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Study protocol for SPARED trial: Phase III study comparing dexamethasone on day 1 with dexamethasone on day 1-4 combined with neurokinin-1 receptor antagonist, palonosetron, and olanzapine in patients receiving cisplatin-based chemotherapy

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Title

Study protocol for SPARED trial: Phase III study comparing dexamethasone on day 1 with dexamethasone on day 1-4 combined with neurokinin-1 receptor antagonist, palonosetron, and olanzapine in patients receiving cisplatin-based chemotherapy

Authors' name

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Abstract

Introduction

Dexamethasone (DEX) is administered for multiple days to prevent chemotherapy-induced nausea and vomiting (CINV) for patients receiving highly emetogenic chemotherapy (HEC); however, its notorious side effects have been widely reported. Although our multicenter randomized double-blind comparative study verified non-inferiority of sparing DEX after day 2 of chemotherapy when combined with neurokinin-1 receptor antagonist (NK1-RA) and palonosetron (Palo) for patients receiving HEC regimen, DEX sparing was not non-inferior in patients receiving cisplatin (CDDP)-based HEC regimens in subgroup analysis. Recently, the efficacy of the addition of olanzapine (OLZ) to standard triple antiemetic therapy on HEC has been demonstrated by several phase III trials. This study aims to confirm non-inferiority of DEX sparing when it is combined with NK-1RA, Palo, and OLZ in patients receiving CDDP-based HEC regimens.

Methods and analysis

This is a randomized, double-blind, phase III trial. Patients who are scheduled to receive CDDP $\geq$ 50mg/m^2 as initial chemotherapy are eligible. Patients are randomly assigned to receive either DEX on day 1 to 4 or DEX on day 1 combined with NK1-RA, Palo, and OLZ (5mg). The primary endpoint is complete response (CR) rate, defined as no emesis and no rescue medications during the delayed phase (24 to120 hours post-CDDP administration). The non-inferiority margin is set at -15.0%. We assume that CR rates would be 75% in both arms. Two hundred sixty-two patients are required for at least

80% power to confirm non-inferiority at a one-sided significance level of 2.5%. After considering the possibility of attrition, we set our final required sample size of 280.

Ethics and dissemination

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

Trial registration number

UMIN000032269

Protocol version

3.0, 24 May 2020.

Strengths and limitations of this study

- This is the first trial to evaluate whether adding olanzapine to neurokinin-1 receptor antagonist, palonosetron (Palo), and dexamethasone (DEX) can spare DEX administration on day 2 to 4 for patients receiving cisplatin-based regimens.
- This study is a multicenter, placebo-controlled, double-blinded, randomized phase III study.
- The limitation of this study is that Palo is administered at a dose of 0.75 mg in Japan; whereas, international antiemetic guidelines recommend a Palo dose of 0.25 mg.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most frequent adverse reactions associated with chemotherapy, and considerably reduces patient quality of life (QOL). CINV has been traditionally assessed in overall (0-120 h post-chemotherapy), acute (0-24 h post-chemotherapy), or delayed (24-120 h post-chemotherapy) phases,[1]. Intravenously administered cytotoxic agents are categorized into 4 emetic risk groups (high, moderate, low, and minimal),[2]. Highly emetogenic chemotherapy (HEC) including cisplatin (CDDP)-based regimen and anthracycline plus cyclophosphamide (AC) regimen can lead to a > 90 % incidence of CINV in patients without an adequate antiemetic prophylaxis,[3].

Dexamethasone (DEX), 5-hydroxytryptamine type 3 receptor antagonists (5-HT3-RA) and neurokinin-1 receptor antagonists (NK1-RA) have been developed to inhibit CINV from HEC,[4-5]. DEX is typically administered for multiple days from the start of chemotherapy to care for delayed CINV,[6];whereas, frequent administration of corticosteroids has been associated with many adverse effects such as insomnia, hyperglycemia and reduced bone mineral density,[7-9]. Our multicenter randomized double-blind comparative study (DEX-1 study) showed the complete response (CR; no emesis, no use of rescue medication) rate in the overall phase of DEX on day 1 provided a non-inferior antiemetic efficacy to a treatment of DEX on day1-3 when combined with NK1-RA and palonosetron (Palo) for patients receiving HEC including AC and CDDP-based regimen. (44.0 % vs. 46.9 %, $P = 0.007$),[10] . In a subgroup analysis of patients receiving CDDP-based regimen, CR rates of acute phase demonstrated a non-inferiority of DEX on day1 to day 1-3 (95.6 % vs 95.6 %, $P = 0.007$); however, CR

rates of the overall and delayed phases DEX on day 1 were lower than those DEX on day 1-3 (57.8 % vs 66.7 %, $P = 0.272$; 57.8 % vs 68.9 %, $P = 0.349$, respectively). Tamura et al reported that the incidence of CINV for the patients receiving CDDP-based regimen peaked on day 4 to 5,[11]. Therefore, some guidelines still recommend multiple-days DEX in combination with 5-HT3-RA and NK1-RA for CDDP-based regimens,[3, 12-14].

Olanzapine (OLZ) is classified as a multi-acting receptor-targeted antipsychotic and blocks dopamine receptors (D_1, D_2, D_4), 5-HT receptors (5-HT_2A, 5-HT_2C, 5-HT_3), α_1 adrenergic receptors, histamine receptors, and multiple muscarine receptors,[15], which might affect CINV. In the randomized, double-blind, phase III trial involving patients receiving HEC regimens, it was more effective to combine OLZ 10mg than placebo with NK1-RA, 5-HT3-RA, and DEX for the prevention of nausea and vomiting in acute and delayed phases,[16]; however, OLZ (10mg) had excessive sedation. Therefore, it is difficult to use OLZ 10mg for all patients in practice setting. Recently, J-FORCE study, which was a randomized, double-blind, placebo-controlled phase III trial evaluating the significance of adding of 5mg OLZ to NK1-RA, Palo, and DEX in CDDP-based regimens, showed that significantly more patients receiving OLZ achieved CR from delayed CINV compared with those who received placebo (79 % versus 66%, $P < 0.001$); moreover, no differences were found between two groups in the incidence of sedation,[17]. The addition of OLZ in combination with NK1-RA, Palo, and DEX has greater benefit and becomes a standard antiemetic therapy in patients receiving CDDP-based regimens.

