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Phase III, international, multi-centre, double-blind, dose increment, parallel-arm, randomised controlled trial of duloxetine versus pregabalin for opioid-unresponsive neuropathic cancer pain: A JORTC-PAL16 Trial Protocol

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STUDY PROTOCOL

Phase III, international, multi-centre, double-blind, dose increment, parallel-arm, randomised controlled trial of duloxetine versus pregabalin for opioid-unresponsive neuropathic cancer pain: A JORTC-PAL16 Trial Protocol

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Abstract

Introduction: Management of cancer patients who experience neuropathic cancer pain (NCP) refractory to regular opioids remains an important challenge. The effectiveness of pregabalin for this population has already been confirmed in two randomised controlled trials (RCTs) compared with placebo, arguably making this a standard of care. Duloxetine offers the potential of analgesia in opioid refractory NCP. However, there are no RCT of duloxetine for the management of opioid-refractory NCP as a first line treatment. Both classes of drug have the potential to reduce NCP, but there has been no head-to-head comparison for the net effect, especially given differing side-effect profiles.

Methods and analysis: An international, multi-centre, double-blind, dose increment, parallel-arm, randomised controlled trial is planned. Inclusion criteria include: adults with cancer experiencing NCP refractory to opioids; Brief Pain Inventory (BPI)-item 3 (worst pain) of ≥4; Neuropathic Pain on the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS) of ≥12; and having had an adequate trial of regular opioid medication (≥60mg/day oral morphine equivalent dose). Patients with chemotherapy-induced peripheral neuropathy (CIPN) are excluded.

The study will recruit from palliative care teams (inpatient and community) in Japan

and Australia. Participants will be randomised (1:1 allocation ratio) to duloxetine or pregabalin arm. Evaluations will be made at baseline (randomisation), days 0,3,7,14 and 21. The primary endpoint is defined as the difference in BPI item 3 for worst pain intensity over the previous 24 hours at day 14 between groups. A sample size of 160 patients will be examined between February 2020 and March 2023.

Ethics and Dissemination: Ethics approval was obtained at Osaka City University Hospital Certified Review Board and South Western Sydney Local Health District Human Research Ethics Committee. The results of this study will be submitted for publication in international journals and the key findings presented at international conferences.

Trial registration number: jRCTs051190097, Date of registration: 27 January 2020. ACTRN12620000656932, Date of registration: 5 June 2020.

Keywords: duloxetine, pregabalin, randomised controlled trial, neuropathic cancer pain, palliative care.

Strengths and limitation of this study

■This is the first study to compare the analgesic effectiveness and harms of duloxetine with pregabalin in patients experiencing neuropathic cancer pain refractory to opioids. The results of the trial will clarify the first-line standard of care for neuropathic cancer pain.

■An international collaborative and adequately powered trial designed to provide a clinically meaningful outcome, and enable the harms following intervention to be prospectively and systematically evaluated.

■Although we have excluded patients with chemotherapy-induced peripheral neuropathy (CIPN) from the study population for accurate evaluation of the pharmacological effects of pregabalin and duloxetine, this study still includes the heterogeneity of other causes of neuropathic cancer pain.

■The primary endpoint is not average pain intensity over the past 24 hours but the difference in worst pain intensity score, which has shown the highest degree of internal consistency for assessing a pain-reduction treatment effect.

■Recommendations for maximum dosing of adjuvant analgesics will be followed, and the results of this RCT will be the first to evaluate the efficacy of pharmacological treatment on well-defined NCP.

Introduction

Management of patients with cancer experiencing opioid-refractory neuropathic pain remains an important challenge. Neuropathic pain requires multi-pharmacological therapy, with adjuvant analgesics such as anticonvulsants and antidepressants, added to opioids; however strong evidence for their efficacy in neuropathic cancer pain (NCP) is limited [1].

According to various guidelines, gabapentinoids (pregabalin, gabapentin), tricyclic antidepressants (TCA) including amitriptyline and selective serotonin noradrenalin reuptake inhibitor (SNRI) including duloxetine are recommended as first-line drugs [2-5]. Among them, the effectiveness of gabapentinoids for this population has already been demonstrated in two randomised controlled trials (RCTs) compared with placebo, arguably making this a standard of care [6,7]. Data support gabapentinoids as promising, safe agents in this setting, warranting further evaluation in robust randomised controlled trials compared with other candidates (e.g. SNRIs and TCAs). The results of two RCTs targeting NCP [7,8], found the effect of TCA is limited and even in small dose (e.g. amitriptyline; 30-50mg/day), many adverse events (AEs) occurred. Pregabalin was superior in terms of analgesic effect and opioid reducing effect in comparisons among

pregabalin, gabapentin, amitriptyline, and placebo[7].

