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STUDY PROTOCOL

Study protocol for a multi-institutional, randomised, double-blinded, placebo-controlled phase Ⅲ trial investigating additive efficacy of duloxetine for neuropathic cancer pain refractory to opioids and gabapentinoids: the DIRECT study

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Abstract

Introduction: Management of cancer patients suffering from neuropathic pain refractory to opioids and gabapentinoids remains an important challenge. Duloxetine is one of the choices after first-line treatment fails. The efficacy of duloxetine has been reported in non-cancer patients and in chemotherapy-induced peripheral neuropathy, but no randomised clinical trials have examined its effects on neuropathic cancer pain refractory to first-line treatment. The objective of this study is to assess the analgesic efficacy of duloxetine in patients suffering from neuropathic cancer pain refractory to opioids and gabapentinoids.

Methods and analysis: A multi-institutional, prospective, randomised, double-blind, placebo-controlled, two-parallel trial is planned. The inclusion criteria are adult cancer patients suffering from neuropathic cancer pain refractory to opioids and gabapentinoids, patients with a numerical rating scale (NRS) pain score of 4 or higher, and patients with a total Hospital Anxiety and Depression Scale (HADS) score of less than 20. Patients with chemotherapy-induced peripheral neuropathy are excluded. The study will take place at 14 sites across Japan. Participants will be randomised (1:1 allocation ratio) to a duloxetine intervention group or a placebo control group. Evaluations will be made at baseline (T0 randomisation), day 0 (T1), day 3 (T2), and day 10 (T3). The primary endpoint is defined as the difference in NRS score for pain intensity (average over the previous 24 hours) at T3 between the duloxetine and placebo groups. A sample size of 70 patients will be examined between July 2015 and March 2018.

Ethics and Dissemination: Ethics approval was obtained at all participating sites. The results of this study will be submitted for publication in international peer-reviewed journals and the key findings presented at international scientific conferences.

Trial registration number: UMIN000017647 Date of registration: 22 July 2015. Protocol version: 2.2, 26 April 2017.

Keywords Duloxetine, Randomised controlled trial, Neuropathic cancer pain, Palliative care.

Strengths and limitation of this study

■This is the first study to assess the analgesic efficacy of duloxetine in patients suffering from neuropathic cancer pain refractory to opioids and gabapentinoids, and the results of the trial will clarify the second-line standard treatment for cancer-related neuropathic cancer pain.

■This is an adequately powered study to provide a clinically meaningful outcome, and adverse effects following interventions will be systematically evaluated.

■We excluded patients with depression from the study population for accurate evaluation of the pharmacological effects of duloxetine on pain.

■This study include the heterogeneity of causes of neuropathic cancer pain.

■The primary endpoint is not worst pain intensity in the last 24 hours but the difference in average pain intensity score at T3 (day 10) between two groups.

Introduction

Pain is a symptom that is experienced by many patients with cancer. Prevalence at the time of diagnosis is 30%, and this increases to 90% in advanced stages [1,2]. Pain in cancer patients is often classified as nociceptive pain or neuropathic pain, but both types are thought to be intermixed. Of patients with cancer-related pain, 33% have neuropathic pain (NP) [1]. In general, NP is often resistant to treatment, whereas nociceptive pain tends to respond well to treatment [2-5].

The efficacy of many drugs for NP has been reported in non-cancer patients, and some have been shown to be effective for NP in cancer patients [6]. These drugs include opioids, tricyclic antidepressants (TCAs), and gabapentinoids (gabapentin and pregabalin) [7-11]. In cancer patients, the efficacy of TCAs and gabapentinoids has been proven in clinical trials [12, 13], and a phase III study revealed moderate analgesic effects of gabapentin in combination with opioids [14]. However, it is unclear which drug is most effective in cases in which first-line treatment with gabapentinoids fails to alleviate NP in cancer patients.

In treatment of non-cancer NP, the efficacy of addition of duloxetine to pregabalin has been shown in a phase III study [15]. There is, however, no empirical data for second-line treatment of NP in cancer patients. The National Comprehensive Cancer Network (NCCN) guidelines list duloxetine as a potential choice for second-line treatment [8], and a phase III study showed the efficacy of duloxetine in treatment of chemotherapy-induced peripheral neuropathy (CIPN) in cancer patients [16]. Furthermore, a small retrospective study reported the beneficial effects of duloxetine in palliation of NP refractory to pregabalin and opioids in 15 cancer patients [17]. In the double-blind randomised placebo-controlled study described here, we will evaluate the efficacy of addition of duloxetine for neuropathic cancer pain refractory to opioids and gabapentinoids. Currently there is no specific standard treatment for neuropathic pain in cancer patients, placebo is used instead of active control. The results of

the trial will clarify the second-line standard treatment for cancer-related NP.

Methods and analysis

Study design

The SPIRIT (Standard Protocol Items for Randomised Trials) statement and its checklist were followed in preparing the protocol. The study design is summarized in Figure 1. A multicentre, prospective, randomised, placebo-controlled, double-blinded, two-parallel group study will be performed to compare the efficacy of addition of duloxetine (intervention group) with the efficacy of addition of a placebo (control group).

Study Settings and Participants

Recruiting will be performed in 14 adult palliative care sites across Japan, with involvement of 10 palliative care teams and 4 palliative care units. The inclusion and exclusion criteria are summarized in box 1. The main inclusion criterion is patients suffering from cancer pain (neuropathic or mixed) refractory to opioids and gabapentinoids. Diagnosis of NP is based on the International Association for the Study of Pain (IASP) algorithm, in which a diagnosis of NP is made for patients with (1) pain with a distinct neuroanatomically plausible distribution; (2) a history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system; (3) a range of pain that is neuroanatomically plausible and symptoms suggesting somatosensory injury or neurological disease (i.e., hyperalgesia, hypoalgesia, dysesthesia, or allodynia along the dermatome); and (4) relevant objective or imaging findings suggesting nervous system injury or disease (i.e., imaging findings showing that a lesion is present). Based on these criteria, the certainty of the presence of NP is grades as definite NP (1 to 4 present) and probable NP (1 and 2, plus 3 or 4) [18]. Definite and probable NP will be considered to indicate NP and patients with these

conditions will be eligible as subjects. Patients with an average numerical rating scale (NRS) pain score in the preceding 24-hour period of 4 or higher [19] and those with total Hospital Anxiety and Depression Scale (HADS) scores of less than 20 will be included, based on criteria for pain intensity used in similar studies on NP [20]. The exclusion criteria are patients with progressive paralysis, a known contraindication to use of duloxetine, or depression. To examine the effects of duloxetine, we believe it is necessary to exclude patients with depression because duloxetine may alleviate pain through improving depression. Patients with CIPN or impaired cognitive function will also be excluded.

