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Doublet therapy and olanzapine for carboplatin-induced nausea and vomiting in patients with thoracic cancer: a multicenter phase II study protocol

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Doublet therapy and olanzapine for carboplatin-induced nausea and vomiting in patients with thoracic cancer: a multicenter phase II study protocol

Short title: Olanzapine for carboplatin-induced CINV

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ABSTRACT

Introduction: Adding neurokinin-1 receptor antagonist (NK_1RA) to 5-hydroxytryptamine-3 receptor antagonist and dexamethasone (DEX) improved carboplatin (CBDCA) -induced chemotherapy-induced nausea and vomiting (CINV) in patients with thoracic cancer. NK1RAs with high drug cost are raising medical expenses. Olanzapine (OLZ) is less expensive and can be expected to have an excellent effect on CINV. This phase II trial aimed to evaluate the efficacy and safety of 5 mg olanzapine plus granisetron (GRN) and DEX in CBDCA combination therapy with AUC ≥ 5 mg/mL/min for the prevention of nausea and vomiting in patients with thoracic cancer.

Methods and analysis: This is open-label, single-arm, multicenter, phase II trial. Patients who receive carboplatin (AUC ≥5)-based therapy and have never been administered moderate to high emetogenic chemotherapy will be enrolled. All patients will receive combination of GRA, DEX, and OLZ. The primary endpoint was complete response (CR) rate, defined as the absence of emetic episodes and no use of rescue medication during 120 h after the initiation of CBDCA. Forty-eight patients were required based on our hypothesis that this regimen can improve CR rate from 65% (null hypothesis) to 80% (alternative hypothesis) with a one-sided type I error of 0.1 and a power of 0.8. We set the target sample size at 50 considering the dropout rate.

Ethics and dissemination: The study protocol was approved by the institutional review board

at each of the participating centers. Data will be presented at international conferences and published in peer-reviewed journals.

Trial registration: This study protocol was registered at the UMIN Clinical Trial Registry as UMIN000031267.

Key words: olanzapine, carboplatin, nausea, vomiting

Strengths and limitations of this study

- This is a first trial to evaluate efficacy and safety of adding 5 mg olanzapine to granisetron and dexamethasone for CINV after AUC ≥5 mg/mL/min CBDCA combination therapy in thoracic cancer patients.
- A positive result of this phase II trial is necessary before a phase III trial can be conducted. The data will be used to inform a future large multicenter double-blind randomized phase III trial.
- Limitations are open-label and single arm design.

INTRODUCTION

Carboplatin (CBDCA) administered to achieve an area under the blood concentration-time curve (AUC) of ≥4 mg/mL/min is ranked as the highest risk drug among the moderately

emetogenic chemotherapy (MEC) agents and/or the highly emetogenic chemotherapy (HEC). The American Society of Clinical Oncology (ASCO) [1], the Multinational Association of Supportive Care in Cancer (MASCC) [2], and the National Comprehensive Cancer Network (NCCN) [3] have recommended emesis prophylaxis using a three-drug combination therapy including 5-hydroxytryptamine-3 receptor antagonist (5-HT_3RA), dexamethasone (DEX), and neurokinin-1 receptor antagonist (NK_1RA).

CBDCA is widely used against various cancers. The complete response (CR) rate (the absence of emetic episodes and no use of rescue medication) for first generation 5-HT_3RA and DEX varies depending on the cancer type; the rate is approximately 50% in patients with gynecological cancer [4-5] and approximately 65% in those with thoracic cancer [6-7]. This difference is due to the background of cancer types. Gynecological cancer patients are only females and are younger than thoracic cancer. Female gender, younger age, non-habitual alcohol intake and non-smoker etc. are known as risk factors for chemotherapy-induced nausea and vomiting (CINV) [8]. Therefore, we believe NK_1RA with high drug cost is unnecessary for carboplatin-based therapy in thoracic cancer patients.

