

BMJ Open Study protocol for an open-label, single-arm, multicentre phase II trial to evaluate the efficacy and safety of combined triplet therapy and olanzapine for prevention of carboplatin-induced nausea and vomiting in gynaecological cancer patients

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ABSTRACT

Introduction Carboplatin (CBDCA) administered at a dosage of 4 mg/mL/min or more area under the blood concentration-time curve (AUC) is considered to be ranked as the highest chemotherapy-induced nausea and vomiting (CINV) risk of the moderately emetogenic chemotherapy agents. The complete response (CR) rate for preventing overall CINV, defined as no emetic episodes and no use of rescue medication, for standard triplet antiemetic therapy (5-HT₃RA, 5-hydroxytryptamine-3 receptor antagonist; NK₁RA, neurokinin-1 receptor antagonist; DEX, dexamethasone) was approximately 60% in gynaecological cancer patients receiving CBDCA-based therapy. Further improvement in antiemetic treatment is needed to optimise care. This trial is to evaluate the efficacy and safety of using 5 mg olanzapine (OLZ) plus standard triplet antiemetic therapy for CINV after AUC ≥4 mg/mL/min CBDCA combination therapy in gynaecological cancer patients.

Methods and analysis This trial is an open-label, single-arm, multicentre phase II trial. Patients who receive CBDCA (AUC ≥4)-based therapy and have never been administered moderate to high emetogenic chemotherapy will be enrolled. All patients will receive OLZ (5 mg oral administration on days 1–4, after supper) in combination with 5-HT₃RA, NK₁RA and DEX. The primary endpoint is the CR rate during the overall period (0–120 hours). Testing the hypothesis that this regimen can improve CR rate from 60% (null hypothesis) to 75% (alternative hypothesis) with a one-sided type I error of 0.1 and power of 0.8 will require 53 patients. Considering the dropout rate, the target sample size is set at 60.

Ethics and dissemination The study protocol was approved by the institutional review board at each of the participating centres. Data will be presented at international conferences and published in peer-reviewed journals.

Trial registration number UMIN000031646.

Strengths and limitations of this study

- This is a first trial to evaluate efficacy and safety of combination of using 5 mg olanzapine (OLZ) plus standard triplet antiemetic therapy for chemotherapy-induced nausea and vomiting after area under the blood concentration-time curve ≥4 mg/mL/min carboplatin combination therapy in gynaecological cancer patients.
- The data will be used to inform a future large multicentre double-blind randomised phase III trial comparing 5 mg of OLZ combination therapy to conventional triplet antiemetic therapy.
- Limitations are open-label and single-arm design.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) lowers patients' quality of life and reduces adherence to treatment; in the worst case, it can affect the treatment effect and curability. CINV frequently occurs after treatment with anticancer agents and patients report it to be the most distressing adverse event during treatment.¹ In the American Society of Clinical Oncology² and International Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO),³ carboplatin (CBDCA) administered at a dosage of a 4 mg/mL/min or more area under the blood concentration-time curve (AUC) is reclassified to be ranked as highest CINV risk of the moderately emetogenic chemotherapy. Furthermore, National Comprehensive Cancer Network,⁴ CBDCA at an AUC of 4 mg/mL/min or more was escalated to the highly emetogenic chemotherapy (HEC)

classification. And all guidelines recommend a three-drug combination therapy of 5-hydroxytryptamine-3 receptor antagonist (5-HT₃RA), dexamethasone (DEX) and neurokinin-1 receptor antagonist (NK₁RA) as antiemetic prophylaxis. However, in a randomised phase III trials of female patients or patients with gynaecological cancer receiving CBDCA, the complete response (CR) rates for this standard antiemetic triplet therapy (5-HT₃RA, NK₁RA and DEX) were 62%⁵ and 61.6%,⁶ respectively. It is quite different from the CR rates reported in lung cancer patients (Ito *et al* 80.3%,⁷ Kusagawa *et al* 80.5%⁸). This difference is due to the background of cancer types. Female sex and younger age are well-known risk factors.^{9–12} Given the insufficiency of these control rates, further improvement in antiemetic treatment is urgently needed, particularly for these sub-groups.

Olanzapine (OLZ) is classified as a multi-acting receptor-targeted antipsychotic that blocks dopaminergic D₁, D₂, D₃ and D₄ receptors, serotonergic 5-HT_{2A}, 5-HT_{2B}, 5-HT₃ and 5-HT₆ receptors, histamine H₁ receptors and muscarinic acetylcholine receptors M₁, M₂, M₃ and M₄.¹³ Based on these known effects, OLZ is expected to improve CINV.

