurokinin-1

OLZ: olanzapine

PALO: palonosetron

PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

QOL: quality of life

TC: total control

VAS: visual analog scale

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Figure legend

Figure 1. The schedule of enrolment, intervention, and assessments.



Supplementary Files

Figures

The schedule of enrolment, intervention, and assessments.

	Trial period																
	Enrollment		Post-enrollment														Close-out
			Course 1							Course 2							
Timepoint	day -30 to -1	day -1	day 1	day 2	day 3	day 4	day 5	day 6	day 7	day -1	day 1	day 2	day 3	day 4	day 5	day 6	day 7
EC treatment			X								X						
Enrollment																	
Eligibility screen	X																
History and Physical	X																
ECOG PS	X																
Laboratory studies	X									X							
Informed consent	X																
Enrollment		X															
Intervention																	
Palonosetron			X								X						
Dexamethasone			X								X						
Fosnetupitant			X								X						
Olanzapine		X	→							X	→						
Assessments																	
Patient diaries		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Patient-selected OLZ dose										X							
PRO-CTCAE									X								X
Patient satisfaction									X								X

CONSORT (or other) checklists

SPIRIT 2025 checklist.

URL: <http://asset.jmir.pub/assets/7b9c28d0d638512b8887cda13a2edc0f.pdf>