Duloxetine has been reported to be effective in the management of chemotherapy-induced peripheral neuropathy (CIPN) [9], but no randomised trials have examined its effects on opioid-refractory NCP. Although there is no standard first line treatment for NCP, a systematic review and meta-analysis suggested gabapentinoids be used first [10]. Although there are few reports of duloxetine in NCP, Matsuoka et al. have conducted a feasibility pre- and post-test [11] and an RCT [12,13], which have shown the benefit of duloxetine (number needed to treat; NNT = 3.4) [12] and superiority for tingling pain[13]. However, there are no RCT of oral duloxetine for the management of opioid-refractory NCP.

In the double-blind RCT described here, we will evaluate the effectiveness and harms of duloxetine and pregabalin for opioid-refractory NCP. Both classes of drug have the potential to reduce NCP, but there has been no head-to-head comparison for the net effect especially given differing side-effect profiles. The results of this RCT will clarify the first-line standard treatment for NCP.

Methods and analysis

Study design

The SPIRIT (Standard Protocol Items for Randomised Trials) statement and its checklist were followed in preparing the protocol. This international, multi-centre, randomised, double-blind, two-parallel arm, dose-increment study will be performed to compare the efficacy and safety of duloxetine and pregabalin for NCP (Figure 1). This study will also have a qualitative sub-study in which patient experience of the intervention will be explored.

Study Settings and Participants

Participants will be recruited from adult palliative care sites across Japan and Australia, including consultative, inpatient and community services. The inclusion and exclusion criteria are summarised in Box 1.

Box 1. Inclusion and exclusion criteria

Inclusion Criteria
• Inpatients and outpatients with diagnoses of cancer and neuropathic pain

• An adequate opioid medication (defined as the maximum tolerated dose or titration to ≥60mg/day oral morphine equivalent dose for 24 hours unless otherwise contra-indicated). • Pain related to cancer with a worst pain score of ≥4 or greater on BPI item 3 (worst pain intensity) score in the past 24 hours. • Neuropathic Pain on LANSS ≥12. • Age 18 years or older (Japan 20 years or older) • AKPS ≥50. • Taking stable regular analgesics (opioids, paracetamol, non-steroidal anti-inflammatory drugs) and any type of regular adjuvant analgesic (e.g. antidepressants, anticonvulsants, antiarrhythmic agents, N-methyl-D-aspartate receptor antagonists, and steroids) within 72 hours before commencing on the study. Short acting and rapid onset breakthrough-opioids as needed may be used ≤4 doses/day and still be considered ”stable”.
Exclusion Criteria
• Chemotherapy-Induced Peripheral Neuropathy (glove and stocking) • Spinal cord compression • Contraindication for duloxetine or pregabalin. • Taking gabapentioids or duloxetine for any reason within 2 weeks. • Taking SSRI or SNRI for any reason. • Taking a monoamine oxidase inhibitor. • Participants who have participated in a clinical trial involving a new chemical entity within four weeks prior to study entry. • Starting a new chemotherapy regimen within 14 days of baseline . • Patients with renal failure defined as eGFR 30ml/min/1.73m2 calculated according to the GFR-EPI equation. • Patients with hepatic failure (Child Pugh B or C). • Patients who have a recent history of drug abuse. • 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 will be adults experiencing cancer pain (neuropathic or mixed) refractory to opioids. Diagnosis of NCP is based on the International Association for the Study of Pain (IASP) criteria, in which a diagnosis of NCP 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 NCP is graded as definite NCP (1 to 4 present) and probable NP (1 to 3) [14]. Definite and probable NCP will be considered to indicate NCP and patients with these conditions will be eligible as subjects. Patients with a worst numerical rating scale (NRS) pain score (BPI-item 3) in the preceding 24-hour period ≥4 [15] and those with LANSS scores ≥12 will be included [16]. The exclusion criteria will be patients with: CIPN (glove and stocking); spinal cord compression; contraindications for duloxetine or pregabalin; or impaired cognitive function.