A study by Navari *et al* revealed the efficacy and safety of the combination of 10 mg OLZ and standard antiemetic triplet therapy in HEC, which included anthracycline/cyclophosphamide and cisplatin in a randomised, double-blind phase III trial.¹⁴ The CR rates in the overall phase were reported as 40.6% (three-drugs) versus 63.6% (four-drugs), however, the patient sedation due to the OLZ has been concerned. It is reported that females are prone to increased blood concentrations of OLZ than male.¹⁵ Because of this reason, there is concern about the enhancement of effect and side effect of OLZ in females.

Three phase II studies have revealed the efficacy and safety of the combination of 5 mg OLZ and standard antiemetic triplet therapy for CINV induced by HEC in Japan.^{16–18} Furthermore, a study by Yanai *et al* reported that 5 mg OLZ and 10 mg OLZ have a comparable effect, with 5 mg OLZ also having a lower sedative effect.¹⁸

Based on these preliminary studies, we planned an open-label, single-arm, multicentre phase II trial to evaluate the efficacy and safety of using 5 mg OLZ plus granisetron (GRA), NK₁RA and DEX for the prevention of nausea and vomiting after AUC ≥4 mg/mL/min CBDCA combination therapy in gynaecological cancer patients.

STUDY PROTOCOL

Objective

The objective of this study is to investigate the efficacy and safety of using 5 mg OLZ plus GRA, NK₁RA (aprepitant (APR) or fosaprepitant) and DEX to prevent nausea and vomiting after AUC ≥4 mg/mL/min CBDCA combination therapy in gynaecological cancer patients. The study protocol was approved by the institutional review

board at each of the participating centres and was independently monitored by the alliance data centre and safety monitoring board.

Study setting

This study is an open-label, single-arm, multicentre phase II trial performed at three centres in Japan.

End-points

The primary end-point is the CR rate, defined as no emetic episodes and no use of rescue medication during the overall assessment period (0–120 hours post-CBDCA). The secondary end-points are: CR rate during the acute assessment period (0–24 hour); CR rate during two delayed assessment periods (24–120 hours and 24–168 hours); CR rate during the overall assessment period (0–168 hours) and the complete control rate, defined as no emetic episodes, no rescue medication use, and no significant nausea in the acute, delayed, and overall assessment periods. Significant nausea is defined as equal to or greater than ‘moderate’ on a four-grade categorical scale (none, mild, moderate, or severe). The total control rate is defined as no emetic episodes, no rescue medication use, and no nausea in the acute, delayed, and overall assessment periods. The levels of nausea, anorexia, sleepiness, impact on life severity and patient satisfaction with antiemetic therapy are also classified using a four-grade categorical scale. Adverse events are graded according to PRO-CTCAE V.1.0 and CTCAE V.4.0.

0–24h after carboplatin administration

from ____ : ____ / ____ . ____ (dd/mm/yyyy)
 to ____ : ____ / ____ . ____ (dd/mm/yyyy)

- 1) How severe was the nausea you had in the past 24 hours?
 none mild moderate severe
- 2) How many times did you vomit and/or retch in the past 24 hours?
 none 1–2 times 3–5 times
 6 times or more almost always
- 3) How many times did you take the rescue medication to stop the symptoms of nausea or emesis in the past 24 hours?
 none 1 time 2 times 3 times or more
- 4) Did you feel you lost your appetite in the past 24 hours?
 none slightly severely very severely
- 5) Did you feel sleepy during the daytime in the past 24 hours?
 none slightly severely very severely
- 6) Did you have difficulty concentrating on daily activities such as reading papers or watching TV due to sleepiness in the past 24 hours?
 none slightly severely very severely

Figure 1 Patient-reported study diaries.

Date collection

The data are collected from patient diaries (figure 1). Patients are required to fill the diary for every 24 hours from the start of chemotherapy to 168 hours periods. PRO-CTCAE is assessed before initiation of the treatment and 168 hours after the start of chemotherapy.

Eligibility criteria

Inclusion criteria

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

- i. Diagnosis of gynaecological cancer and scheduled to receive CBDCA-based chemotherapy (AUC ≥4).
- ii. Aged 20–79 years at time of enrolment.
- iii. Eastern Cooperative Oncology Group performance status of 0, 1, or 2.
- iv. Absence of symptomatic brain metastasis and carcinomatosis.
- v. No history of administration of moderate-to-high emetogenic chemotherapy drugs.
- vi. No current use of any drug with antiemetic or somnolent activity, including 5-HT₃RA, NK₁RA, corticosteroids, dopamine receptor antagonists, phenothiazine tranquilisers, antihistamine drugs (paclitaxel administration allowed during premedication) and benzodiazepine agents.
- vii. Within the following standard ranges for general clinical tests:
 - a. Aspartate aminotransferase ≤100 U/L.
 - b. Alanine aminotransferase ≤100 U/L.
 - c. Total bilirubin ≤2.0 mg/dL.
- viii. Provided written informed consent.