Treatment with OLZ was associated with metabolic effects, including elevated glucose concentrations manifesting as insulin resistance,[18]. A phase III study showed

that grade 3 hyperglycemia was observed more frequently in the OLZ versus placebo group,[16]. Therefore, there is a concern that the combination of OLZ and multiple-days DEX may worsen glucose intolerance. In another study, Navari et al. also demonstrated that OLZ, combined with a single dose of DEX and Palo was very effective at controlling acute and delayed phase CINV in patients receiving HEC; moreover, this regimen was not associated with significant hyperglycemia,[19].

Based on these results, we speculate that the antiemetic regimen of OLZ 5mg, NK1-RA, Palo, and a single dose of DEX could be effective and safe for delayed phase CINV in patients receiving CDDP-based regimen. We planned this randomized, double-blind, phase III trial to evaluate the non-inferiority of DEX on day1 compared with DEX on day1 to 4 when combined with NK1-RA, Palo, and OLZ in patients receiving CDDP-based regimens.

Methods and Analysis

Study Design

The Standard Protocol Items for Randomized Trials (SPIRIT) statement and checklist were followed in preparing the protocol. This multicenter, placebo-controlled, double-blinded, randomized, non-inferiority, phase III study aims to confirm the non-inferiority of DEX on day 1 compared to DEX on days 1 to 4 combined with NK1-RA, Palo and OLZ 5mg to prevent CINV in patients with solid malignant tumor receiving CDDP-based regimens.

Study setting and participants

Recruiting will be performed in 10 sites across Japan. The inclusion and exclusion criteria are summarized in box 1.

Box.1

Inclusion criteria

I. Patients with malignant tumor, excluding hematologic malignancies, receiving first-line treatment with CDDP $\geq$ 50mg/m^2.

II. Aged: 20-74 years at registration

III. Absence of nausea and vomiting within 24 hours prior to registration.

IV. Eastern Cooperative Oncology Group performance status of 0-1.

V. Meeting the following standard vales of general clinical tests within 2 weeks prior to enrolment:

a. alanine aminotransferase < 100 IU/L.

b. aspartate aminotransferase < 100 IU/L.

c. total bilirubin < 2.0 mg/dL.

d. serum creatinine < 1.5 mg/dL.

VI. Patients with expected prognosis of 3 months or more.

VII. Patients who provided written informed consent.

Exclusion criteria

I. Presence of systemic glucocorticoid therapy.

II. Patients using antiemetics other than the trial drug.

III. Patients receiving moderately emetogenic chemotherapy within 6 days before and after CDDP administration.

IV. Patients who cannot be hospitalized until after 120 hours have passed since starting CDDP administration.

V. Patients receiving radiation therapy to abdomen or pelvis within 6 days prior to enrolment until six days after CDDP administration.

VI. Presence of diabetes mellitus receiving treatment with insulin and/ or oral hypoglycemic agents, or patients with HbA1c (NGSP) > 6.5 % (> 6.1 % in the event of JDS).

VII. Presence of symptomatic brain metastasis, convulsive disorder requiring treatment with anticonvulsants, and mental illness or psychiatric symptoms that impede activities of daily life.

VIII. Patients who are incapable of taking oral agents.

IX. History of allergy to study drugs or similar compounds.

X. Breastfeeding, pregnant women, or patients not willing to use contraception.

XI. Patients deemed inappropriate for the study by the investigator.

The main inclusion criterion is patients who are eligible in the study are 20 to 74 years old with malignant tumor, excluding hematological malignancies, receiving first-line treatment with CDDP $\geq$ 50 mg/m^2 (previous use of moderately or low emetogenic chemotherapy is permitted). The main exclusion criteria are as followed: (1) presence of systemic glucocorticoid therapy; (2) patients using antiemetics other than the trial drug; (3) patients receiving moderately emetogenic chemotherapy within six days before and after CDDP administration (Minimally to low emetogenic agents are allowed); (4) patients receiving radiation therapy to abdomen or pelvis within six days prior to enrollment until six days after CDDP; (5) presence of symptomatic brain metastasis, diabetes mellitus, and convulsive disorder; (6) patients who are incapable of taking oral agents.

Recruitment, randomization, masking, and follow-up

Recruitment

Eligible patients satisfying the screening inclusion and exclusion criteria will be invited to participate in the study by site investigators.

Randomization

Physicians will introduce the trial to patients. On enrolment and after providing informed consent, Eligible patients will be randomly assigned to receive either DEX on day 1 to 4 or DEX on day 1 with placebo on days 2 to 4 as part of prophylactic antiemetic therapy. Randomization is centrally performed by random allocation modules of electronic data captures (EDC) using the minimization method with balancing prognostic factors for age (< 60 vs ≥ 60 years), sex, CDDP dose level (≥ 70mg/m^2 vs < 70mg/m^2), and institution.