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 and informed consent will be obtained.

Randomisation

Physicians will introduce the trial to patients after screening for eligibility by nurse or staff. Upon enrollment, patients will be randomly allocated to duloxetine or pregabalin 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) worst pain intensity measured by the NRS in the last 24 h (≤6, ≥7); (2) dose of opioid (≥90mg oral morphine equivalent dose, 60-90mg, <60mg); (3) Hospital Anxiety and Depression Score (HADS) total score (≤10, ≥11); (4) body weight (≥80kg or <80kg); (5) race (Australian (Asian descent; e.g.; China, India, Vietnam, Philippines, etc.), Australian (partial or no Asian descent), Japanese, others (e.g.; Italy South, Africa, etc.)), and (6) study site.

Masking

Patients and clinicians responsible for treatment will be blinded to administration of

duloxetine or pregabalin. Both the duloxetine and the pregabalin capsules will be indistinguishable by encapsulation and only unblinded pharmacists at each site will know the allocation result of each patient. Duloxetine (Cymbalta®) and pregabalin (Lyrica®) will be administered with a change in dosage form: the capsules will be covered with a No. 1 capsule (length 19mm) of the same material to make an over-capsule.

Data management, central monitoring, and audit

Evaluations will be performed at six time points: eligibility, the day before the start of treatment (day 0; the time of randomisation), day 3, day 7, day 14, and day 21 after initiation of treatment. The timing and details of evaluations are given in Table 1.

Table 1. Schedule of study measures

	Eligibility* Baseline/D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D 9-13**	**D 14**	**D 15-20**	**D 21**	**Exit/ WD**
Investigations													
Consent Randomisation	○*												
Liver function, eGFR	○*									○			○
Study Drug Administration	○	○	○	○	○	○	○	○	○	○	○	○	○
Medical file review													
Demographics, Diagnosis	○*												

	Eligibility* Baseline/D1	D2	D3	D4	D5	D6	D7	D8	D 9-13	D 14	D 15-20	D 21	Exit/ WD
Selected medications (e.g., opioid)	○	○	○	○	○	○	○	○	○	○	○	○	○
Breakthrough medications	○	○	○	○	○	○	○	○	○	○	○	○	○
Patient assessed (PRO assessments)													
Daily Diary	○	○	○	○	○	○	○	○	○	○	○	○	○
BPI-SF	○									○			○
Worst pain (BPI-item 3)	○*	○	○	○	○	○	○	○	○		○	○	
Average pain (BPI-item 5)	○*	○	○	○	○	○	○	○	○		○	○	
SF-MPQ-2	○									○			○
EORTC-QLQ-PAL-C15	○									○			○
HADS	○*									○			○
Global impression of change				○				○		○		○	○
Pain expectation	○												
PRO-AEs	○							○		○		○	○
Clinician assessed													
Medical assessment	○*												
Height and Weight	○												
Vital signs	○									○		○	○

	Eligibility* Baseline/D1	D2	D3	D4	D5	D6	D7	D8	D 9-13	D 14	D 15-20	D 21	Exit/ WD
KPS/AKPS	○*		○				○			○			○
LANSS	○*												
Personalised pain goal	○												
Adverse events	○		○				○			○	○		○
Substudies (if consented)													
Qualitative patient interview										○			

Once a patient is enrolled or randomised, the study site will make every 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, 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 site will maintain individual records for each patient as source data, which will 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 JORTC Data Center (Japan) and the IMPACCT Trials Coordination Centre (Australia) will oversee the intra-study data sharing process in each country. The clinical data entry, data management and central monitoring will be performed using the electric data capture VIEDOC 4 (PCG

Solutions, Sweden) in Japan and REDCap (Vanderbilt University, USA) in Australia. An interim analysis will not be performed. Audit may take place by JORTC Audit Committee in Japan and by an external agency in Australia.

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. All serious adverse events (SAEs) must be reported to Osaka City University Hospital Certified Review Board (CRB) and a Medical Monitor within Australia, with annual safety reporting to the Human Research Ethics Committee (HREC), and to investigators in all sites. Participants that are enrolled into the study will be treated by health care services at no cost to participants.

Measurement tools

All the appropriate permissions were obtained for the use for the assessment instruments.