Olanzapine (OLZ) is classified as a multi-acting receptor-targeted antipsychotic and blocks dopaminergic D_1, D_2, D_3, and D_4 receptors; serotonergic 5-TH_{2A}, 5-HT_{2B}, 5-HT_3, and 5-HT_6 receptors; histamine H_1 receptors; and muscarinic acetylcholine M_1, M_2, M_3, and M_4 receptors [9]. Among its other uses, OLZ is used to improve CINV. Navari et al. reported that 10mg

OLZ combined with palonosetron (PALO) and DEX has an equivalent antiemetic effect to an antiemetic regimen consisting of PALO, DEX, and aprepitant (APR), in CR rate, and excellent in control of nausea in highly emetogenic chemotherapy (HEC) [10]. Moreover, in Europe and the United States, the effectiveness of a combination of 10 mg OLZ and standard antiemetic therapy has been demonstrated for HEC in randomized control trials; however, the resulting patient sedation due to the therapy may be a concern [11-14]. In Japan, three phase II studies revealed the efficacy and safety of the combination of 5 mg OLZ and standard triplet therapy for CINV induced by HEC [15-17]. In a trial, Yanai et al. reported that OLZ at 5 mg and 10 mg showed comparable CR effects, but the 5 mg dose was less sedative [17].

However, the effectiveness of OLZ against CBDCA-induced CINV has not been demonstrated. The cost per treatment cycle of 5 mg of OLZ (brand: 733.60 JPY, generic: 180.80 JPY) is less than that of PALO (14851.00 JPY) or NK_1RA (APR: 11638.20 JPY, fosaprepitant: 14545.00 JPY), and confirming the effectiveness of the combination use of OLZ, first generation 5-HT_3RA, and DEX would change the standard antiemetic treatment for CBDCA-based chemotherapy in thoracic cancer. We planned this open-label, single-arm, multicenter, phase II trial to evaluate the efficacy and safety of 5 mg olanzapine plus granisetron (GRN) and DEX in CBDCA combination therapy with AUC $\geq$ 5 mg/mL/min for the prevention of CINV in patients with thoracic cancer.

Study Protocol

Objective

Our objective was to evaluate the efficacy and safety of 5 mg olanzapine plus GRA and DEX for the prevention of nausea and vomiting during CBDCA combination therapy achieving AUC ≥ 5 mg/mL/min in patients with thoracic cancer. The study was approved by the institutional review board at each participating center and was independently monitored by the alliance data center and safety monitoring board.

Study setting

This study was an open-label, single-arm, multicenter, phase II trial conducted in four centers in Japan.

End points

We chose the CR rate as the primary endpoint, defined as the absence of emetic episodes and no use of rescue medication during the overall assessment period (0–120 h) after the initiation of CBDCA.

Secondary endpoints were the CR rate at the early assessment period (0–24 h), the CR rate at the delayed assessment period (25–120 h), and the complete control rate (defined as the

absence of nausea and emetic episodes and no use of rescue medication during the overall assessment period). We used a four-grade categorical scale (none, mild, moderate, or severe) to stratify nausea and chose the moderate and severe categories to define significant nausea. The total control rate was defined as the absence of nausea and emetic episodes and no use of rescue medication for the acute, delayed, and assessment periods. The time to treatment failure was defined as the time to the first emetic episode or the use of rescue medication. Severity has been classified into a four-grade categorical scale, including nausea, anorexia, sleepiness, and the impact on life. Patient satisfaction with antiemetic therapy.

Adverse events were graded according to the CTCAE version 4.0.

Eligibility criteria

Inclusion criteria

(i) Patients with thoracic cancer scheduled to receive carboplatin-based chemotherapy (AUC ≥ 5)

(ii) Age, 20–79 years at registration

(iii) Eastern Cooperative Oncology Group performance status of 0, 1, or 2

(iv) Absence of symptomatic brain metastasis and carcinomatosis

(v) Absence of a history of the administration of moderate-to-high emetogenic chemotherapy

(vi) No current use of any drug with antiemetic activity or inducing somnolence, such as 5-HT_3RA, NK_1RA, corticosteroids, dopamine receptor antagonists, phenothiazine tranquilizers, antihistamine drugs (paclitaxel administration allowed during premedication), and benzodiazepine agents