Masking

Patients and clinicians responsible for treatment will be blinded to administration of DEX or placebo. Only an unblinded pharmacist who prepares the study drug, but is not involved in patient care will know the assignment and outcome. All study drugs will be prepared by this pharmacist. As a rule, no data will be disclosed until fixed. However, during the trial period, when it is considered necessary to know the details of the trial drug to ensure participant safety, such as for serious adverse events, the study representative and study secretariat will make an inquiry to and discuss the need for disclosure with the Efficacy and Safety Evaluation Committee. When disclosure is deemed necessary as a result of this consultation, the details will be communicated to the study secretariat, and the details of the trial drug will be disclosed.

Data management, central monitoring, and auditing

The data center is located in the Department of Clinical Trial Data Management, Graduate School of Medicine, Tokyo University, Tokyo, Japan. Enrollment, randomization, data collection, and monitoring will be performed using EDC system Viedoc 4 and Viedoc me (Viedoc Technologies). Data entry to the electronic case report form is performed by investigators using EDC at each site. Patient-Reported Outcomes (PRO) data are collected electronically from patients through an electronic tablet device. No personally identifiable information is entered into the EDC, and the data center does not collect personal information. The central monitoring will be conducted by the data center, and monthly and semi-annually monitoring reports will be disseminated to investigators to inform about the trial progress and discuss data quality-related issues. The Protocol Review Committee and independent Data Monitoring Committee will assess the protocol amendments, serious adverse events reports, and monitoring reports and provide any necessary recommendation to investigators. Auditing will be conducted as necessary in this study.

Harms

Investigators must record all adverse events in the medical records and web systems. The Common Terminology Criteria for Adverse Events (CTCAE, v4.0) will be used to grade each adverse event. In conjunction with the CTCAE to grade adverse events, the Patient Reported Outcomes CTCAE (PRO-CTCAE) will be also administered to

patients for their completion to complement information about subjective symptoms. All adverse events are to be followed up continually during the course of treatment. All severe adverse events must be reported to the Institutional Review Board (IRB) and reported to investigators in all sites and discussed through a mail. Patients who are enrolled into the study will be treated by the health care services that are provided by their health insurance.

Treatment

All patients receive Palo (0.75 mg intravenous infusion on day 1 at 30 min before the start of chemotherapy), NK1-RA (aprepitant 125 mg oral administration on day1 and 80 mg on days 2 and 3, or fosaprepitant 150 mg intravenous infusion on day 1 at 1 hour before the start of chemotherapy), and OLZ (5mg oral administration on days 1 to 4 after dinner). DEX is administered as follows: patients in both arms receive DEX 9.9 mg intravenous infusion on day 1; patients receive DEX 6.6 mg or placebo intravenous infusion on days 2 to 4. When using fosaprepitant, the dose level is increased on days 3 and 4 due to interaction with DEX up to day 2, therefore patients receive an intravenous DEX 13.2 mg or placebo on days 3 and 4. Patients were allowed to take rescue medication throughout the study period for nausea or vomiting, if necessary. The choice of recommended rescue is determined by each investigator from among prochlorperazine, metoclopramide, domperidone, chlorpheniramine, alprazolam, lorazepam, and haloperidol.

Study Endpoints

The primary endpoint is CR rate (no emesis and no rescue medications) during the delayed phase (24 to 120 hours post-CDDP administration). Secondary endpoints are as follows: (1) CR rate during the acute phase (24 hours post-CDDP administration) and the overall phase (120 hours post-CDDP administration); (2) complete control (CC; no emesis, no rescue use, and no significant nausea) rate; (3) total control (TC; no emesis, no rescue use, and no nausea) rate; (4) no emesis rate and no nausea rate in the overall, acute, and delayed phase; (5) time to treatment failure (i.e., time to first emesis or using rescue, whichever occurred first); and (6) severity of nausea during the overall phase. Adverse events.

Outcome Assessments

Figure 1 provides details of the schedule of enrolment, interventions and assessments. Presence of emesis and severity of nausea will be assessed by patients using a 2-point categorical scale and 11-point numerical rating scale (NRS), respectively. Significant nausea is defined as 3 points or greater on the NRS. The use of rescue medications will be assessed by pharmacists.

Adverse events will be evaluated according to the CTCAE v4.0 Japanese Clinical Oncology Group (JCOG) version, and the PRO-CTCAE v1.0. The Japanese version of PRO-CTCAE is linguistically and psychometrically validated,[20-21]. Quality of life (QOL) will be assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) v.3 that is also validated in the Japanese version,[22].

Patients are asked to assess QOL before CDDP administration and on Day 8, with emesis and nausea assessed the PRO-CTCAE every 24 hours until 120 hours after CDDP administration ~~(figure)~~. The data from the PRO-CTCAE are assessed electronically using a tablet device in the hospital setting, except for QOL on Day 8, which is assessed on paper-based questionnaire at home. The PRO-CTCAE data will be not reviewed by the site investigators during the protocol treatment.

Statistical analysis

Sample size calculation is based on an analysis of the primary endpoint. In previous studies with OLZ added to conventional antiemetic treatment for CDDP,[19, 23-24], the delayed phase CR rate ranged from 75% to 85 %, therefore we expect that CR rate in the delayed phase would be 75% in both arms. The non-inferiority margin is set at -15.0%. Two hundred sixty-two patients are required for at least 80 % power to confirm non-inferiority at a one-sided significance level of 2.5 %. After considering the possibility of attrition we set our final required sample size of 280. Point estimates and confidence intervals for the CR rate will be calculated and will be compared between groups by using the Mantel-Haenszel test with adjustment for allocation factors. Interim analysis is not planned.