Recruitment, randomisation, 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.

Randomisation

Physicians will introduce the trial to patients. Upon enrollment and after providing informed consent, patients will be randomly allocated to intervention (duloxetine) or control (placebo) groups in a web-based central randomisation system using minimisation methods and a computer-generated randomisation schedule with a 1:1 allocation ratio. In performing this allocation, we will minimise the following adjustment factors to avoid a large bias: (1) average pain intensity measured by the NRS in the last 24 h (≤7, ≥8), (2) type of pain (spinal cord infiltration or others), (3) HADS total score (≤10, ≥11), (4) treatment setting (inpatient or outpatient), (5) response to gabapentinoids (non-responsive or intolerance due to side effects), and (6) study site.

Masking

Patients and clinicians responsible for treatment will be blinded to administration of duloxetine or placebo. Only a clinical trial pharmacist who generate capsules, but is not involved in patient care, will know the allocation and outcomes. All study drugs will be packaged by this pharmacist. Duloxetine (Cymbalta®) will be administered with a change in dosage form: the capsules will be covered with a No. 3 capsule of the same material to make an overcapsule.

Data management, central monitoring, and audit

Evaluations will be performed at four time points: baseline (time of randomisation, T0), the day before the start of treatment (day 0, T1), and 3 days (day 3, T2) and 10 days (day 10, T3) after initiation of treatment. The timing and details of evaluations are given in Table 1.

Once a patient is enrolled or randomised, the study site will make every reasonable effort to follow the patient for the entire study period. Patients will not be allowed to cross over from one group to another group until the end of the study (T3), however, they can choose to leave the study for any reasons at any time without detriment to the provision or quality of their clinical care. The investigators at each study sites will maintain individual records for each patient as source data, which include a copy of informed consent, medical records, laboratory data and other records or notes. All data will be collected by the independent data management centre. The data management centre will oversee the intra-study data sharing process. The clinical data entry, data management and central monitoring will be performed using the electric data capture VIEDOC 3 (PCG Solutions, Sweden). An interim analysis will not be performed. Also auditing is not planned in this study.

Harms

Investigators must record all adverse events (AEs) in the medical records and web systems. The National Cancer Institute's CTCAE (Ver.4.0) will be used to grade each adverse event (AE). All AEs are to be followed up continually during their course up. All severe adverse events (SAEs) must be reported to Institutional Review Board (IRB) and investigators in all sites, and discussed through a FAX. Patients that are enrolled into the study will be treated by health care services provided by health insurance.

Measurement tools

Numerical Rating Scale (NRS)

The 11-point NRS will be used to measure pain intensity from 0 (no pain) to 10 (worst possible pain), based on average pain in the past 24 hours [21].

Pain Relief Scale

A self-assessment will be performed by the patients using the Pain Relief Scale. Patients will determine for themselves the efficacy of analgesics using a four-point scale of complete relief, a lot of relief, slight relief, and no change.

Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2, Japanese version)

The SF-MPQ-2 will be used to examine differences in effects due to pain mechanisms. The reliability and validity of the Japanese version have been verified [22].

European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL

EORTC QLQ-C15-PAL will be used for evaluation of patient QOL. The reliability and validity of the Japanese version have been confirmed [23].

Hospital Anxiety and Depression Scale (HADS)

The HADS will be used for measurement of psychiatric symptoms (anxiety and depression) of patients with a physical disease. HADS is a screening tool that allows assessment based on a small number of items. Its reliability and validity have been verified internationally [24, 25]. A HADS score <20 points as a cutoff for exclusion of cancer patients with severe depression will be used, based on a previous report [25].

Pain Catastrophizing Scale (PCS)

The severity of cancer-related pain is influenced by engagement of patients in catastrophic thinking, such as "my pain will undoubtedly never improve" [26]. This effect will be measured using the Japanese version of the PCS, for which the validity and reliability have been shown [27].

Common Terminology Criteria for Adverse Events (CTCAE)

The worst grade of an adverse event during the preceding period will be assessed using the CTCAE v.4.0, Japanese Clinical Oncology Group (JCOG) version. Five adverse events of somnolence, dizziness, nausea, palpitations, and hypertension will be investigated if they occur at a relatively high frequency. Other adverse events may also be assessed.

Performance Status (PS)

The European Cooperative Oncology Group (ECOG) PS system will be used for evaluation of PS by primary physicians [28].

Treatment

Pre-intervention treatment

Opioids (morphine, oxycodone, fentanyl, tapentadol) will be given to all patients. If AEs of gabapentinoids are severe, they will be discontinued or reduced in dose, but if the adverse effects are tolerable but the therapeutic effect is insufficient, gabapentinoids will be administered concomitantly with duloxetine. Pregabalin and gabapentin will be used in the study at the established effective doses of 300 mg and 1800 mg, respectively [14, 29].

Interventions

Duloxetine or placebo will be administered for 10 days. Duloxetine (20 mg/day, one capsule) will be taken orally by participants in the intervention group starting after breakfast on Day 1. To determine if titration is necessary, pain relief will be evaluated using the Pain Relief Scale on Day 3 (T2). Changes in symptoms, adverse events, and medication compliance will be evaluated. Patients who have "complete relief" or "a lot of relief" of pain will continue to receive doses of 20 mg/day from Day 4. In all other cases, the dose will be increased to 40 mg/day (two capsules) from Day 4. If an intolerable AE such as nausea occurs at 40 mg/day, the dose will be reduced as required. If an intolerable AE occurs at 20 mg/day, the protocol will be discontinued. AEs that may be caused by duloxetine, such as somnolence, dizziness, nausea, palpitations, and hypertension, will be evaluated to determine whether duloxetine treatment should be interrupted.

Placebo (22.4 mg lactose in a No. 4 capsule) will be administered to participants in the control group by oral administration (one capsule/day) starting after breakfast on Day 1. To determine if titration is necessary, pain relief will be evaluated using the Pain Relief Scale on Day 3 (T2), and changes in symptoms, AEs, and medication compliance will be examined. Patients with "complete relief" or "a lot of relief" of pain will continue to receive one capsule/day from Day 4. In all other cases, the dose will be increased to 2 capsules/day from Day 4. If an intolerable AE such as nausea occurs at 2 capsules/day, the dose will be reduced

as side effects dictate. If there is an intolerable AE at one capsule/day, the protocol will be discontinued. To improve adherence to intervention protocols, participants will return the unused tablets at the last visit, and unused tablets will be counted and recorded on the medical records. Currently there is no specific standard treatment for neuropathic pain in cancer patients, placebo is used instead of active control.

