



BMJ Open Study protocol for a double-blind, comparative, randomised Japanese trial of triplet standard antiemetic therapies with or without 5 mg olanzapine to prevent chemotherapy-induced nausea and vomiting for patients with breast cancer treated with an anthracycline/cyclophosphamide regimen (JTOP-B)

Rie Ozeki ¹, Hirotohi Iihara ², Mototsugu Shimokawa,³ Hironobu Hashimoto,⁴ Masakazu Abe,⁵ Toru Mukohara,⁶ Hiroko Bando,⁷ Toshinobu Hayashi,⁸ Hitoshi Kawazoe,⁹ Masayo Komoda,¹⁰ Takako Yanai Takahashi,⁴ Mitsue Saito¹

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For numbered affiliations see end of article.

Correspondence to

Professor Mitsue Saito; mitsue@juntendo.ac.jp and Dr Hirotohi Iihara; dai0920@gifu-u.ac.jp

ABSTRACT

Introduction Triple antiemetic therapy with neurokinin-1 receptor antagonist, 5-hydroxytryptamine type 3 receptor antagonist, and dexamethasone has been widely recommended for high emetogenic chemotherapeutic (HEC) agents and regimens, including anthracycline combined with cyclophosphamide (AC). The addition of olanzapine (OLZ) 5 mg or 10 mg to the recommended triple antiemetic therapy has demonstrated superiority in antiemetic efficacy compared with the standard triplet therapy for a cisplatin-based HEC regimen. Although OLZ plus the triple antiemetic treatment may also be effective for patients on an AC-based HEC regimen, no study has investigated its efficacy at a lower dose of 5 mg.

Methods and analysis To assess whether 5 mg OLZ, as compared with placebo, in combination with triple combination therapy, significantly improves nausea and vomiting, we are conducting a randomised, parallel-group controlled clinical trial with a total of 500 patients at 15 study centres in Japan. The primary outcome is the complete response rate, defined as no emetic episodes and no use of rescue medication during 120 hours after the initiation of chemotherapy. Treatment group comparison for the primary endpoint will be done by using the Cochran-Mantel-Haenszel test.

Ethics and dissemination The study was approved by the institutional review board of Juntendo University Hospital and relevant approval was obtained from all participating centres. All participants will be required to provide written informed consent. The trial results will be reported at conferences and in peer-reviewed journals.

Trial registration number Japan Registry of Clinical Trials (jRCT) jRCT1031200134; protocol date: 30 July 2020, version: 1.3, approval: 25 August 2020.

Strengths and limitations of this study

- The randomised controlled trial design adopted in this study is widely accepted as the best design for evaluating the efficacy and safety of a new treatment and can be used to achieve similarity of groups in terms of all the factors, whether known or unknown, that may affect the outcome.
- Investigators, patients and study-related staff including clinical research coordinators are kept blinded until the study completion to prevent performance bias and detection bias.
- The study design includes a placebo arm, which facilitates the evaluation of the actual additional effect of the olanzapine (OLZ) to the standard antiemetic therapy.
- The study evaluates the efficacy of OLZ for both acute and delayed phases, from 0 to 24 hours and 25 to 120 hours, respectively, after the start of chemotherapy.
- Limitations include difficulty in objectively assessing compliance due to the use of oral medications and selective inclusion of patients from women in Asia, which may reduce the external validity of the study.

INTRODUCTION

Most anticancer therapies, especially chemotherapeutic agents, have the side-effects which have an impact on the overall outcome of the therapy. Chemotherapy-induced nausea and vomiting (CINV) is one such side effect noted predominantly in the highly emetogenic chemotherapeutic (HEC) agents.

Anthracycline combined with cyclophosphamide (AC), a standard treatment regimen for patients with breast cancer, is categorised as an HEC agent and more than 90% of patients experience acute emesis. CINV can affect the quality of life of the patient and might lead to poor compliance with, or withdrawal from, potentially curative anticancer therapy.¹ In general, significant patient-related risk factors for CINV include younger age and sex (female).²

By 2017, the clinical practice guidelines for antiemetics in oncology, including those from the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the Multinational Association of Supportive Care in Cancer, the European Society for Medical Oncology and the Japanese Society of Clinical Oncology, have recommended triple combination treatment comprising 5-hydroxytryptamine 3 receptor antagonist (5-HT₃RA), neurokinin 1 receptor antagonist (NK₁RA), and dexamethasone (DEX) as a standard antiemetic therapy for HEC.²⁻⁵