(vii) Meeting the following standard values of general clinical tests:

(a) aspartate aminotransferase ≤ 100U/L

(b) alanine aminotransferase ≤ 100U/L

(c) total bilirubin ≤ 2.0 mg/dL

(viii) Patients who provided written informed consent

Exclusion criteria

(i) History of hypersensitivity or allergy to study drugs or similar compounds

(ii) Antiemetics needed at the time of enrollment

(iii) Started opioid intake in the 48 h prior to enrollment

(iv) Presence of unstable angina, ischemic heart disease, cerebral hemorrhage or apoplexy, or active gastric or duodenal ulcer within 6 months prior to enrollment

(v) Presence of convulsive disorders requiring anticonvulsants 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 d prior to enrollment

(xi) Presence of diabetes mellitus

(xii) Being a habitual smoker at the time of enrollment

(xiii) Patients deemed inappropriate for the study by the investigator

Registration

The accrual started in February 2018.

Treatment methods

All patients received GRA (1 mg intravenous infusion on day 1, 30 min before chemotherapy), DEX (9.9 mg intravenous infusion or 12 mg oral administration on day 1, 30 min before chemotherapy, and 6.6 mg intravenous infusion or 8 mg oral administration on days 2–3), and OLZ (5 mg oral administration on days 1–4, after supper). In addition, when paclitaxel was used, DEX was administered at 19.8 mg intravenously or 20 mg orally on day 1.

Follow up

We scheduled physical and blood examinations of patients before the initiation of treatment and once between days 5 and 15 after treatment initiation. The data are collected from patient diaries. Patients are required to fill the diary for every 24 h from the start of chemotherapy to 120 h periods. After the overall assessment period (0–120 h), patient-reported study diaries were collected (figure 1. provides details of the schedule of enrolment, interventions, and assessments).

Study design and statistical methods

The hypothesis of this study was that the CR rate for 5 mg olanzapine plus GRA and DEX during CBDCA combination therapy achieving AUC ≥ 5 mg/mL/min would be significantly higher than that for standard antiemetic doublet therapy.

Other trials have shown CR rates of approximately 65% [6, 7]. An improvement of the treatment effect has to be >10% to amend the guideline of the MASCC/ESMO2016 [2] according to previous studies in which the CR ratio of antiemesis treatment by PALO, DEX, and APR was 80.5%–92% [18-20]. We think an improvement of >15% in the CR rate can be clinically meaningful.

Therefore, assuming a null hypothesis of the CR rate to be ≤ 65% and an alternative hypothesis to be 80%, we calculated that a minimum of 48 patients are required to achieve a one-sided type I error of 0.1 and 80% of power based on the exact binomial distribution.

Because some dropouts are expected, we set the target sample size at 50.

Patient and Public Involvement

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

Ethics and dissemination

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

University hospital medical information network (UMIN) registration

This study protocol was registered at the UMIN Clinical Trial Registry (UMIN-CTR) on February 14, 2018, as UMIN000031267 (http://www.umin.ac.jp/ctr/index-j.htm).

Participating institutions

Gifu University Hospital, Gifu Municipal Hospital, Murakami Memorial Hospital Asahi University, and Gunma Prefectural Cancer Center.

Funding statement

This work was supported by self-funding from the Department of Cardiology and Respirology at the Gifu University Graduate School of Medicine.

Competing interests statement

None declared.

Authors' contributions

HI, MS, TG, YF, and YO made a significant contribution to the conception and design of the study protocol. MS provided statistical expertise. The protocol was written by HI, MS, TG, YF, TY, NF, KM, DK, TO, MY, and CH and critically reviewed by AS, and YO. HI, MS, TG, and YF drafted the manuscript. All the authors read and approved the final paper.

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Table 1. Antiemetic administrations

Antiemetics		day1	day2	day3	day4
granisetoron	i.v.	1mg			
dexamethasone	p.o.	12mg*	8mg	8mg	
or					
dexamethasone	i.v.	9.9mg*	6.6mg	6.6mg	
olanzapine	p.o.	5mg	5mg	5mg	5mg

*When paclitaxel is used, on day 1 DEX is administered 19.8 mg intravenously or 20 mg orally.