Cotreatments

Concomitantly administered analgesics such as opioids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or other adjuvant analgesics such as anticonvulsants, antidepressants, antiarrhythmics, N-methyl-D-aspartate (NMDA) receptor antagonists, and steroids will not be changed during the follow-up period. In principle, new analgesics will not be started. When nausea occurs during the period of duloxetine administration, use of an antiemetic will be permitted. Currently used immediate-release opioids will be used in cases of breakthrough pain. Immediate-release rescue opioids will be freely permitted without limitation on the number of doses.

Study endpoints

Primary endpoint

The primary endpoint is a comparison of pain intensity (average pain over the previous 24 hours) at T3 (Day 10) measured using the NRS in the duloxetine and placebo groups.

Secondary endpoints

Efficacy will also be assessed using seven secondary endpoints: the nature of pain using the SF-MPQ-2, EORTC QLQ-C15-PAL scores, daily opioid dose, changes in HADS score, degree of catastrophic thinking on the PCS, adverse events (CTCAE v.4.0-JCOG), and the

difference in NRS scores for pain intensity (average over the previous 24 hours) measured at T3 in subgroups of patients who are unresponsive or intolerant to gabapentinoids. Subgroup analyses will be performed on two patients groups; patients unresponsive to gabapentinoids and patients intolerant to gabapentinoids.

Statistical considerations

Statistical hypothesis

Comparison of the primary endpoint of the NRS score for pain at Day 10 (T3) (average pain over the previous 24-hour period) between the duloxetine and placebo groups will be conducted using a one-sided t-test at a significance level of 5% according to the intention-to-treat (ITT) principle. Point estimates and 90% confidence intervals for the difference between two group means will be calculated.

The secondary endpoints of efficacy (SF-MPQ-2, EORTC QLQ-C15-PAL, HADS, PCS, daily opioid dose, and group comparison of average pain on the NRS in the previous 24 hours in patients who are unresponsive or intolerant to gabapentinoids) will be evaluated similarly to the primary endpoint. The distribution of grades of adverse events (CTCAE v.4.0-JCOG) and the incidence of adverse events of Grade 3 or higher and of Grade 4 or higher will be determined. A Mantel test will be performed for group comparison.

Sample size calculation

The difference between group mean NRS scores for pain in the previous 24 hours on Day 10 (T3) is assumed to be one point and the standard deviation of the NRS is taken to be 1.5 points. Assuming a rate of exclusion of 10 percent, 35 subjects are needed in each group (70 subjects in total) to achieve a statistical power of 80% with a one-sided significance level of 5%.

Ethical issues

All patients will be required to provide written informed consent. The study will be performed in accordance with the Declaration of Helsinki and the Japanese ethical guidelines for clinical research. The protocol was approved by the Institutional Review Board at each study site. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000017647. Modifications in the study protocol will be communicated to the Institutional Review Board at each study site as well as the Independent Data Monitoring Committee**.** Each Ethics Committee or Institutional Review Board will revise informed consent materials given to participants and adapt according to their own institution's guidelines.

Discussion

To our knowledge, there has been no randomised study of the analgesic efficacy of duloxetine in patients with neuropathic cancer pain refractory to opioids and gabapentinoids. In our planned trial, we will use a randomised, double-blind, placebo-controlled design, which is the most appropriate design to demonstrate the efficacy of a new therapy. Our findings using this approach may also allow international recommendations to be updated. We also considered a crossover design, but a parallel design was finally chosen, given that the crossover design has several limitations [30]. The crossover design is suitable for patients in a stable condition, but this is not the situation for cancer patients with neuropathic pain (NP) refractory to opioids and gabapentinoids. We also believe that the treatment might have carryover effects and alter the response to subsequent treatments, and that patients may not be in a comparable condition at the start of each treatment period in a crossover trial.

Several issues related to the content of the trial require discussion. There are three major

concerns: (i) the heterogeneity of causes of NP, (ii) the choice of the primary endpoint, and (iii) the role of depression. To address the heterogeneous causes of NP, we excluded patients with CIPN, but the trial might still be criticized due to combination of peripheral and central NP in one study. Narrower criteria are theoretically possible, but accrual of patients who meet these criteria is likely to be difficult. We thus decided to include both peripheral and central NP in the study, and subgroup analyses will be performed. Second, the primary endpoint is the difference in average pain intensity score at T3 (day 10) between two groups. Although we had acknowledged that some authors recommend worst pain intensity in the last 24 hours as primary end-points because it satisfies most key recommendations in the draft guidance by the FDA [31], average pain intensity is adopted by many clinical trials about NP [32], including only one placebo-controlled RCT in cancer patients with NP [14]. Furthermore, to evaluate chronic pain, especially taking into account the nature of NP in this setting, we concluded that it is better to use the "average pain intensity in the last 24 hours" as the primary endpoint after discussion among the members of the steering committee. Finally, since depression affects the assessment of pain, we excluded patients with depression from the study population for accurate evaluation of the pharmacological effects of duloxetine on pain. Therefore, the planned placebo-controlled double-blind multicentre RCT will be the first to evaluate the efficacy of pharmacological treatment on well-defined NP in patients with cancer.

Trial status

At the time of manuscript submission (April 2017), the status of the trial is 'ongoing'.

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 maintained in a separate locked cabinet and password-protected hard drive at each institution. Data will be analysed by ID number only. Records will be retained for 5 years after study completion and then destroyed by the data center.

Dissemination

The results of this study will be submitted for publication in international peer-reviewed journals and the key findings presented at conferences. Participants will be informed of the results of the trial by the investigators. Authorship will be ascribed in accordance with the International Committee of Medical Journal Editors guidance.

Data Sharing Statement

The data obtained in this study can only be accessed if approved by Japanese Organisation for Research and Treatment of Cancer (JORTC) Protocol Review Committee or Independent Data Monitoring Committee.

Access to data

JORTC Data Center and JORTC Independent Data Monitoring Committee have access to the final trial dataset. There is no contractual agreement regarding investigators' access restrictions on dataset.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Institutional Review Board at each study site. Informed

consent for participation in the trial will be obtained from all patients.

Competing interests

The authors declare that they have no competing interests.

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Sponsor detail

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Abbreviations

NRS: Numerical Rating Scale; NP: Neuropathic pain; TCA: Tricyclic Antidepressant; NCCN: National Comprehensive Cancer Network; CIPN: Chemotherapy-Induced Peripheral

Neuropathy; IASP: International Association for the Study of Pain; HADS: Hospital Anxiety and Depression Scale; PS: Performance Status; PRS: Pain Relief Scale; ECOG: European Cooperative Oncology Group; SF-MPQ: Short-Form McGill Pain Questionnaire; EORTC: European Organization for Research and Treatment; CTCAE: Common Terminology Criteria for Adverse Events; JCOG: Japan Clinical Oncology Group; PCS: Pain Catastrophizing Scale; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NMDA: N-methyl-D-aspartate; JORTC: Japanese Organization for Research and Treatment of Cancer

Authors' contributions

HM, HI, SI, AK, YK, TM, YM, TM, KA, participated in the design of the study. TY, TK, 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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Figure Legends

Figure 1. Flow chart of the procedures in the study. Participants will be randomized (1:1 allocation ratio) into the duloxetine intervention group or the placebo control group. Evaluations will be made at baseline (T0 randomization), and on day 0 (T1), day 3 (T2), and day 10 (T3).