Patient and public involvement

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

Ethics and dissemination

All patients will be required to provide written informed consent. The study will be performed in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects published by Japan's Ministry of Education, Science, and Technology and the Ministry of Health, Labour, and Welfare and the modified Act on the Protection of Personal Information. The protocol was approved by the IRB at each study site. This trial has been registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000032269. Modifications in the study protocol will be communicated to the IRB at each study site as well as to the protocol review committee. Each Ethics Committee or IRB will revise informed consent materials given to participants and adapt the informed consent according to their own institution's guidelines. The main result will be presented at an international conference and published in an English journal. Authorship will be ascribed in accordance with the International Committee of Medical Journal Editors guidance.

Access to data

Only clinical data managers at the central data center have access to collected data through the EDC system during the study. Site investigators have access to case data within their institutions. After study closure, final dataset and related materials will be archived in UMIN Individual Case Data Repository.

Participating institutions

St. Marianna University School of Medicine Hospital, St. Marianna University Kawasakishi Muncipal Tama Hospital, St. Marianna University Yokohama City Seibu Hospital, Showa University Northern Yokohama Hospital, Yokohama Rosai Hospital, Nippon Medical School Musashi Kosugi Hospital, Aichi Cancer Center Hospital, Gifu University Hospital, Kitasato University Hospital, Shizuoka Cancer Center.

Trial status

This protocol was approved by the Ethics Committee on July 27, 2018. The trial started in October 2018 and 183 subjects were randomized by May 2020. The recruitment is scheduled to be completed in March 2021.

Confidentially

Data will be retained in accordance with the Japanese ethical guidelines for clinical research. Participants will be allocated a unique identification (ID) number at entry. The master list linking participant personal information and ID number will be managed at each institution. Data will be analyzed by ID number only. Records will be retained for 5 years after study completion and then will be destroyed at each institution.

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Authors' contributions

H.M, N.I, T.K, T.M, T.Y and T.EN participated in the design of the study. T.K, T.M and T.Y designed the statistical analysis plan. All authors contributed to writing and revising the manuscript critically, and all gave their final approval of the version to be published.

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Competing interests statement

N.I has received honoraria from Takeda Pharma CO., Ltd, Eli Lilly, Japan, Ono Pharma CO., Ltd, and Daiichi Sankyo Company. Author H.A has received grant from Taiho, Chugai and Nippon Kayaku; personal fees from Novartis, Sanofi, Ono, Kyowa Kirin and Takeda. Author T.Y has received grant and personal fees from ONO

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Figure caption

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

Minatogawa et al, Figure 1

	Enrolment	Enrolment	Post- enrolment							
TIMEPOINT	***-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									
Informed consent	X									
Enrolment		X								
INTERVENTIONS:										
Fosaprepitant (APR) administration			X	(X)	(X)					
PALO administration			X							
OLZ administration			X	X	X	X				
DEX administration			X							
DEX or placebo administration				X	X	X				
ASSESSMENTS:										
Risk factor		X								
PRO-CTCAE			X	X	X	X	X	X		
QOL		X								X
Presence of vomiting			X	X	X	X	X	X		
Nausea (NRS)			X	X	X	X	X	X		
Use of rescue medication			X	X	X	X	X	X		
CTCAE v4.0-JCOG			X	X	X	X	X	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	5
	2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	2-3
	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	17
	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)	11

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	6-8
	6b	Explanation for choice of comparators	6-8
Objectives	7	Specific objectives or hypotheses	9
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)	9
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	9
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)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	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)	12-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-13
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	13-14
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)	SPIRIT figure

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	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10-11
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	11,13-14

	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	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	11
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	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	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)	14
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	14
	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	14
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	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14-15

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)	14-15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14-15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
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	15
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	12
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	14-15
	31b	Authorship eligibility guidelines and any intended use of professional writers	14-15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

*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.

BMJ Open

Study protocol for SPARED trial: Randomized noninferiority phase III trial comparing dexamethasone on day 1 with dexamethasone on day 1-4 combined with neurokinin-1 receptor antagonist, palonosetron, and olanzapine (5 mg) in patients receiving cisplatin-based chemotherapy

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	Therapy
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Palliative care
Keywords:	CHEMOTHERAPY, Adult palliative care < PALLIATIVE CARE, Clinical trials < THERAPEUTICS, Adverse events < THERAPEUTICS

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Title

Study protocol for SPARED trial: Randomized noninferiority phase III trial comparing dexamethasone on day 1 with dexamethasone on day 1–4, combined with neurokinin-1 receptor antagonist, palonosetron, and olanzapine (5 mg) in patients receiving cisplatin-based chemotherapy

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Key words

Nausea, Vomiting, Dexamethasone, Olanzapine, Cisplatin

Word count

3633 words

ABSTRACT

Introduction

Dexamethasone (DEX) is administered for multiple days to prevent chemotherapy-induced nausea and vomiting (CINV) for patients receiving highly emetogenic chemotherapy (HEC); however, its notorious side effects have been widely reported. Although our multicenter randomized double-blind comparative study verified noninferiority of sparing DEX after day 2 of chemotherapy when combined with neurokinin-1 receptor antagonist (NK1-RA) and palonosetron (Palo) for patients receiving HEC regimen, DEX sparing was not non-inferior in patients receiving cisplatin (CDDP)-based HEC regimens in subgroup analysis. Recently, the efficacy of the addition of olanzapine (OLZ) to standard triple antiemetic therapy on HEC has been demonstrated by several phase III trials. This study aims to confirm noninferiority of DEX sparing when it is combined with NK-1RA, Palo, and OLZ in patients receiving CDDP-based HEC regimens.