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

	Enrolment	Enrolment	Post- Enrolment					
TIMEPOINT	***-8 days***	**0**	***day1***	***day2***	***day3***	***day4***	***day5***	***day6***
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
Adverce events		X	X	X	X	X	X	X
Patient related factor survey								X
Patient satisfaction								X

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	12
	2b	All items from the World Health Organization Trial Registration Data Set	12
Protocol version	3	Date and version identifier	12
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	1, 13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	none
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10, 11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10, 11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10, 11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	single arm
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	single arm
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	single arm
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	non- blinded
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	non- blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10, 11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	no plans
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	no interim analysis
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10, 11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	no plans
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	no plans
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	none
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	none
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	9
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	none

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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Clinical trial protocol of doublet therapy and olanzapine for carboplatin-induced nausea and vomiting in patients with thoracic cancer: a multicenter phase II trial

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
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Clinical trial protocol of doublet therapy and olanzapine for carboplatin-induced nausea and vomiting in patients with thoracic cancer: a multicenter phase II trial

Short title: Olanzapine for carboplatin-induced CINV

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ABSTRACT

Introduction: Adding neurokinin-1 receptor antagonist (NK_1RA) to 5-hydroxytryptamine-3 receptor antagonist and dexamethasone (DEX) improved carboplatin (CBDCA) -induced chemotherapy-induced nausea and vomiting (CINV) in patients with thoracic cancer. NK1RAs with high drug cost are raising medical expenses. Olanzapine (OLZ) is less expensive and can be expected to have an excellent effect on CINV. This phase II trial aimed to evaluate the efficacy and safety of 5 mg olanzapine plus granisetron (GRN) and DEX in CBDCA combination therapy with AUC ≥ 5 mg/mL/min for the prevention of nausea and vomiting in patients with thoracic cancer.

Methods and analysis: This is an open-label, single-arm, multicenter, phase II trial. Patients who receive CBDCA (AUC ≥5)-based therapies and have never been administered moderate to high emetogenic chemotherapy will be enrolled. All patients will receive a combination of GRA, DEX, and OLZ. The primary endpoint is complete response (CR) rate, defined as the absence of emetic episodes and no use of rescue medication during 120 h after the initiation of CBDCA. Forty-eight patients are required based on our hypothesis that this regimen can improve CR rate from 65% (null hypothesis) to 80% (alternative hypothesis) with a one-sided type I error of 0.1 and a power of 0.8. We set the target sample size at 50 considering the dropout rate.

Ethics and dissemination: The study protocol was approved by the institutional review board

at each of the participating centers. Data will be presented at international conferences and published in peer-reviewed journals.

Trial registration: This study protocol was registered at the UMIN Clinical Trial Registry as UMIN000031267.

Key words: olanzapine, carboplatin, nausea, vomiting

Strengths and limitations of this study

- This is a first trial to evaluate efficacy and safety of adding 5 mg olanzapine to granisetron and dexamethasone for CINV after AUC ≥5 mg/mL/min CBDCA combination therapy in thoracic cancer patients.
- A positive result of this phase II trial is necessary before a phase III trial can be conducted. The data will be used to inform a future large multicenter double-blind randomized phase III trial.
- Limitations are open-label and single arm design. And the study is conducted within the Japanese population.

INTRODUCTION

In recent guidelines, carboplatin (CBDCA) is reclassified at the upper limit of the moderately emetogenic chemotherapy (MEC) category and/or the highly emetogenic

chemotherapy (HEC) [1-3]. The Multinational Association of Supportive Care in Cancer (MASCC) (regardless of the CBDCA dose) [1], the American Society of Clinical Oncology (ASCO) (CBDCA at a dose of ≥4 mg/mL/min) [2], and the National Comprehensive Cancer Network (NCCN) (CBDCA at a dose of ≥4 mg/mL/min) [3] have recommended emesis prophylaxis using a three-drug regimen including 5-hydroxytryptamine-3 receptor antagonist (5-HT_3RA), dexamethasone (DEX), and neurokinin-1 receptor antagonist (NK_1RA) in patients receiving CBDCA-based chemotherapy.