Brief Pain Inventory-Short Form (BPI-SF)

The Brief Pain Inventory – Short Form will be used as it is a brief and easy tool for the assessment of pain within both the clinical and research settings. It has been validated in both the chronic pain and cancer settings. The numerical rating scale of 0 to 10 is simple for participants to use and reflects common clinical assessment of pain [17].

Global Impression of Change

The Global Impression of Change is a participant-rated 7- point scale (1-7) that provides information about the participants' perception of their overall change in pain since commencing the study. This will allow the investigators to compare the pain rating using the NRS with participant perception of improvement. The results of this scale over the study period will assist to determine the clinical significance of any improvement seen [18].

Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)

The LANSS estimates the probability that neuropathic mechanisms contribute to the chronic pain experience in each participant. It has 85% sensitivity for detecting neuropathic pain. It is a seven-item scale including sensory description and

examination. A score of ≥12 indicates that neuropathic mechanisms are likely to contribute to the participant's pain. It will be used to define a population with neuropathic pain [19]. The LANSS will be collected to determine eligibility.

Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2)

The Short Form McGill Pain Questionnaire 2 (SF-MPQ-2) [20] will be used to examine differences in effects due to pain mechanisms. The SF-MPQ-2 and its Japanese version have been validated in cancer neuropathic pain [21]. It is a 22-item questionnaire covering the domains of superficial and deep spontaneous pain, paroxysmal pain, evoked pain and paresthesia/dysaesthesia. We also used this tool in the pilot study that underpins the current trial [12,13] and consider the possibility of effective pain types. This time it will be used to make a comparison for that verification.

Personalised pain goal

The personalised pain goal [22] is a tool used to tailor pain management to individual needs. "Participants are asked to describe on a 0-10 scale, the level/intensity of pain that will allow the patient to achieve comfort in physical, functional, and psychosocial domains" [22] This will be asked by the research nurse or staff at baseline, and may

include explanation of terminology. Zero will represent no pain and ten will represent worst pain. This is not a validated tool. We use this scale because some argued that neither between-group difference in mean values nor changes in pain intensity (e.g. absolute or relative values) correctly evaluated the patient's discomfort.

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

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL will be used for evaluation of patient quality of life. The reliability and validity of the original version [23] and Japanese version [24] have been confirmed.

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) [25] 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 [25, 26].

Patient Expectation

Patient's expectation of a decrease in pain of each patient will be examined as one study has shown the effect of expectation of pain decrease influenced pain prognosis in cancer pain [27].

CTCAE/PRO-CTCAE

Any new or worse adverse events will be evaluated and classified according to CTCAE criteria [28] and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). PRO-CTCAE was developed by the National Cancer Institute (NCI) as an adverse event assessment system to evaluate patients' subjective symptoms. Its content validity and psychometric validity have been verified in the original English version [28,29]. Japanese version of the PRO-CTCAE had acceptable reliability and linguistic [30] and psychometric [31] validity for common and clinically important symptoms.

Interventions

All participants will take blinded opaque capsules each morning after breakfast and bedtime for 14 days. Participants will increase the study drugs to stage 2 on day 4 and to stage 3 on day 8. Participants will be assessed for AEs during the study period. If a

person experiences mild, moderate, or severe AEs, as classified by the NCI Criteria, they will be treated symptomatically. If symptoms persist, participants will continue the previous dose prior to adverse symptoms being noted (or if on the amount of stage 1 will exit the study). If participants experience unacceptable AEs on: days 1 - 3 on the stage 1 drug (30mg duloxetine or 50mg pregabalin daily dose) they will be withdrawn from the study; days 4 - 7 on the stage 2 drug (30mg duloxetine or 150mg pregabalin daily dose) they will continue in the study to day 14 on stage 1 drug (30mg duloxetine or 50mg pregabalin daily dose); days 8 - 14 on the stage 3 drug (60 mg duloxetine or 300mg pregabalin daily dose) they will continue in the study to day 14 on stage 2 drug (30mg duloxetine or 150mg pregabalin daily dose) . Assessments to determine net clinical effect will be conducted on day 14. The dose will be tapered down until the amount of stage 1 (stage 3→2→1 or stage 2→1) and the medication will be stopped to avoid a discontinuation syndrome, mirroring the schedule for initial upwards titration (i.e. duloxetine 30mg/pregabalin 150 mg for 4 days, 30mg/50mg for 3 days then cease <from stage 3; days 15-21> or duloxetine 30mg/pregabalin 50mg for 3 days then cease < from stage 2; days 15-17 >). Rescue opioids will be available on an ‘as needed’ basis, up to eight doses of currently prescribed breakthrough opioid in any 24-hour period. Following cessation of study medications, participants will be reviewed by their treating

clinician regarding any future open label prescribing of the study medications. If pain is present or re-occurs during the downward titration phase the treating clinician should determine the most appropriate open label pain medication and monitor the patient closely.