Methods and analysis

This is a randomized, double-blind, phase III trial. Patients who are scheduled to receive CDDP $\geq$ 50mg/m^2 as initial chemotherapy are eligible. Patients are randomly assigned to receive either DEX on day 1–4 or DEX on day 1 combined with NK1-RA, Palo, and OLZ (5mg). The primary endpoint is complete response (CR) rate, defined as no emesis and no rescue medications during the delayed phase (24 to120 hours post-CDDP administration). The noninferiority margin is set at -15.0%. We assume that CR rates would be 75% in both arms. Two hundred sixty-two patients are required for at least

80% power to confirm noninferiority at a one-sided significance level of 2.5%. After considering the possibility of attrition, we set our final required sample size of 280.

Ethics and dissemination

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

Trial registration number

UMIN000032269

Protocol version

3.0, 24 May 2020.

Strengths and limitations of this study

- This is the first trial to evaluate whether adding olanzapine to neurokinin-1 receptor antagonist, palonosetron (Palo), and dexamethasone (DEX) can spare DEX administration on day 2 to 4 for patients receiving cisplatin-based regimens.
- This study is a multicenter, placebo-controlled, double-blinded, randomized phase III study.
- A limitation of this study is that it was conducted solely within the Japanese population.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is one of the most frequent adverse reactions associated with chemotherapy, and considerably reduces patient quality of life (QOL). CINV has been traditionally assessed in overall (0-120 h post-chemotherapy), acute (0-24 h post-chemotherapy), or delayed (24-120 h post-chemotherapy) phases,[1]. Intravenously administered cytotoxic agents are categorized into four emetic risk groups (high, moderate, low, and minimal),[2]. Highly emetogenic chemotherapy (HEC) including cisplatin (CDDP)-based regimen and anthracycline plus cyclophosphamide (AC) regimen can lead to a > 90 % incidence of emesis in patients without an adequate antiemetic prophylaxis,[3]. When patients were administered prophylactic antiemetics prior to HEC treatment, the incidence of emesis (or requiring additional antiemetics) was found to be 35% according to a recent study.[4].

Dexamethasone (DEX), 5-hydroxytryptamine type 3 receptor antagonists (5-HT3-RA) and neurokinin-1 receptor antagonists (NK1-RA) have been developed to inhibit CINV from HEC,[5-6]. DEX is typically administered for multiple days from the start of chemotherapy to care for delayed CINV,[7];whereas, frequent administration of corticosteroids has been associated with many adverse effects such as insomnia, hyperglycemia and reduced bone mineral density,[8-10]. Therefore, corticosteroid-minimizing (DEX-sparing) strategies, which administer DEX in the acute phase (day 1) and omit DEX in the delayed phase (day 2 and later), have been evaluated,[11]. Our multicenter randomized double-blind comparative study (DEX-1 study) showed the complete response (CR; no emesis, no use of rescue medication) rate

in the overall phase of DEX on day 1 provided a non-inferior antiemetic efficacy to a treatment of DEX on day1-3 when combined with NK1-RA and palonosetron (Palo) for patients receiving HEC including AC and CDDP-based regimen. (44.0 % vs. 46.9 %, P = 0.007),[12]. In a subgroup analysis of patients receiving CDDP-based regimen, CR rates of acute phase demonstrated a noninferiority of DEX on day1 to day 1-3 (95.6 % vs 95.6 %, P = 0.007); whereas, CR rates of the overall and delayed phases DEX on day 1 were lower than those DEX on day 1-3 (57.8 % vs 66.7 %, P = 0.272; 57.8 % vs 68.9 %, P = 0.349, respectively). However, the DEX-1 study was underpowered to evaluate whether multiple days of DEX can be spared for CDDP-based regimens because patients who received the CDDP-based regimen represented only 23% of the total sample population,[13]. Therefore, the plausibility of DEX sparing in CDDP remains inconclusive. Some guidelines still recommend multiple-days DEX in combination with 5-HT3-RA and NK1-RA for CDDP-based regimens,[3, 14-16].

Olanzapine (OLZ) is classified as a multi-acting receptor-targeted antipsychotic and blocks dopamine receptors (D_1, D_2, D_4), 5-HT receptors (5-HT_2A, 5-HT_2C, 5-HT_3), α_1 adrenergic receptors, histamine receptors, and multiple muscarine receptors,[17], which might affect CINV. In the randomized, double-blind, phase III trial involving patients receiving HEC regimens, it was more effective to combine OLZ 10mg than placebo with NK1-RA, 5-HT3-RA, and DEX for the prevention of nausea and vomiting in acute and delayed phases,[4]; however, OLZ (10 mg) had excessive sedation. Therefore, it is difficult to use OLZ 10 mg for all patients in practice setting. Recently, J-FORCE study, which was a randomized, double-blind, placebo-controlled phase III trial evaluating the significance of adding of 5 mg OLZ to NK1-RA, Palo, and DEX in CDDP-based regimens, showed that significantly more patients receiving OLZ achieved

CR from delayed CINV compared with those who received placebo (79 % versus 66%, $P < 0.001$); moreover, no differences were found between two groups in the incidence of sedation,[18]. The addition of OLZ in combination with NK1-RA, Palo, and DEX has greater benefit and becomes a standard antiemetic therapy in patients receiving CDDP-based regimens.

Treatment with OLZ was associated with metabolic effects, including elevated glucose concentrations manifesting as insulin resistance,[19]. A phase III study showed that grade 3 hyperglycemia was observed more frequently in the OLZ versus placebo group,[4]. Therefore, there is a concern that the combination of OLZ and multiple-days DEX may worsen glucose intolerance. In another study, Navari et al. also demonstrated that OLZ, combined with a single dose of DEX and Palo was very effective at controlling acute and delayed phase CINV in patients receiving HEC; moreover, this regimen was not associated with significant hyperglycemia,[20].