CBDCA is widely used against various cancers. The complete response (CR) rate (the absence of emetic episodes and no use of rescue medication) for first generation 5-HT_3RA and DEX varies depending on the cancer type; the rate is approximately 50% in patients with gynecological cancer [4-5] and approximately 65% in those with thoracic cancer [6-7]. This difference is due to the background of cancer types. Gynecological cancer patients are only females and are younger than thoracic cancer patients. Female gender, younger age, non-habitual alcohol intake and non-smoker etc. are known as risk factors for chemotherapy-induced nausea and vomiting (CINV) [8]. Therefore, we believe NK_1RA with high drug cost is unnecessary for CBDCA-based therapy in thoracic cancer patients. Furthermore, because of the inhibition of cytochrome P450 3A4, clinically significant pharmacokinetic interactions of apreitant (APR) and fosaprepitant have been reported not only general agents but also chemotherapy agents [9]. Therefore, the development of antiemetic

therapy without NK_1RA is beneficial in complicated cancer chemotherapy.

Olanzapine (OLZ) is classified as a multi-acting receptor-targeted antipsychotic and blocks dopaminergic D_1, D_2, D_3, and D_4 receptors; serotonergic 5-TH_{2A}, 5-HT_{2B}, 5-HT_3, and 5-HT_6 receptors; histamine H_1 receptors; and muscarinic acetylcholine M_1, M_2, M_3, and M_4 receptors [10]. Among its other uses, OLZ is used to improve CINV. Navari et al. performed a phase III trial to confirm the superiority of 10mg OLZ combined with palonosetron (PALO) and DEX to an antiemetic regimen consisting of PALO, DEX, and APR in highly emetogenic chemotherapy (HEC). The study could not demonstrate that the OLZ regimen is superior to the APR regimen. However, the CR rates for the acute, delayed, and overall period were not significantly different between the OLZ regimen and the APR regimen. On the other hand, the OLZ regimen showed excellent control of nausea in the delayed and overall period [11]. Moreover, in the United States and Asia, the effectiveness of a combination of 10 mg OLZ and standard antiemetic therapy has been demonstrated for HEC in randomized control trials; however, the resulting patient sedation due to the therapy may be a concern [12-15]. In Japan, three phase II studies revealed the efficacy and safety of the combination of 5 mg OLZ and standard triplet therapy for CINV induced by HEC [16-18]. In a trial, Yanai et al. reported that OLZ at 5 mg and 10 mg showed comparable CR effects, but the 5 mg dose was less sedative [18].

However, the effectiveness of OLZ against CBDCA-induced CINV has not been

demonstrated. The cost per treatment cycle of 5 mg of OLZ (brand: 733.60 JPY, generic: 180.80 JPY) is less than that of PALO (14851.00 JPY) or NK_1RA (APR: 11638.20 JPY, fosaprepitant: 14545.00 JPY), and confirming the effectiveness of the combination use of OLZ, first generation 5-HT_3RA, and DEX would change the standard antiemetic treatment for CBDCA-based chemotherapy in thoracic cancer.

In recent years, immune checkpoint inhibitor (ICI) in combination with chemotherapy is available in clinical settings for lung cancer. Arbour et al. reported that baseline corticosteroid use was associated with poorer outcomes in patients who were treated with ICI [19]. Therefore, there is a concern that DEX as emesis prophylaxis may affect the effects of ICI combination chemotherapy. The noninferiority of DEX sparing on day 2 and 3, combined with PALO has been demonstrated for MEC in randomized control trials [20-22]. Therefore, to use PALO can reduce corticosteroid. Among the ICI combination therapies, the pembrolizumab combined with CBDCA and pemetrexed is one of the most often used regimens for advanced non–small-cell lung cancer. In the KEYNOTE-189 trial that proved the effectiveness of this regimen, for prophylaxis of cutaneous reaction, the administration of DEX 8 mg per day for 2 days besides DEX of day 1 used for antiemetic therapy had been regulated by the protocol [23]. Therefore, we plan to administer DEX for 3 days.