Co-treatments

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. New analgesics will not be started. If nausea occurs during the treatment period, use of an antiemetic will be permitted.

Study endpoints

Primary endpoint

The primary endpoint is a comparison of worst pain intensity over the previous 24 hours at day 14 measured using the BPI items 3 in the duloxetine and pregabalin groups.

Secondary endpoints

Efficacy will be assessed using the following secondary endpoints: the average pain intensity (BPI items 5) at days 14 and 21; the worst pain intensity (BPI items 3) at day 21; the SF-MPQ-2 scores; EORTC QLQ-C15-PAL scores; changes in HADS score; and daily opioid dose (on each day). AEs will also be assessed using NCI CTCAE and PRO-CTCAE.

Additionally we will calculate percentage of participants with a reduction (BPI-I items 3) of 1 point; 2 point; > 2 points; 30% and 50% pain decrease from the baseline on day3, day7 and day14, percentage of participants in whom increase to the maximum dose is achieved, percentage of participants in whom can achieve personal pain goal, percentage of participants in whom need to adjust baseline opioids and adjuvant analgesics, the completion rate of the study medication and procedures, total daily dose of adjuvant analgesics use (on each day), prospectively sought adverse events with the likelihood of relationship to intervention (toxicity), and health service utilisation-planned and unplanned contact, investigations, hospitalisations.

Statistical considerations

All statistical procedures were detailed in the statistical analysis plan before data evaluation, including the handling of missing values and necessity of sensitivity analysis.

Statistical hypothesis

Comparison of the primary endpoint of the worst pain intensity (BPI items 3) at day 14 between duloxetine groups and pregabalin groups will be conducted using a two-sided Student's t-test at a significance level of 5% according to the intention-to-treat principle. Point estimates and 95% CIs for the difference between two group means will be calculated.

The secondary endpoints of efficacy (BPI items 5, SF-MPQ-2, EORTC QLQ-C15-PAL, HADS, daily opioid dose, and group comparison of worst pain on the BPI-item3 in the previous 24 hours) will be evaluated similarly to the primary endpoint.

Longitudinal changes in BPI-item 3 and BPI-item 5 will be evaluated using mean scores and 95% CIs. The distribution of grades of adverse events (NCI CTCAE and PRO-CTCAE) and the incidence of adverse events of Grade 3 or higher and of Grade 4 will be determined.

Sample size calculation

The difference between group BPI-item 3 on day 14 is assumed to be one point and the standard deviation of the NRS is taken to be 2.0 points [13, 32, 33]. As there was no consensus about the minimal clinically important differences in NCP at the planning stage of the study, we decided to adopt 1-point difference compared to pregabalin as the clinical significant difference, according to the recommendation of interpreting the clinical importance of group differences in chronic pain clinical trials [32].

Based on our primary outcome, which is worst pain intensity (BPI-item 3) at day 14, we will estimate 64 participants per group would detect a mean difference of 1.0 (SD 2.0; 80% power with a two-sided significance level of 0.05 for comparison).

Considering withdrawal and drop-out of 20%, we plan to recruit 160 participants into the study.

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 and Australian ethical guidelines for clinical research. The protocol was approved by the Osaka City University Hospital Certified Review Board (CRB) and a Medical Monitor

within Australia, with annual safety reporting to the Human Research Ethics Committee (HREC). This trial has been registered with the clinical trials registries within both Japan and Australia. Modifications in the study protocol will be communicated to approving CRB (Japan) and HRECs (Australia). 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 RCT of the analgesic efficacy of oral duloxetine for the management of opioid refractory NCP as a first line treatment. In our planned trial, the use of a randomised, double-blind, two-parallel arm design, 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, especially in this population [34], namely; the treatment might have carryover effects and alter the response to subsequent treatments; and palliative patients may not be in a comparable condition at the start of the crossover trial treatment period.

Several issues related to the content of the trial require discussion. There will be three major concerns: (i) the heterogeneity of causes of NCP, (ii) the choice of the primary endpoint and (iii) the dose schedule of each drugs.