However, clinical studies that investigated the efficacy of the aforementioned triple combination therapy found a complete response (CR) rate, defined as no emetic episodes and no use of rescue medication for 120 hours following the initiation of chemotherapy (overall period), of less than 50%, indicating that one in every two patients receiving HEC experience significant CINV.^{6,7}

Hence, there is a need for the inclusion of additional antiemetic agents to the regimen to manage CINV effectively. The utility of olanzapine (OLZ) is being investigated in this regard. OLZ is an atypical antipsychotic agent that is an antagonist of multiple receptors involved in CINV, including dopamine, serotonin, histamine and acetylcholine-muscarine receptors. A phase III randomised trial that assessed adding OLZ or placebo to the aforementioned triple-combination therapy showed the quadruple regimen with 10mg OLZ significantly increased the CR rate compared with placebo over the 120 hours after chemotherapy (64% vs 41%; $p < 0.001$).⁸ Based on this trial, the latest version of NCCN and ASCO guidelines recommend the quadruple antiemetic regimen for patients receiving HEC regimens.^{9,10}

In Japan, studies investigating the efficacy and safety of the quadruple combination therapy including OLZ demonstrated a promising antiemetic effect against CINV caused by cisplatin-based HEC regimens also.¹¹⁻¹³ A dose-finding study evaluating the efficacy and safety of two doses (10 mg and 5 mg) of OLZ against HEC with cisplatin reported that 5 mg OLZ demonstrated equivalent efficacy and a lower incidence of sedation-related adverse events, including somnolence, compared with 10 mg OLZ.^{14,15} The subsequent phase III randomised trial (J-FORCE) reported the superiority of 5 mg OLZ compared with placebo plus triplet-combination therapy for the prevention of CINV (CR rate 79% vs 66%; $p < 0.0001$).¹⁶

Most of these trials, however, have included patients with cancer who received cisplatin-based chemotherapies. Whether a quadruple combination therapy

including 5 mg OLZ is effective for AC-based regimens remained unclear. Breast cancer is the most common cancer in Japan and both age-adjusted mortality and mobility rates of breast cancer have been increasing over the past 40 years.¹⁷ The future trend is expected to be the same as before, indicating more patients receiving AC therapy who are at risk of high occurrence of nausea and vomiting will also be increasing in the future. The objective of this phase III trial is to test the superiority of 5 mg OLZ, as compared with placebo, plus triple combination therapy for the prevention of CINV caused by AC-based regimens in the overall period after treatment in patients with breast cancer.

METHODS AND ANALYSIS

Study setting

This study is a multicentre (15 centres), randomised, double-blind, placebo-controlled, phase III trial conducted in university hospitals (11), cancer centres (3) and a general hospital in Japan with a planned enrolment of 500 study participants over roughly 2 years. The first patient was enrolled and randomised in October 2020, and the study is scheduled to be continued until March 2025 (allowing for possible delays due to the COVID-19 pandemic, and including time for completion of data analysis).

Study participants

Inclusion criteria

Patients included in the clinical trial must meet all the following criteria:

1. Primary breast cancer stage I to III.
2. Receiving first-line AC therapy.
3. Female.
4. Age at registration is 20 years or older.
5. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
6. No history of the administration of moderately or highly emetogenic chemotherapy.
7. Patient is not currently on any of the drugs with antiemetic activity or inducing somnolence, such as 5-HT₃RA, NK₁RA, selective serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, serotonin-dopamine antagonist, multiacting receptor-targeted antipsychotic, corticosteroids, antihistamine drugs, phenothiazine tranquilisers, dopamine receptor antagonists, barbiturate drugs and benzodiazepine agents.
8. The latest test values within 1 month before registration satisfies all of the following: (a) total bilirubin ≤ 2.0 mg/dL, (b) aspartate aminotransferase ≤ 100 U/L, (c) alanine aminotransferase ≤ 100 U/L.
9. Provided written informed consent.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the trial:

1. History of allergy to the drugs or similar compounds used in this study.
2. Patient needs antiemetics at the time of enrollment.
3. Started taking strong opioids within 48 hours before enrollment.
4. History of one or more: unstable angina, cerebral haemorrhage, myocardial infarction, cerebral infarction and active gastric ulcer or duodenal ulcer in the past 6 months before enrolment.
5. Convulsive disorders requiring treatment with anticonvulsants.
6. Gastrointestinal obstruction, such as gastric pyloric stenosis or intestinal obstruction.
7. Pregnant or breastfeeding women, or women who may be pregnant or are not willing to contracept.
8. Mental illness or psychiatric symptoms interfering with the daily routine of the patient and might lead to difficulty in participating in the study.
9. Patients with diabetes who have been treated with at least one of insulin and oral hypoglycemic agents, and patients with HbA1c (NGSP) of 6.5% or more and HbA1c (JDS) of 6.1% or more at the time of registration. In addition to the prescribed tests, patients who may measure blood glucose and thereby reduce or discontinue DEX will also be excluded.
10. Patient is a habitual smoker at the time of enrolment.
11. Patients who are deemed inappropriate for the study by the investigator.