The efficacy of OLZ has been demonstrated in both combinations with the first and second generation 5HT_3RA in HEC [11-18, 24]. Therefore, granisetron (GRN) was chosen as

$5HT_3RA$ in the study.

Given the above, we plan this open-label, single-arm, multicenter, phase II trial to evaluate the efficacy and safety of 5 mg olanzapine plus granisetron (GRN) and DEX in CBDCA combination therapy with AUC ≥ 5 mg/mL/min for the prevention of CINV in patients with thoracic cancer.

Study Protocol

Objective

Our objective is to evaluate the efficacy and safety of 5 mg olanzapine plus GRA and DEX for the prevention of nausea and vomiting during CBDCA combination therapy achieving AUC ≥ 5 mg/mL/min in patients with thoracic cancer. The study was approved by the institutional review board at each participating center and was independently monitored by the alliance data center and safety monitoring board.

Study setting

This study is an open-label, single-arm, multicenter, phase II trial conducted in four centers in Japan.

End points

We choose the CR rate as the primary endpoint, defined as the absence of emetic episodes and no use of rescue medication during the overall assessment period (0–120 h) after the initiation of CBDCA.

Secondary endpoints are the CR rate at the early assessment period (0–24 h), the CR rate at the delayed assessment period (25–120 h), and the complete control rate defined as no significant nausea, no emetic episodes, and no use of rescue medication for the acute, delayed, and overall assessment periods. We use a four-grade categorical scale (none, mild, moderate, or severe) to stratify nausea and choose the moderate and severe categories to define significant nausea. The total control rate is defined as the absence of nausea and emetic episodes and no use of rescue medication for the acute, delayed, and overall assessment periods. The time to treatment failure is defined as the time to the first emetic episode or the use of rescue medication. 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. These data are collected from patient diaries. Adverse events are graded according to the CTCAE version 4.0.

Eligibility criteria

Inclusion criteria

(i) Patients with thoracic cancer scheduled to receive CBDCA-based chemotherapy (AUC ≥ 5)

(ii) Age, 20–79 years at registration

(iii) Eastern Cooperative Oncology Group performance status of 0, 1, or 2

(iv) Absence of symptomatic brain metastasis and carcinomatosis

(v) Absence of a history of the administration of moderate-to-high emetogenic chemotherapy

(vi) No current use of any drug with antiemetic activity or inducing somnolence, such as 5-HT_3RA, NK_1RA, corticosteroids, dopamine receptor antagonists, phenothiazine tranquilizers, antihistamine drugs (paclitaxel administration allowed during premedication), and benzodiazepine agents

(vii) Meeting the following standard values of general clinical tests:

(a) aspartate aminotransferase ≤ 100U/L

(b) alanine aminotransferase ≤ 100U/L

(c) total bilirubin ≤ 2.0 mg/dL

(viii) Patients who provided written informed consent

Exclusion criteria

(i) History of hypersensitivity or allergy to study drugs or similar compounds

(ii) Antiemetics needed at the time of enrollment

(iii) Started opioid intake in the 48 h prior to enrollment

(iv) Presence of unstable angina, ischemic heart disease, cerebral hemorrhage or apoplexy, or active gastric or duodenal ulcer within 6 months prior to enrollment

(v) Presence of convulsive disorders requiring anticonvulsants 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 enrollment

(xi) Presence of diabetes mellitus

(xii) Being a habitual smoker at the time of enrollment

(xiii) Patients deemed inappropriate for the study by the investigator (From daily behavior, patients who may not be able to keep medication adherence and/or fulfill patient diary etc.)

Registration

The accrual started in February 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), DEX (9.9 mg intravenous infusion or 12 mg oral administration on day 1, 30 min before chemotherapy, and 6.6 mg intravenous infusion or 8 mg oral administration on days 2–3), and OLZ (5 mg oral administration on days 1–4, after supper). In addition, when paclitaxel is used, DEX is administered at 19.8 mg intravenously or 20 mg orally on day 1. Dexamethasone injection is

provided as dexamethasone sodium phosphate. The 8 mg of dexamethasone sodium phosphate contains 6.6 mg of dexamethasone.