Box 1. Inclusion and exclusion criteria

Inclusion Criteria
• Inpatients and outpatients with diagnoses of cancer and neuropathic pain • Currently receiving opioids • Unresponsive or intolerant to gabapentinoids: a) receiving doses of pregabalin of 300 mg/day or higher or gabapentin of 1800 mg/day or higher; b) cannot receive increased doses of pregabalin or gabapentin due to side effects • NRS pain score of 4 or higher • HADS score <20 • Age 20 years or older • Creatinine clearance rate (Ccr) ≥30 mL/min (Cockcroft-Gault formula) • Serum aspartate aminotransferase (AST) <100 IU/L, alanine aminotransferase (ALT) <100 IU/L, and total bilirubin (T-bil) <2.0 mg/dL • Expected survival of one month or longer
Exclusion Criteria
• Chemotherapy-induced peripheral neuropathy • Progressive paralytic symptoms • Contraindication for duloxetine • Taking any type of antidepressants • A change in steroids, opioids, antidepressants, anticonvulsants, antipsychotic drugs, antiarrhythmic agents, or N-methyl-D-aspartate (NMDA) receptor antagonists within two days of initiation of administration of the study drug. Cases in which the patient has taken a hypnotic (including benzodiazepines such as zolpidem, zopiclone, eszopiclone, triazolam, ramelteon, suvorexant, brotizolam, flunitrazepam, rilmazafone, and etizolam) as needed are not included. • Drug abusers or patients who are addicted to drugs or have a history of addiction • Patients with psychiatric disorders such as cognitive impairment who are unable to communicate • Patients who are pregnant, breastfeeding, or may possibly be pregnant • Other patients who are determined to be inappropriate for participation in the study by the clinical investigator.

Table 1. Study procedure and time points for actions and evaluations

	T0 Inclusion	T1 Day 0	T2 Day 3	T3 Day 10
Consent, Randomization	○	—	—	—
NRS for pain	○	○	○	○
Pain Relief Scale	—	—	○	—
SF-MPQ-2	—	○	—	—
Opioid consumption	—	○	○	○
EORTC-QLQ-C15 Pal	—	○	—	○
HADS	○	—	—	○
Pain Catastrophizing Scale	—	○	—	—
ECOG PS	○	○	—	○
Adverse events	—	○	○	○

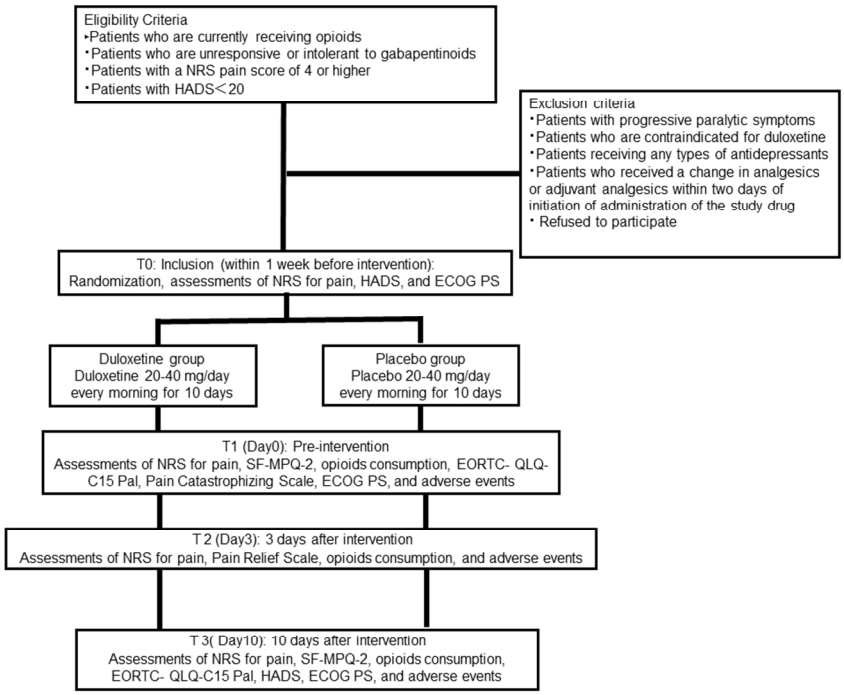

Fig.1. Flow chart of the procedures in the study

300x225mm (96 x 96 DPI)

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	4
	2b	All items from the World Health Organization Trial Registration Data Set	※ 1
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	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	Not applicable
	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)	※ 1
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
	6b	Explanation for choice of comparators	13
Objectives	7	Specific objectives or hypotheses	6
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)	6
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	7
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)	7, Box1
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)	12-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	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)	9, Table1

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	14-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8,9
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	8
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	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9
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	10
	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	※ 2
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)	※ 3
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	※ 1
	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	9
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	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)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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	17
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	10
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	※4
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not planned
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15
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	Not applicable

*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.

※1 : Not stated in the protocol paper due to word limits.

※2 : There is a statement in the data management plan, however not stated in the protocol paper due to word limits.

※3 : There is a statement in the statistical analyses plan (definition of analysis population relating to protocol non-adherence, and any statistical methods to handle missing data) however not stated in the protocol paper due to word limits.

※4 : There is a statement in the Informed consent form, however, not stated in the protocol paper due to word limits.

BMJ Open

Study protocol for a multi-institutional, randomised, double-blinded, placebo-controlled phase Ⅲ trial investigating additive efficacy of duloxetine for neuropathic cancer pain refractory to opioids and gabapentinoids: the DIRECT study

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Primary Subject Heading:	Palliative care
Secondary Subject Heading:	Palliative care
Keywords:	Adult palliative care < PALLIATIVE CARE, Cancer pain < ONCOLOGY, PAIN MANAGEMENT

STUDY PROTOCOL

Study protocol for a multi-institutional, randomised, double-blinded, placebo-controlled phase Ⅲ trial investigating additive efficacy of duloxetine for neuropathic cancer pain refractory to opioids and gabapentinoids: the DIRECT study

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Abstract

Introduction: Management of cancer patients suffering from neuropathic pain refractory to opioids and gabapentinoids remains an important challenge. Duloxetine is one of the choices after first-line treatment fails. The efficacy of duloxetine has been reported in non-cancer patients and in chemotherapy-induced peripheral neuropathy, but no randomised clinical trials have examined its effects on neuropathic cancer pain refractory to first-line treatment. The objective of this study is to assess the analgesic efficacy of duloxetine in patients suffering from neuropathic cancer pain refractory to opioids and gabapentinoids.