To address the heterogeneous causes of NCP, we excluded patients with CIPN and central NP, and targeted patients with NCP non-responsive or intolerant to opioid therapy, but the trial might still be criticised due to combination of various peripheral NCPs in one study. Narrower criteria are theoretically possible, but accrual of patients who meet these criteria is likely to be difficult. Furthermore, in palliative care field, a framework for classifying research subpopulations to which the research findings are being applied by clinicians, health planners, and funders in real-world settings has been suggested [35]. We thus decided to include various types of peripheral NCP in the study, and sub-group analyses will be performed.

Second, the primary endpoint is the difference in worst pain intensity score at day 14 between two groups. Although we had acknowledged that the average pain intensity is adopted by many clinical trials about NCP [36], including three RCTs [6,7,13] in patients with NCP, some authors recommend worst pain intensity in the last 24 hours as primary endpoints because it satisfies most key recommendations in the draft guidance [15]. Furthermore, to evaluate chronic pain, especially considering the nature of NCP in this

setting, we concluded that it is better to use the "worst pain intensity in the last 24 hours" as the primary endpoint after discussion among the members of the study's steering committee.

Finally, the following dose titration schedule has been devised to maximize the likelihood of benefit while minimizing the risk of adverse events. The participant will commence duloxetine or pregabalin at 30mg and 50mg respectively and will be titrated according to response in increments of cessation to a maximum of 60mg (duloxetine) and 300mg (pregabalin). Dworkin et al. conducted a systematic review of pharmacologic management of NCP and made the recommendations for maximum dosing [37] and according to the National Comprehensive Cancer Network (NCCN) guideline of adult cancer pain [2] we have defined initiation dose and maximum dose of both drugs.

Moreover, we set a dose decrement titration periods instead of doing key open to avoid a discontinuation syndrome of each drug and to keep scientific reliability. Therefore, the planned international double-blind multi-centre RCT will be the first to evaluate the efficacy and harms of duloxetine and pregabalin treatment in patients suffering from well-defined NCP refractory to opioids, and the results of the trial will clarify the first-line standard treatment for NCP.

Trial status

The trial opened in January 2020. At the time of manuscript submission (February 2021), twenty one patients have been randomised. We expect to complete the recruitment by September 2022 and to finish this trial by March 2023.

Confidentially

Data will be retained in accordance with the Japanese Clinical Research Act and the Australian regulations for Good Clinical Practice. 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 15 years after study completion and then destroyed by the data centre.

Dissemination

The results of this trial 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

Immediately after the publication of the primary results, de-identified individual participant data that underlie the results reported in the article(s) and other documents (study protocol and statistical analysis plan) will be available for any purpose, only if approved by JORTC Independent Data Monitoring Committee (IDMC) and the CST Scientific Advisory 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

The protocol was approved by the Osaka City University Hospital Certified Review Board and South Western Sydney Local Health District Human Research Ethics

Committee (Australia). Informed consent for participation in the trial will be obtained from all patients.

Patient and Public Involvement

The invaluable contribution of healthcare consumers (patients and caregivers) is recognised by ensuring that all research undertaken takes into account consumer experience and perspectives.Consumer representatives were actively involved in all aspects of our research including the design, implementation, evaluation, and dissemination of this randomised control clinical trial. As a member of the protocol investigator team, the consumer representative ensures that the physical and emotional wellbeing of patients and caregivers were taken into consideration when planning this clinical trial and implementing the result findings into practice.

Competing interests

The authors declare that they have no competing interests.

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Abbreviations

NP: Neuropathic pain; NCP: Neuropathic cancer pain; TCA: Tricyclic Antidepressant; SNRI: Serotonin & Norepinephrine Reuptake Inhibitors; IASP: International Association for the Study of Pain; BPI: Brief pain inventory; LANSS: the Leeds assessment of neuropathic symptoms and signs; CIPN: Chemotherapy-Induced Peripheral Neuropathy; NRS: Numerical Rating Scale; HADS: Hospital Anxiety and Depression Scale; AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SF-MPQ: Short-Form McGill Pain Questionnaire; EORTC: European Organization for Research and Treatment; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NMDA: N-methyl-D-aspartate; JORTC: Japanese Organization for Research and Treatment of Cancer

Authors' contributions

HM, KC, BF, LB, HI, YM, HH, KA, JL, BL, PA, SK, NF, TM, ML, MA, ES, SI, JP, AK, and DC participated in the design of the study. SO, TY, 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 group or the pregabalin group.