Based on these results, we speculate that the antiemetic regimen of OLZ 5mg, NK1-RA, Palo, and a single dose of DEX could be effective and safe for delayed phase CINV in patients receiving CDDP-based regimen. We planned this randomized, double-blind, phase III trial to evaluate the noninferiority of DEX on day1 compared with DEX on day1 to 4 when combined with NK1-RA, Palo, and OLZ in patients receiving CDDP-based regimens.

METHODS AND ANALYSIS

Study design

The Standard Protocol Items for Randomized Trials statement and checklist were followed in preparing the protocol. This multicenter, placebo-controlled, double-blinded, randomized, noninferiority, phase III study aims to confirm the noninferiority of DEX on day 1 compared to DEX on days 1 to 4 combined with NK1-RA, Palo and OLZ 5mg to prevent CINV in patients with solid malignant tumor receiving CDDP-based regimens.

Study setting and participants

Recruiting will be performed in 10 sites across Japan. The inclusion and exclusion criteria are summarized in box 1.

Box.1

Inclusion criteria

I. Patients with malignant tumor, excluding those with hematologic malignancies or those receiving first-line treatment with CDDP $\geq$50mg/m^2 (previous use of moderate or low emetic chemotherapy is permitted).

II. Age: 20–74 years at the time of enrollment.

III. Absence of nausea and vomiting within 24 hours prior to registration.

IV. Eastern Cooperative Oncology Group performance status of 0–1.

V. Meeting the following standard values of general clinical tests within 2 weeks prior to enrollment:

a. alanine aminotransferase < 100 IU/L.

b. aspartate aminotransferase < 100 IU/L.

c. total bilirubin < 2.0 mg/dL.

d. serum creatinine < 1.5 mg/dL.

VI. Patients with an expected prognosis of 3 months or more.

VII. Patients who provided written informed consent.

Exclusion criteria

I. Patients undergoing systemic glucocorticoid therapy.

II. Patients using antiemetics other than the trial drug.

III. Patients receiving moderately emetogenic chemotherapy within 6 days before and after CDDP administration.

IV. Patients who cannot be hospitalized until after 120 hours of starting CDDP administration as the study requires daily use of an electronic patient reported outcome (ePRO) system.

V. Patients receiving radiation therapy for the abdomen or pelvis within 6 days prior to registration until 6 days after CDDP administration.

VI. Patients with diabetes mellitus receiving treatment with insulin and/ or oral hypoglycemic agents or patients with HbA1c (NGSP) >6.5 % (>6.1 % in the event of JDS).

VII. Patients with symptomatic brain metastasis, convulsive disorder requiring treatment with anticonvulsants, and mental illness or psychiatric symptoms that impede activities of daily life.

VIII. Patients who are incapable of taking oral agents.

IX. Patients with a history of allergy to study drugs or similar compounds.

X. Breastfeeding women, pregnant women, or patients not willing to use contraception.

XI. Patients deemed ineligible for the study by the investigator (e.g., patients who are unable to maintain medication adherence or who may experience difficulty using electronic devices).

The main inclusion criterion is patients who are eligible in the study are 20 to 74 years old with malignant tumor, excluding hematological malignancies, receiving first-line treatment with CDDP $\geq$ 50 mg/m^2 (previous use of moderately or low emetogenic chemotherapy is permitted). The main exclusion criteria are as follows: (1) presence of systemic glucocorticoid therapy; (2) patients using antiemetics other than the trial drug; (3) patients receiving moderately emetogenic chemotherapy within 6 days before and after CDDP administration (Minimally to low emetogenic agents are allowed); (4) patients receiving radiation therapy to abdomen or pelvis within 6 days prior to enrollment until 6 days after CDDP; (5) patients with symptomatic brain metastasis, diabetes mellitus, and convulsive disorder; and (6) patients who are incapable of taking oral agents.

Recruitment, randomization, masking, and follow-up

Recruitment

Eligible patients satisfying the screening inclusion and exclusion criteria will be invited to participate in the study by site investigators.

Randomization

Physicians will introduce the trial to patients. On enrollment and after providing informed consent, Eligible patients will be randomly assigned to receive either DEX on day 1 to 4 or DEX on day 1 with placebo on days 2 to 4 as part of prophylactic antiemetic therapy. Randomization is centrally performed by random allocation modules of electronic data captures (EDC) using the minimization method with balancing prognostic factors for age (< 60 vs ≥ 60 years), sex, CDDP dose level (≥ 70mg/m^2 vs < 70mg/m^2), and institution.

Masking

Patients and clinicians responsible for treatment will be blinded to administration of DEX or placebo. Only an unblinded pharmacist who prepares the study drug, but is not involved in patient care will know the assignment and outcome. All study drugs will be prepared by this pharmacist. As a rule, no data will be disclosed until fixed. However, during the trial period, when it is considered necessary to know the details of the trial

drug to ensure participant safety, such as for serious adverse events, the study representative and study secretariat will make an inquiry to and discuss the need for disclosure with the Efficacy and Safety Evaluation Committee. When disclosure is deemed necessary as a result of this consultation, the details will be communicated to the study secretariat, and the details of the trial drug will be disclosed.

Data management, central monitoring, and auditing

The data center is located in the Department of Clinical Trial Data Management, Graduate School of Medicine, Tokyo University, Tokyo, Japan. Enrollment, randomization, data collection, and monitoring will be performed using EDC system Viedoc 4 and Viedoc me (Viedoc Technologies). Data entry to the electronic case report form is performed by investigators using EDC at each site. Patient-Reported Outcomes (PRO) data are collected electronically from patients through an electronic tablet device. No personally identifiable information is entered into the EDC, and the data center does not collect personal information. The central monitoring will be conducted by the data center, and monthly and semi-annually monitoring reports will be disseminated to investigators to inform about the trial progress and discuss data quality-related issues. The protocol review committee and independent Data Monitoring Committee will assess the protocol amendments, serious adverse events reports, and monitoring reports and provide any necessary recommendation to investigators. Auditing will be conducted as necessary in this study.