Methods and analysis: A multi-institutional, prospective, randomised, double-blind, placebo-controlled, two-parallel trial is planned. The inclusion criteria are adult cancer patients suffering from neuropathic cancer pain refractory to opioids and gabapentinoids, patients with a numerical rating scale (NRS) pain score of 4 or higher, and patients with a total Hospital Anxiety and Depression Scale (HADS) score of less than 20. Patients with chemotherapy-induced peripheral neuropathy are excluded. The study will take place at 14 sites across Japan. Participants will be randomised (1:1 allocation ratio) to a duloxetine intervention group or a placebo control group. Evaluations will be made at baseline (T0 randomisation), day 0 (T1), day 3 (T2), and day 10 (T3). The primary endpoint is defined as the difference in NRS score for pain intensity (average over the previous 24 hours) at T3 between the duloxetine and placebo groups. A sample size of 70 patients will be examined between July 2015 and March 2018.

Ethics and Dissemination: Ethics approval was obtained at all participating sites. The results of this study will be submitted for publication in international peer-reviewed journals and the key findings presented at international scientific conferences.

Trial registration number: UMIN000017647 Date of registration: 22 July 2015. Protocol version: 2.2, 26 April 2017.

Keywords Duloxetine, Randomised controlled trial, Neuropathic cancer pain, Palliative care.

Strengths and limitation of this study

■This is the first study to assess the analgesic efficacy of duloxetine in patients suffering from neuropathic cancer pain refractory to opioids and gabapentinoids, and the results of the trial will clarify the second-line standard treatment for cancer-related neuropathic cancer pain.

■This is an adequately powered study to provide a clinically meaningful outcome, and adverse effects following interventions will be systematically evaluated.

■We excluded patients with depression from the study population for accurate evaluation of the pharmacological effects of duloxetine on pain.

■This study include the heterogeneity of causes of neuropathic cancer pain.

■The primary endpoint is not worst pain intensity in the last 24 hours but the difference in average pain intensity score at T3 (day 10) between two groups.

Introduction

Pain is a symptom that is experienced by many patients with cancer. Prevalence at the time of diagnosis is 30%, and this increases to 90% in advanced stages [1,2]. Pain in cancer patients is often classified as nociceptive pain or neuropathic pain, but both types are thought to be intermixed. Of patients with cancer-related pain, 33% have neuropathic pain (NP) [1]. In general, NP is often resistant to treatment, whereas nociceptive pain tends to respond well to treatment [2-5].

The efficacy of many drugs for NP has been reported in non-cancer patients, and some have been shown to be effective for NP in cancer patients [6]. These drugs include opioids, tricyclic antidepressants (TCAs), and gabapentinoids (gabapentin and pregabalin) [7-11].

In cancer patients, the efficacy of TCAs and gabapentinoids has been proven in clinical trials [12, 13], and a phase III study revealed moderate analgesic effects of gabapentin in combination with opioids [14]. However, it is unclear which drug is most effective in cases in which first-line treatment with gabapentinoids fails to alleviate NP in cancer patients.

In treatment of non-cancer NP, the efficacy of addition of duloxetine to pregabalin has been shown in a phase III study [15]. There is, however, no empirical data for second-line treatment of NP in cancer patients. The National Comprehensive Cancer Network (NCCN) guidelines list duloxetine as a potential choice for second-line treatment [8], and a phase III study showed the efficacy of duloxetine in treatment of chemotherapy-induced peripheral neuropathy (CIPN) in cancer patients [16]. Furthermore, a small retrospective study reported the beneficial effects of duloxetine in palliation of NP refractory to pregabalin and opioids in 15 cancer patients [17]. On the other hands, duloxetine has the potential for adverse events such as dry mouth, sweating, fatigue, nausea, constipation, loss of appetite, dizziness, diarrhea, hot flashes, hypertension, hyperhidrosis, palpitations, insomnia, and drug-drug interactions as well as a risk of serotonergic syndrome and therefore should be used carefully

[18-20]. According to the meta-analysis in 2015 [12], 7 studies demonstrated clinical effects of duloxetine but two studies revealed negative results.

In the double-blind randomised placebo-controlled study described here, we will evaluate the efficacy of addition of duloxetine for neuropathic cancer pain refractory to opioids and gabapentinoids. Currently there is no specific standard treatment for neuropathic pain in cancer patients, placebo is used instead of active control. The results of the trial will clarify the second-line standard treatment for cancer-related NP.

Methods and analysis

Study design

The SPIRIT (Standard Protocol Items for Randomised Trials) statement and its checklist were followed in preparing the protocol. The study design is summarized in Figure 1. A multicentre, prospective, randomised, placebo-controlled, double-blinded, two-parallel group study will be performed to compare the efficacy of addition of duloxetine (intervention group) with the efficacy of addition of a placebo (control group).

Study Settings and Participants

Recruiting will be performed in 14 adult palliative care sites across Japan, with involvement of 10 palliative care teams and 4 palliative care units. The inclusion and exclusion criteria are summarized in box 1.

Box 1. Inclusion and exclusion criteria

Inclusion Criteria
• Inpatients and outpatients with diagnoses of cancer and neuropathic pain • Currently receiving opioids • Unresponsive or intolerant to gabapentinoids: a) receiving doses of pregabalin of 300 mg/day or higher or gabapentin of 1800 mg/day or higher; b) cannot receive increased doses of pregabalin or gabapentin due to side effects • NRS pain score of 4 or higher

• HADS score <20 • Age 20 years or older • Creatinine clearance rate (Ccr) ≥30 mL/min (Cockcroft-Gault formula) • Serum aspartate aminotransferase (AST) <100 IU/L, alanine aminotransferase (ALT) <100 IU/L, and total bilirubin (T-bil) <2.0 mg/dL • Expected survival of one month or longer
Exclusion Criteria
• Chemotherapy-induced peripheral neuropathy • Progressive paralytic symptoms • Contraindication for duloxetine • Taking any type of antidepressants • A change in steroids, opioids, antidepressants, anticonvulsants, antipsychotic drugs, antiarrhythmic agents, or N-methyl-D-aspartate (NMDA) receptor antagonists within two days of initiation of administration of the study drug. Cases in which the patient has taken a hypnotic (including benzodiazepines such as zolpidem, zopiclone, eszopiclone, triazolam, ramelteon, suvorexant, brotizolam, flunitrazepam, rilmazafone, and etizolam) as needed are not included. • Drug abusers or patients who are addicted to drugs or have a history of addiction • Patients with psychiatric disorders such as cognitive impairment who are unable to communicate • Patients who are pregnant, breastfeeding, or may possibly be pregnant • Other patients who are determined to be inappropriate for participation in the study by the clinical investigator.