Procedure and treatment

The study includes two periods: a screening period of less than 1 month before the initiation of the AC regimen (day 1) followed by a 7-day treatment period, from time 0 to 168 hours after the start of the AC treatment. After signing the informed consent form, patients complete baseline assessments including physical examinations, blood tests, demographic data and ECOG PS. Patients' background factors related to nausea and vomiting are also recorded.

Treatment

The study consists of two arms including the study treatment group and the placebo group. The details of both arms are shown in [table 1](#). All eligible patients are randomised into one of the two arms.

Table 1 Antiemetic administration					
Antiemetics		Day 1	Day 2	Day 3	Day 4
Palonosetron	IV	0.75 mg			
Aprepitant or Fosaprepitant	PO	125 mg	80 mg	80 mg	
Dexamethasone	IV	9.9 mg			
Olanzapine or Placebo	PO	5 mg	5 mg	5 mg	5 mg

IV, intravenous injection; PO, per os.

All patients receive palonosetron (on day 1: 30 min prior to chemotherapy, 0.75 mg intravenous infusion), aprepitant (APR) (on day 1: 1 hour prior to chemotherapy, 125 mg oral administration, and on days 2 and 3: 80 mg in the morning), DEX (on day 1: 30 min prior to chemotherapy, 9.9 mg intravenous infusion) and 5 mg OLZ or placebo (on day 1: within 5 hours after chemotherapy, oral administration and on days 2 to 4: after supper, oral administration). If the patient has received fosaprepitant (1 hour prior to chemotherapy, 150 mg intravenous infusion) instead of APR, additional dose of APR is not administered on days 2 and 3. Rescue medications can be used when CINV is not controlled with the study treatment or the standard antiemetics. All patients are allowed to receive rescue medications according to the predefined administration guidance (either metoclopramide, domperidone, or prochlorperazine maleate is defined as the first choice).

Follow-up

During the 7-day treatment period, all participants will be asked to complete the following: standardised patient diary on nausea, vomiting and need for rescue medication; severity of nausea, appetite loss, sleepiness in the daytime and the incidence of concentration impairment due to sleepiness graded as none, mild, moderate or severe; and patient satisfaction with antiemetic therapy using a seven-grade categorical scale (very satisfied, satisfied, somewhat satisfied, rather satisfied, rather dissatisfied, dissatisfied, or very dissatisfied). PRO-CTCAE V.1.0 and CTCAE V.5.0, MedDRA/J V.21.1 are used to grade adverse events.

Between 7 days after the initiation of the AC regimen and before the second cycle, blood tests are performed once. The study is independently monitored by the alliance data centre and safety monitoring board. [Figure 1](#) illustrates the schedule of enrolment, interventions and assessments.

Endpoints

We chose the CR rate as the primary endpoint, defined as the proportion of patients without emetic episodes or the use of rescue medication during the overall assessment period (0–120 hours) after the initiation of AC-based regimens.

The secondary endpoints are CR rate for the assessment periods other than 0–120 hour, complete control rate, total control rate and time to treatment failure. CR rate is evaluated immediately (acute assessment period, 0–24 hours), twice during the delayed assessment periods (25–120 hours and 25–168 hours) and overall (0–168 hours). Absence of emesis, or significant nausea, and did not use rescue medication in acute, delayed and overall assessment periods is defined as complete control. Nausea equal to or greater than 'moderate' in severity is considered as significant nausea. The total control is defined as no emetic episodes, no rescue medication use and no nausea in the acute, delayed and overall assessment

	Screening	Enrolment	Treatment							Close-out	
TIMEPOINT	-1 month	0	0–24h	25–48h	49–72h	73–96h	97–120h	121–144h	145–168h	Before second cycle	
ENROLMENT:											
Eligibility screen	x										
History and Physical	x										
ECOG PS	x										
Laboratory studies	x									x	
Informed consent	x										
Enrolment		x									
INTERVENTIONS:											
AC regimen			x								
Antiemetic administrations			←—————→								
Study drug			x	x	x	x					
ASSESSMENTS:											
Patient diaries		x	x	x	x	x	x	x	x		
PRO-CTCAE		x								x	
Adverse events		x								x	
Patient satisfaction										x	

Figure 1 Schedule for enrolment, interventions and assessments.

periods. From the time of initiation of AC-based regimens to the first emetic episode or the use of rescue medication, whichever comes first, is considered as time to treatment failure.