Harms

Investigators must record all adverse events in the medical records and web systems. The Common Terminology Criteria for Adverse Events (CTCAE, v4.0) will be used to grade each adverse event. In conjunction with the CTCAE to grade adverse events, the Patient Reported Outcomes CTCAE (PRO-CTCAE) will be also administered to patients for their completion to complement information about subjective symptoms. All adverse events are to be followed up continually during the course of treatment. All severe adverse events must be reported to the institutional review board (IRB) and reported to investigators in all sites and discussed through a mail. Patients who are enrolled into the study will be treated by the health care services that are provided by their health insurance.

Treatment

All patients receive Palo (0.75 mg intravenous infusion on day 1 at 30 min before the start of chemotherapy), NK1-RA (aprepitant 125 mg oral administration on day1 and 80 mg on days 2 and 3, or fosaprepitant 150 mg intravenous infusion on day 1 at 1 hour before the start of chemotherapy), and OLZ (5mg oral administration on days 1 to 4 after dinner). DEX is administered as follows: patients in both arms receive DEX 9.9 mg intravenous infusion on day 1; patients receive DEX 6.6 mg or placebo intravenous infusion on days 2 to 4. When using fosaprepitant, the dose level is increased on days 3 and 4 due to interaction with DEX up to day 2, therefore patients receive an intravenous DEX 13.2 mg or placebo on days 3 and 4. Patients were allowed to take rescue

medication throughout the study period for nausea or vomiting, if necessary. The choice of recommended rescue is determined by each investigator from among prochlorperazine, metoclopramide, domperidone, chlorpheniramine, alprazolam, lorazepam, and haloperidol.

Study endpoints

The primary endpoint is CR rate (no emesis and no rescue medications) during the delayed phase (24 to 120 hours post-CDDP administration). Secondary endpoints are as follows: (1) CR rate during the acute phase (24 hours post-CDDP administration) and the overall phase (120 hours post-CDDP administration); (2) complete control (no emesis, no rescue use, and no significant nausea) rate; (3) total control (no emesis, no rescue use, and no nausea) rate; (4) no emesis rate and no nausea rate in the overall, acute, and delayed phase; (5) time to treatment failure (i.e., time to first emesis or using rescue, whichever occurred first); and (6) severity of nausea during the overall phase. Adverse events are associated with antiemetic therapy (CTCAE v4.0 Japanese Clinical Oncology Group [JCOG] version and the PRO-CTCAE v1.0.).

Outcome assessments

Figure 1 provides details of the schedule of enrollment, interventions, and assessments. Presence of emesis and severity of nausea will be assessed by patients using a 2-point categorical scale and 11-point numerical rating scale (NRS), respectively. Significant nausea is defined as 3 points or greater on the NRS. The use of rescue medications will be assessed by pharmacists.

Adverse events will be evaluated according to the CTCAE v4.0 (JCOG) version, and the PRO-CTCAE v1.0. The Japanese version of PRO-CTCAE is linguistically and psychometrically validated,[21-22]. QOL will be assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) v.3 that is also validated in the Japanese version,[23].

Patients are asked to assess QOL before CDDP administration and on day 8, with emesis and nausea assessed the PRO-CTCAE every 24 hours until 120 hours after CDDP administration. The data from the PRO-CTCAE are assessed electronically using a tablet device in the hospital setting, except for QOL on day 8, which is assessed on paper-based questionnaire at home. The PRO-CTCAE data will be not reviewed by the site investigators during the protocol treatment.

Statistical analysis

Sample size calculation is based on an analysis of the primary endpoint. In previous studies with OLZ added to conventional antiemetic treatment for CDDP,[20, 24-25], the delayed phase CR rate ranged from 75% to 85 %, therefore we expect that CR rate in the delayed phase would be 75% in both arms. The noninferiority margin is set at -15.0%. Two hundred sixty-two patients are required for at least 80 % power to confirm noninferiority at a one-sided significance level of 2.5 %. After considering the possibility of attrition we set our final required sample size of 280. Point estimates and confidence intervals for the CR rate will be calculated and will be compared between groups by using the Mantel-Haenszel test with adjustment for allocation factors. Interim analysis is not planned. We will use a full analysis set. It consists of the registered

participant population who received at least a part of the protocol treatment; however, participants who were deemed as ineligible for the study after registration and those who were not administered CDDP-based regimens will be excluded from the analysis set. For the primary analysis, we will impute non-CR for missing primary endpoints.

Patient and public involvement

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

Ethics and dissemination

All patients will be required to provide written informed consent (supplement 1). The study will be performed in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects published by Japan's Ministry of Education, Science, and Technology and the Ministry of Health, Labour, and Welfare and the modified Act on the Protection of Personal Information. The protocol was approved by the IRB at each study site. This trial has been registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000032269. Modifications in the study protocol will be communicated to the IRB at each study site as well as to the protocol review committee. Each Ethics Committee or IRB will revise informed consent materials given to participants and adapt the informed consent according to their own institution's guidelines. The main result will be presented at an international conference and

published in an English journal. Authorship will be ascribed in accordance with the International Committee of Medical Journal Editors guidance.

Access to data

Only clinical data managers at the central data center have access to collected data through the EDC system during the study. Site investigators have access to case data within their institutions. After study closure, final dataset and related materials will be archived in UMIN Individual Case Data Repository.