The main inclusion criterion is patients suffering from cancer pain (neuropathic or mixed) refractory to opioids and gabapentinoids. Diagnosis of NP is based on the International Association for the Study of Pain (IASP) algorithm, in which a diagnosis of NP is made for patients with (1) pain with a distinct neuroanatomically plausible distribution; (2) a history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system; (3) a range of pain that is neuroanatomically plausible and symptoms suggesting somatosensory injury or neurological disease (i.e., hyperalgesia, hypoalgesia, dysesthesia, or allodynia along the dermatome); and (4) relevant objective or imaging findings suggesting nervous system injury or disease (i.e., imaging findings showing that a lesion is present). Based on these criteria, the certainty of the presence of NP is grades as definite NP (1 to 4 present) and probable NP (1 and 2, plus 3 or 4) [21]. Definite and probable NP will be

considered to indicate NP and patients with these conditions will be eligible as subjects. Patients with an average numerical rating scale (NRS) pain score in the preceding 24-hour period of 4 or higher [22] and those with total Hospital Anxiety and Depression Scale (HADS) scores of less than 20 will be included, based on criteria for pain intensity used in similar studies on NP [23]. The exclusion criteria are patients with progressive paralysis, a known contraindication to use of duloxetine, or depression. To examine the effects of duloxetine, we believe it is necessary to exclude patients with depression because duloxetine may alleviate pain through improving depression. Patients with CIPN or impaired cognitive function will also be excluded.

Recruitment, randomisation, 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.

Randomisation

Physicians will introduce the trial to patients. Upon enrollment and after providing informed consent, patients will be randomly allocated to intervention (duloxetine) or control (placebo) groups in a web-based central randomisation system using minimisation methods and a computer-generated randomisation schedule with a 1:1 allocation ratio. In performing this allocation, we will minimise the following adjustment factors to avoid a large bias: (1) average pain intensity measured by the NRS in the last 24 h (≤7, ≥8), (2) type of pain (spinal cord infiltration or others), (3) HADS total score (≤10, ≥11), (4) treatment setting (inpatient or outpatient), (5) response to gabapentinoids (non-responsive or intolerance due to side effects), and (6) study site.

Masking

Patients and clinicians responsible for treatment will be blinded to administration of duloxetine or placebo. Only a clinical trial pharmacist who generate capsules, but is not involved in patient care, will know the allocation and outcomes. All study drugs will be packaged by this pharmacist. Duloxetine (Cymbalta®) will be administered with a change in dosage form: the capsules will be covered with a No. 3 capsule of the same material to make an overcapsule.

Data management, central monitoring, and audit

Evaluations will be performed at four time points: baseline (time of randomisation, T0), the day before the start of treatment (day 0, T1), and 3 days (day 3, T2) and 10 days (day 10, T3) after initiation of treatment. The timing and details of evaluations are given in Table 1.

Table 1. Study procedure and time points for actions and evaluations

	T0 Inclusion	T1 Day 0	T2 Day 3	T3 Day 10
Consent, Randomization	○	—	—	—
NRS for pain	○	○	○	○
Pain Relief Scale	—	—	○	—
SF-MPQ-2	—	○	—	—
Opioid consumption	—	○	○	○
EORTC-QLQ-C15 Pal	—	○	—	○
HADS	○	—	—	○
Pain Catastrophizing Scale	—	○	—	—
ECOG PS	○	○	—	○
Adverse events	—	○	○	○

Once a patient is enrolled or randomised, the study site will make every reasonable effort to follow the patient for the entire study period. Patients will not be allowed to cross over from one group to another group until the end of the study (T3), however, they can choose to leave

the study for any reasons at any time without detriment to the provision or quality of their clinical care. The investigators at each study sites will maintain individual records for each patient as source data, which include a copy of informed consent, medical records, laboratory data and other records or notes. All data will be collected by the independent data management centre. The data management centre will oversee the intra-study data sharing process. The clinical data entry, data management and central monitoring will be performed using the electric data capture VIEDOC 3 (PCG Solutions, Sweden). An interim analysis will not be performed. Also auditing is not planned in this study.

Harms

Investigators must record all adverse events (AEs) in the medical records and web systems. The National Cancer Institute's CTCAE (Ver.4.0) will be used to grade each adverse event (AE). All AEs are to be followed up continually during their course up. All severe adverse events (SAEs) must be reported to Institutional Review Board (IRB) and investigators in all sites, and discussed through a FAX. Patients that are enrolled into the study will be treated by health care services provided by health insurance.

Measurement tools

Numerical Rating Scale (NRS)

The 11-point NRS will be used to measure pain intensity from 0 (no pain) to 10 (worst possible pain), based on average pain in the past 24 hours [24].

Pain Relief Scale

A self-assessment will be performed by the patients using the Pain Relief Scale. Patients will determine for themselves the efficacy of analgesics using a four-point scale of complete

relief, a lot of relief, slight relief, and no change.

Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2, Japanese version)

The SF-MPQ-2 will be used to examine differences in effects due to pain mechanisms. The reliability and validity of the Japanese version have been verified [25].

European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL

EORTC QLQ-C15-PAL will be used for evaluation of patient QOL. The reliability and validity of the Japanese version have been confirmed [26].

Hospital Anxiety and Depression Scale (HADS)

The HADS will be used for measurement of psychiatric symptoms (anxiety and depression) of patients with a physical disease. HADS is a screening tool that allows assessment based on a small number of items. Its reliability and validity have been verified internationally [27, 28]. A HADS score <20 points as a cutoff for exclusion of cancer patients with severe depression will be used, based on a previous report [28].

Pain Catastrophizing Scale (PCS)

The severity of cancer-related pain is influenced by engagement of patients in catastrophic thinking, such as "my pain will undoubtedly never improve" [29]. This effect will be measured using the Japanese version of the PCS, for which the validity and reliability have been shown [30].

Common Terminology Criteria for Adverse Events (CTCAE)

The worst grade of an adverse event during the preceding period will be assessed using the

CTCAE v.4.0, Japanese Clinical Oncology Group (JCOG) version. Five adverse events of somnolence, dizziness, nausea, palpitations, and hypertension will be investigated if they occur at a relatively high frequency. Other adverse events may also be assessed.

Performance Status (PS)

The European Cooperative Oncology Group (ECOG) PS system will be used for evaluation of PS by primary physicians [31].