Exclusion criteria

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

- i. History of hypersensitivity or allergy to study drugs or similar compounds.
- ii. Need for antiemetics at the time of enrolment.
- iii. Started opioid intake within 48 hours prior to enrolment.
- iv. Presence of unstable angina, ischaemic heart disease, cerebral haemorrhage or apoplexy, or active gastric or duodenal ulcer within 6 months prior to enrolment.
- v. Presence of convulsive disorders requiring anticonvulsant therapy.
- vi. Presence of ascites effusion requiring paracentesis.
- vii. Presence of gastrointestinal obstruction.
- viii. Breastfeeding or pregnant women or those not willing to use contraception.
- ix. Presence of psychosis or psychiatric symptoms that interfere with daily life.
- x. Abdominal or pelvic irradiation within 6 days prior to enrolment.
- xi. Presence of diabetes mellitus.
- xii. Being a habitual smoker at the time of enrolment.
- xiii. Patients deemed inappropriate for the study by the investigator.

Table 1 Antiemetic administrations

Antiemetics		Day 1	Day 2	Day 3	Day 4
Granisetron	IV	1 mg			
Aprepitant or fosaprepitant	PO	125 mg	80 mg	80 mg	
	IV	150 mg			
Dexamethasone	PO or	12 mg*			
	IV	9.9 mg*			
Olanzapine	PO	5 mg	5 mg	5 mg	5 mg

IV, intravenous infusion; PO, per os.

*When more than 135 mg/m² of paclitaxel is used, on day 1 DEX is administered 19.8 mg intravenously or 20 mg orally.

Registration

Patient registration started in April 2018.

Treatment methods

The study antiemetics administrations are shown in table 1. All patients receive GRA (1 mg intravenous infusion on day 1, 30 min before chemotherapy), APR (125 mg oral administration on day 1, 1 hour before chemotherapy and 80 mg in the morning on days 2 and 3), DEX (9.9 mg intravenous infusion or 12 mg oral administration on day 1, 30 min before chemotherapy) and OLZ (5 mg oral administration on days 1–4, after supper). In cases where fosaprepitant (150 mg intravenous infusion, 1 hour before chemotherapy) is used instead of APR on day 1, no additional APR is administered on days 2–3. In addition, when more than 135 mg/m² of paclitaxel is used, on day 1 DEX is administered 19.8 mg intravenously or 20 mg orally.

Follow-up

Physical and blood examinations are scheduled for each patient before initiation of the treatment and daily from days 5–15. The study diaries are collected from

TIMEPOINT	Enrolment	Enrolment	Post-enrolment								
	-8 days	0	day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8	
ENROLMENT:											
Eligibility screen	X										
History and physical	X										
ECOG PS	X										
Laboratory studies	X							X			
Informed consent	X										
Enrolment		X									
INTERVENTIONS:											
Antiemetic administrations			←————→								
ASSESSMENTS:											
Patient diaries		X	X	X	X	X	X	X	X	X	
PRO-CTCAE		X								X	
Adverse events		X	X	X	X	X	X	X	X	X	
Patient related factor survey										X	
Patient satisfaction										X	

Figure 2 The schedule of enrolment, interventions and assessments.

the patients after the assessment period (0–168 hours). **Figure 2** provides details of the schedule of enrolment, interventions and assessments.

Study design and statistical methods

The hypothesis of this study is that the CR rate for 5 mg OLZ plus GRA, NK₁RA (aprepitant or fosaprepitant) and DEX for AUC \geq 4 mg/mL/min CBDCA combination therapy is significantly higher than the CR rate for standard antiemetic triplet therapy.

Two previous randomised controlled trials reported a CR rate around 60%.^{5,6} An improvement of the treatment effect has to be $>10\%$ to amend the guideline of the MASCC/ESMO 2016.³ Based on research by Navari *et al*,¹⁴ improvement around 15% in the CR rate is expected. Considering the safety of OLZ, an improvement of more than 15% would be clinically meaningful.

Assuming a null hypothesis of the CR rate $\leq 60\%$ and an alternative hypothesis of 75%, a minimum of 53 patients is required to achieve a one-sided type I error of 0.1% and 80% power based on the exact binomial distribution. The target sample size is set at 60 as some patient dropout is expected.

Patient and public involvement

Patients and/or public were not involved in the design of this study.

ETHICS AND DISSEMINATION

Data will be presented at international conferences and published in peer-reviewed journals.

Participating institutions

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Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval The study protocol was approved by the institutional review board at each of the participating centres.

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