Participating institutions

St. Marianna University School of Medicine Hospital, St. Marianna University Kawasakishi Muncipal Tama Hospital, St. Marianna University Yokohama City Seibu Hospital, Showa University Northern Yokohama Hospital, Yokohama Rosai Hospital, Nippon Medical School Musashi Kosugi Hospital, Aichi Cancer Center Hospital, Gifu University Hospital, Kitasato University Hospital, Shizuoka Cancer Center.

Trial status

This protocol was approved by the Ethics Committee (approval ID 4035) of St. Marianna University School of Medicine on July 27, 2018. The trial started in October 2018 and 183 subjects were randomized by May 2020. The recruitment is scheduled to be completed in March 2021.

Confidentiality

Data will be retained in accordance with the Japanese ethical guidelines for clinical research. Participants will be allocated a unique identification (ID) number at entry. The master list linking participant personal information and ID number will be managed at each institution. Data will be analyzed by ID number only. Records will be retained for 5 years after study completion and then will be destroyed at each institution.

Acknowledgments

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Authors' contributions

HM, NI and T.EN contributed to the trial conception and are the principal investigators. HM, NI, TK, TM, TY, and T.EN participated in the design of the study. TY played a primary role in designing statistical analysis. TK and TM played a primary role in designing the data management approach. HM, NI, KS, KH, HI, YO, YI, HA, HM, NH, MS, CK, SN, HI, AT, and TT have carried out recruitment and collected the data. Data analysis and interpretation will be conducted by HM, NI, TK, TM, TY, and T.EN. HM and NI wrote the first draft of the manuscript. All authors have read, approved the paper and meet the criteria for authorship as established by the International Committee of Medical Journals Editors.

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Competing interests

Author N.I has received honoraria from Takeda Pharma CO., Ltd, Eli Lilly, Japan, Ono Pharma CO., Ltd, and Daiichi Sankyo Company. Author H.A has received grant from Taiho, Chugai and Nippon Kayaku; personal fees from Novartis, Sanofi, Ono, Kyowa Kirin and Takeda. Author T.Y has received grant and personal fees from ONO PHARMACEUTICAL CO., LTD.Author. T.EN has received grant and personal fee from Taiho Pharmaceutical Co., Chugai Pharmaceutical Co., Takeda Pharmaceutical Co., Sanofi K.K., Daiichi Sankyo Co., Eli Lilly Japan K.K., Nippon Kayaku Co., Ono Pharmaceutical Co. and MSD K.K.; personal fees from Mochida Pharmaceutical, Celltrion Healthcare Japan, Merck Serono Co., Sawai Pharmaceutical Co., Bayer Yakuhin, Bristol-Myers Squibb, Teijin Pharma, Pfizer Japan Inc., Novartis Japan, Yakult Honsha Co. and Nipro Co; grant from Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Eisai Co and Solasia Pharma K.K.. The other authors have declared no conflicts of interest.

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519 Figure caption

520 Figure 1. The schedule of enrollment, interventions and assessments.

Minatogawa et al, Figure 1

	Enrolment	Enrolment	Post- enrolment							
TIMEPOINT	***-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									
Informed consent	X									
Enrolment		X								
INTERVENTIONS:										
Fosaprepitant (APR) administration			X	(X)	(X)					
PALO administration			X							
OLZ administration			X	X	X	X				
DEX administration			X							
DEX or placebo administration				X	X	X				
ASSESSMENTS:										
Risk factor		X								
PRO-CTCAE			X	X	X	X	X	X		
QOL		X								X
Presence of vomiting			X	X	X	X	X	X		
Nausea (NRS)			X	X	X	X	X	X		
Use of rescue medication			X	X	X	X	X	X		
CTCAE v4.0-JCOG			X	X	X	X	X	X		

Consent Form

St. Marianna University School of Medicine Hospital

Dear Hospital Director:

Title of the study: Randomized noninferiority phase III trial comparing dexamethasone on day 1 with dexamethasone on day 1-4 combined with neurokinin-1 receptor antagonist, palonosetron, and olanzapine (5 mg) in patients receiving cisplatin-based chemotherapy

Description

1. Introduction about clinical trials.
2. The purpose of this study.
3. The method of this study.
4. The expected duration of participation in this study.
5. The expected number of participants in this study.
6. The expected effects of the medication under investigation and the possible side effects.
7. If you do not use this medication, other treatment options are available.
8. Participation in this study is voluntary.
9. If you agree to participate in the study, it requires observation of your first 5 days of chemotherapy.
10. Potential harmful effects to your health, which may occur during this study.
11. The chance that we may stop using this medication.
12. If you participate in this study, your medical records and other information may be examined during and after this study.
13. Your identity will not be revealed if the results of this study are made public.
14. We will keep you informed regarding this medication.
15. Your cost burden.
16. Information regarding the bioethics committee.
17. The institution participating in the study.
18. Information about your physician and consultation.

[Patient's signature line]

I have been fully informed of the above information, have received the letter of consent, and fully understand the details of this study. I voluntarily consent to participate in this study.

Date of consent: _____

Patient's name: (Signed)_____

[Physician's signature line]

I have fully briefed the patient on this clinical trial.

Date of presentation: _____

Affiliation: _____

Name: (Signed)_____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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	5
	2b	All items from the World Health Organization Trial Registration Data Set	17
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 19
	5b	Name and contact information for the trial sponsor	3
	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	20
	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)	13

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	6-8
	6b	Explanation for choice of comparators	6-8
Objectives	7	Specific objectives or hypotheses	8
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)	9
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	9,18
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)	9-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-15
	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)	12-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14-15
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	15-16
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)	15, figure 1

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	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	18
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	12
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	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12-13
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	15-16

	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	13
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	13
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	16-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
	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)	16-17
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	13
	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	13
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	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17

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)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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	18
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	14
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	17-18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	17, supplement 1
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	NA

*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.