Treatment

Pre-intervention treatment

Opioids (morphine, oxycodone, fentanyl, tapentadol) will be given to all patients. If AEs of gabapentinoids are severe, they will be discontinued or reduced in dose, but if the adverse effects are tolerable but the therapeutic effect is insufficient, gabapentinoids will be administered concomitantly with duloxetine. Pregabalin and gabapentin will be used in the study at the established effective doses of 300 mg and 1800 mg, respectively [14, 32].

Interventions

Duloxetine or placebo will be administered for 10 days. Duloxetine (20 mg/day, one capsule) will be taken orally by participants in the intervention group starting after breakfast on Day 1. To determine if titration is necessary, pain relief will be evaluated using the Pain Relief Scale on Day 3 (T2). Changes in symptoms, adverse events, and medication compliance will be evaluated. Patients who have "complete relief" or "a lot of relief" of pain will continue to receive doses of 20 mg/day from Day 4. In all other cases, the dose will be increased to 40 mg/day (two capsules) from Day 4. If an intolerable AE such as nausea occurs at 40 mg/day, the dose will be reduced as required. If an intolerable AE occurs at 20

mg/day, the protocol will be discontinued. AEs that may be caused by duloxetine, such as somnolence, dizziness, nausea, palpitations, and hypertension, will be evaluated to determine whether duloxetine treatment should be interrupted.

Placebo (22.4 mg lactose in a No. 4 capsule) will be administered to participants in the control group by oral administration (one capsule/day) starting after breakfast on Day 1. To determine if titration is necessary, pain relief will be evaluated using the Pain Relief Scale on Day 3 (T2), and changes in symptoms, AEs, and medication compliance will be examined. Patients with "complete relief" or "a lot of relief" of pain will continue to receive one capsule/day from Day 4. In all other cases, the dose will be increased to 2 capsules/day from Day 4. If an intolerable AE such as nausea occurs at 2 capsules/day, the dose will be reduced as side effects dictate. If there is an intolerable AE at one capsule/day, the protocol will be discontinued. To improve adherence to intervention protocols, participants will return the unused tablets at the last visit, and unused tablets will be counted and recorded on the medical records. Currently there is no specific standard treatment for neuropathic pain in cancer patients, placebo is used instead of active control.

Cotreatments

Concomitantly administered analgesics such as opioids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or other adjuvant analgesics such as anticonvulsants, antidepressants, antiarrhythmics, N-methyl-D-aspartate (NMDA) receptor antagonists, and steroids will not be changed during the follow-up period. In principle, new analgesics will not be started. When nausea occurs during the period of duloxetine administration, use of an antiemetic will be permitted. Currently used immediate-release opioids will be used in cases of breakthrough pain. Immediate-release rescue opioids will be freely permitted without limitation on the number of doses.

Study endpoints

Primary endpoint

The primary endpoint is a comparison of pain intensity (average pain over the previous 24 hours) at T3 (Day 10) measured using the NRS in the duloxetine and placebo groups.

Secondary endpoints

Efficacy will also be assessed using seven secondary endpoints: the nature of pain using the SF-MPQ-2, EORTC QLQ-C15-PAL scores, daily opioid dose, changes in HADS score, degree of catastrophic thinking on the PCS, adverse events (CTCAE v.4.0-JCOG), and the difference in NRS scores for pain intensity (average over the previous 24 hours) measured at T3 in subgroups of patients who are unresponsive or intolerant to gabapentinoids. Subgroup analyses will be performed on two patients groups; patients unresponsive to gabapentinoids and patients intolerant to gabapentinoids. Additionally we will calculate percentages of the patients with 33% or 50% decrease.

Statistical considerations

Statistical hypothesis

Comparison of the primary endpoint of the NRS score for pain at Day 10 (T3) (average pain over the previous 24-hour period) between the duloxetine and placebo groups will be conducted using a one-sided t-test at a significance level of 5% according to the intention-to-treat (ITT) principle. Point estimates and 90% confidence intervals for the difference between two group means will be calculated.

The secondary endpoints of efficacy (SF-MPQ-2, EORTC QLQ-C15-PAL, HADS, PCS, daily opioid dose, and group comparison of average pain on the NRS in the previous 24 hours in patients who are unresponsive or intolerant to gabapentinoids) will be evaluated similarly

to the primary endpoint. The distribution of grades of adverse events (CTCAE v.4.0-JCOG) and the incidence of adverse events of Grade 3 or higher and of Grade 4 or higher will be determined. A Mantel test will be performed for group comparison.

Sample size calculation

The difference between group mean NRS scores for pain in the previous 24 hours on Day 10 (T3) is assumed to be one point and the standard deviation of the NRS is taken to be 1.5 points [17]. As there was no consensus about the minimal clinically important differences of duloxetine in cancer neuropathic pain at the planning stage of the study, we decided to adopt 1-point difference compared to placebo as the clinical significant difference, according to the meta-analysis of neuropathic non-cancer pain [33]. During this study periods, Hui et al. reported that the optimal cutoff was ≥ 1 point for improvement in cancer pain [34].

Assuming a rate of exclusion of 10 percent, 35 subjects are needed in each group (70 subjects in total) to achieve a statistical power of 80% with a one-sided significance level of 5%. As our primary interest is to clarify whether duloxetine is more effective than placebo, we adopted a one-sided test.

Ethical issues

All patients will be required to provide written informed consent. The study will be performed in accordance with the Declaration of Helsinki and the Japanese ethical guidelines for clinical research. The protocol was approved by the Institutional Review Board at each study site (Osaka; Kindai University Hospital, Kansai Medical University Hospital, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai City Medical Center, Izumi Municipal Hospital, and Sakai Hospital Kindai University Faculty of Medicine, Tokyo; National Cancer Center Hospital, Chiba; National Cancer Center Hospital East, Nara; Nara

Medical University Hospital, Nagoya; Nagoya University Hospital, Hyogo; Hyogo Prefectural Amagasaki General Medical Center, Kobe University Graduate School of Medicine and Hyogo Prefectural Kakogawa Medical Center, and Fukuoka; National Hospital Organization Kyusyu Cancer Center). This trial has been registered at the UMIN Clinical Trials Registry as UMIN000017647. Modifications in the study protocol will be communicated to the Institutional Review Board at each study site as well as the Independent Data Monitoring Committee**.** Each Ethics Committee or Institutional Review Board will revise informed consent materials given to participants and adapt according to their own institution's guidelines.

Discussion

To our knowledge, there has been no randomised study of the analgesic efficacy of duloxetine in patients with neuropathic cancer pain refractory to opioids and gabapentinoids. In our planned trial, we will use a randomised, double-blind, placebo-controlled design, which is the most appropriate design to demonstrate the efficacy of a new therapy. Our findings using this approach may also allow international recommendations to be updated. We also considered a crossover design, but a parallel design was finally chosen, given that the crossover design has several limitations [35]. The crossover design is suitable for patients in a stable condition, but this is not the situation for cancer patients with neuropathic pain (NP) refractory to opioids and gabapentinoids. We also believe that the treatment might have carryover effects and alter the response to subsequent treatments, and that patients may not be in a comparable condition at the start of each treatment period in a crossover trial.