Follow up

We schedule physical and blood examinations of patients before the initiation of treatment and once between days 5 and 15 after treatment initiation. The data are collected from patient diaries. Patients are required to fill the diary for every 24 h from the start of chemotherapy to 120 h periods. After the overall assessment period (0–120 h), patient-reported study diaries are collected (figure 1. provides details of the schedule of enrollment, interventions, and assessments).

Study design and statistical methods

The hypothesis of this study is that the CR rate for 5 mg olanzapine plus GRA and DEX during CBDCA combination therapy achieving AUC ≥ 5 mg/mL/min will be significantly higher than that for standard antiemetic doublet therapy.

Other trials have shown CR rates of approximately 65% [6, 7]. An improvement of the treatment effect has to be >10% to amend the guideline of the MASCC/ESMO2016 [2] according to previous studies in which the CR ratio of antiemesis treatment by PALO, DEX, and APR was 80.5%–92% [25-27]. We think an improvement of >15% in the CR rate can be clinically meaningful.

Therefore, assuming a null hypothesis of the CR rate to be ≤ 65% and an alternative hypothesis to be 80%, we calculate that a minimum of 48 patients are required to achieve a one-sided type I error of 0.1 and 80% of power based on the exact binomial distribution. Because some dropouts are expected, we set the target sample size at 50. A sample size calculation was performed by SAS 9.4 (Cary, NC, USA).

Patient and Public Involvement

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

Ethics and dissemination

The study protocol was approved by the institutional review board at each of the participating centers. A signed informed consent form is obtained from all patients before enrollment. Data will be presented at international conferences and published in peer-reviewed journals.

University hospital medical information network (UMIN) registration

This study protocol was registered at the UMIN Clinical Trial Registry (UMIN-CTR) on February 14, 2018, as UMIN000031267 (http://www.umin.ac.jp/ctr/index-j.htm).

Participating institutions

Gifu University Hospital, Gifu Municipal Hospital, Murakami Memorial Hospital Asahi University, and Gunma Prefectural Cancer Center.

Trial status

February 2018: protocol approval by the Ethics Committee.

February 2018: Start of inclusion.

December 2019: End of inclusion.

We will submit the manuscript during the first half of 2020.

Funding statement

This work is supported by self-funding from the Department of Cardiology and Respirology at the Gifu University Graduate School of Medicine.

Competing interests statement

None declared.

Authors' contributions

HI, MS, TG, YF, and YO made a significant contribution to the conception and design of the study protocol. MS provided statistical expertise. The protocol was written by HI, MS, TG, YF, TY, NF, KM, DK, TO, MY, and CH and critically reviewed by AS, and YO. HI, MS,

TG, and YF drafted the manuscript. All the authors read and approved the final paper.

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Table 1. Antiemetic administrations

Antiemetics		day1	day2	day3	day4
granisetoron	i.v.	1mg			
dexamethasone	p.o.	12mg*	8mg	8mg	
or					
dexamethasone	i.v.	9.9mg*	6.6mg	6.6mg	
olanzapine	p.o.	5mg	5mg	5mg	5mg

*When paclitaxel is used, on day 1 DEX is administered 19.8 mg intravenously or 20 mg orally.

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

	Enrolment	Enrolment	Post- Enrolment					
TIMEPOINT	***-8 days***	**0**	***day1***	***day2***	***day3***	***day4***	***day5***	***day6***
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
Adverce events		X	X	X	X	X	X	X
Patient related factor survey								X
Patient satisfaction								X

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	12
	2b	All items from the World Health Organization Trial Registration Data Set	12
Protocol version	3	Date and version identifier	12
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	1, 13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	none
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10, 11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10, 11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10, 11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	single arm
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	single arm
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	single arm
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	non- blinded
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	non- blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10, 11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	no plans
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	no interim analysis
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10, 11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	no plans
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	no plans
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	none
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	none
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	9
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	none

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.