Blinding and randomisation

Patients are enrolled by physicians and automatically randomised 1:1 to either the 5 mg OLZ group or placebo group via the central registration system. The blocked stratification method will be used with investigational site and age (≥ 55 years or < 55 years) as factors.

Patients in both groups, investigators and study-related staff including clinical research coordinators are kept blinded to treatment allocation until the study completion. Designated unblinded staff include those who receive a randomisation list from the person in charge of creating the list and those who are responsible for preparing the study treatment according to the randomisation schedule.

Patient and public involvement

Patient and public representatives were not involved in the design of the study protocol.

Sample size and statistical analysis

Sample size

The study was designed to detect a clinically relevant efficacy of 13% increase in the CR rate (within 120 hours after starting AC treatment) with a statistical power of 80% at the 5% (two-sided) level of significance,¹³ assuming a CR rate of 45% in the control arm. With the assumption of an approximately 10% of a drop-out rate, a total of 500 patients are required to be enrolled.

Statistical analysis

The primary analysis will be performed for the full analysis set, defined as patients exposed to at least one dose and having at least one efficacy evaluation. Point estimates and CIs for the CR rate will be calculated, and a treatment difference in CR rate (all treatment periods) will be compared between groups by using the

Cochran-Mantel-Haenszel test with randomisation stratification factors excluding site as strata, with associated 95% CI.

ETHICS AND DISSEMINATION

The study was approved by the institutional review board of Juntendo University Hospital and relevant approval was obtained from all participating centres: Juntendo University Hospital (reference no: J20-007), Sapporo Medical University School of Medicine (reference no: Toku2-11), Iwate Medical University Hospital (reference no: SCR2020-005), Juntendo University Urayasu Hospital (reference no: 2-3), Juntendo University Shizuoka Hospital (reference no: J20-007 rin-757 20.418), Juntendo University Nerima Hospital (reference no: J20-007 (tokutei20-02)), Shizuoka General Hospital (reference no: houkenkyu2020041), Gifu University Hospital (reference no: N.A.), Tottori University Hospital (reference no: J-20-007), University of Tsukuba Hospital (reference no: TCRB20-008), Toho University Omori Medical Center (reference no: C_M20005), National Hospital Organization Shikoku Cancer Center (reference no: J20-007), National Cancer Center Hospital East (reference no: CTA-E20005), National Cancer Center Hospital (reference no: CTA-C20011), and Tokyo Medical University Hospital (reference no: N.A.). All participants will be required to provide written informed consent (online supplemental file). This study protocol was registered at the Japan Registry of Clinical Trials (jRCT) on 30 September 2020, as jRCT1031200134 (<https://jrct.niph.go.jp/>). Auditing of the trial conduct will be done independent from investigators.

Access to the final dataset generated from this trial will be accorded to the principal investigators and statistician who are bound by the data sharing agreement as per the institutional practices. The study results will be presented at conferences and published in a peer-reviewed journal.

PARTICIPATING INSTITUTIONS

Juntendo University Hospital, Sapporo Medical University School of Medicine, Iwate Medical University Hospital, Juntendo University Urayasu Hospital, Juntendo University Shizuoka Hospital, Juntendo University Nerima Hospital, Shizuoka General Hospital, Gifu University Hospital, Tottori University Hospital, University of Tsukuba Hospital, Toho University Omori Medical Center, National Hospital Organization Shikoku Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital and Tokyo Medical University Hospital.

Author affiliations

¹Department of Breast Oncology, Juntendo University School of Medicine, Tokyo, Japan

²Department of Pharmacy, Gifu University Hospital, Gifu, Japan

³Department of Biostatistics, Yamaguchi University Graduate School of Medicine, Ube, Japan

⁴Department of Pharmacy, National Cancer Center Hospital, Tokyo, Japan

⁵Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, Shizuoka, Japan

⁶Department of Medical Oncology, National Cancer Center-Hospital East, Kashiwa, Japan

⁷Department of Breast and Endocrine Surgery, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

⁸Department of Comprehensive Pharmaceutical Care, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka, Japan

⁹Division of Pharmaceutical Care Sciences, Center for Social Pharmacy and Pharmaceutical Care Sciences, Keio University Faculty of Pharmacy, Tokyo, Japan

¹⁰Faculty of Pharmaceutical Sciences, Tokyo University of Science, Chiba, Japan

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ORCID iDs

Rie Ozeki <http://orcid.org/0000-0002-2431-7403>

Hirotohi Iihara <http://orcid.org/0000-0002-4171-454X>

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