Several issues related to the content of the trial require discussion. There are three major concerns: (i) the heterogeneity of causes of NP, (ii) the choice of the primary endpoint, and (iii) the role of depression. To address the heterogeneous causes of NP, we excluded patients

with CIPN, but the trial might still be criticized due to combination of peripheral and central NP in one study. Narrower criteria are theoretically possible, but accrual of patients who meet these criteria is likely to be difficult. We thus decided to include both peripheral and central NP in the study, and subgroup analyses will be performed. Second, the primary endpoint is the difference in average pain intensity score at T3 (day 10) between two groups. Although we had acknowledged that some authors recommend worst pain intensity in the last 24 hours as primary end-points because it satisfies most key recommendations in the draft guidance by the FDA [36], average pain intensity is adopted by many clinical trials about NP [37], including only one placebo-controlled RCT in cancer patients with NP [14]. Furthermore, to evaluate chronic pain, especially taking into account the nature of NP in this setting, we concluded that it is better to use the "average pain intensity in the last 24 hours" as the primary endpoint after discussion among the members of the steering committee. Finally, since depression affects the assessment of pain, we excluded patients with depression from the study population for accurate evaluation of the pharmacological effects of duloxetine on pain. Therefore, the planned placebo-controlled double-blind multicentre RCT will be the first to evaluate the efficacy of pharmacological treatment on well-defined NP in patients with cancer.

Trial status

The enrollment started in July 2015. At the time of manuscript submission (June 2017), two thirds of patients have participated. We thus expect to complete the recruitment by December 2017.

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 maintained in a separate locked cabinet and password-protected hard drive at each institution. Data will be analysed by ID number only. Records will be retained for 5 years after study completion and then destroyed by the data center.

Dissemination

The results of this study will be submitted for publication in international peer-reviewed journals and the key findings presented at conferences. Participants will be informed of the results of the trial by the investigators. Authorship will be ascribed in accordance with the International Committee of Medical Journal Editors guidance.

Data Sharing Statement

The data obtained in this study can only be accessed if approved by Japanese Organisation for Research and Treatment of Cancer (JORTC) Protocol Review Committee or Independent Data Monitoring Committee.

Access to data

JORTC Data Center and JORTC Independent Data Monitoring Committee have access to the final trial dataset. There is no contractual agreement regarding investigators' access restrictions on dataset.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Institutional Review Board at each study site. Informed

consent for participation in the trial will be obtained from all patients.

Competing interests

The authors declare that they have no competing interests.

Funding

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Sponsor detail

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Abbreviations

NRS: Numerical Rating Scale; NP: Neuropathic pain; TCA: Tricyclic Antidepressant; NCCN: National Comprehensive Cancer Network; CIPN: Chemotherapy-Induced Peripheral

Neuropathy; IASP: International Association for the Study of Pain; HADS: Hospital Anxiety and Depression Scale; PS: Performance Status; PRS: Pain Relief Scale; ECOG: European Cooperative Oncology Group; SF-MPQ: Short-Form McGill Pain Questionnaire; EORTC: European Organization for Research and Treatment; CTCAE: Common Terminology Criteria for Adverse Events; JCOG: Japan Clinical Oncology Group; PCS: Pain Catastrophizing Scale; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NMDA: N-methyl-D-aspartate; JORTC: Japanese Organization for Research and Treatment of Cancer

Authors' contributions

HM, HI, SI, AK, YK, TM, YM, TM, KA, participated in the design of the study. TY, TK, 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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Figure Legends

Figure 1. Flow chart of the procedures in the study. Participants will be randomized (1:1 allocation ratio) into the duloxetine intervention group or the placebo control group. Evaluations will be made at baseline (T0 randomization), and on day 0 (T1), day 3 (T2), and day 10 (T3).

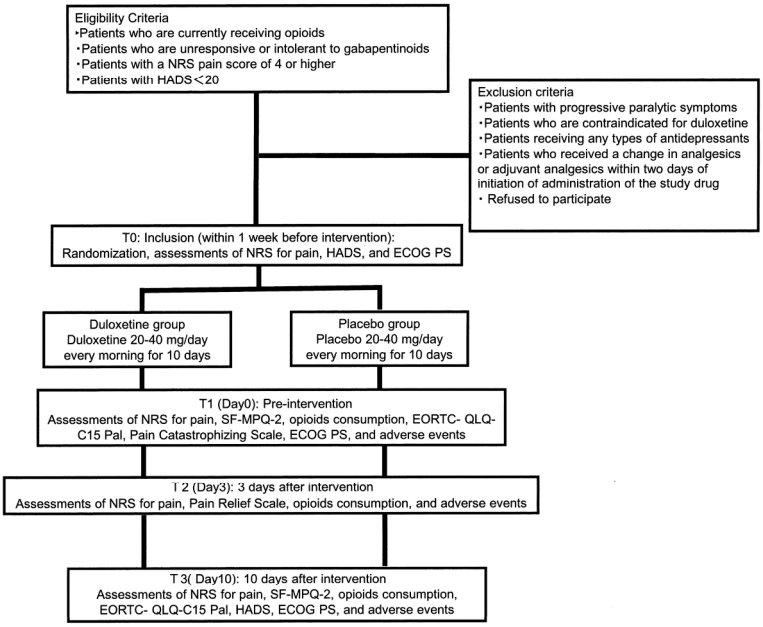

Fig.1. Flow chart of the procedures in the study

210x148mm (300 x 300 DPI)

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	4
	2b	All items from the World Health Organization Trial Registration Data Set	※ 1
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	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	Not applicable
	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)	※ 1
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
	6b	Explanation for choice of comparators	13
Objectives	7	Specific objectives or hypotheses	6
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)	6
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	7
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)	7, Box1
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)	12-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	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)	9, Table1

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	14-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8,9
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	8
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	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9
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	10
	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	※ 2
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)	※ 3
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	※ 1
	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	9
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	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)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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	17
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	10
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	※4
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not planned
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15
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	Not applicable

*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.

※1 : Not stated in the protocol paper due to word limits.

※2 : There is a statement in the data management plan, however not stated in the protocol paper due to word limits.

※3 : There is a statement in the statistical analyses plan (definition of analysis population relating to protocol non-adherence, and any statistical methods to handle missing data) however not stated in the protocol paper due to word limits.

※4 : There is a statement in the Informed consent form, however, not stated in the protocol paper due to word limits.