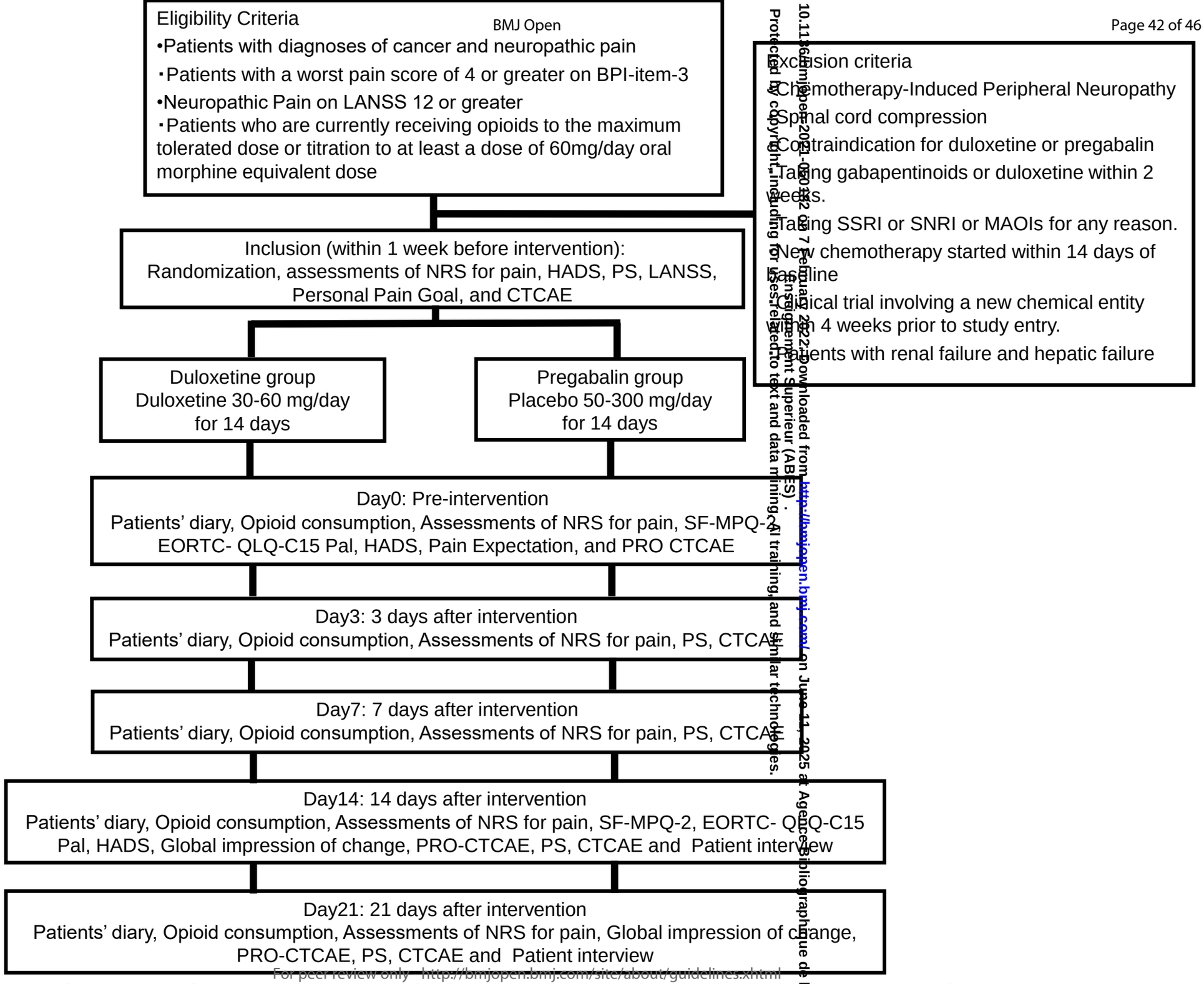

Fig.1. Flow chart of the procedures in the study

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	3
	2b	All items from the World Health Organization Trial Registration Data Set	※ 1
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	27
	5b	Name and contact information for the trial sponsor	25-26
	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	5-6
	6b	Explanation for choice of comparators	5-6
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	15-16
	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)	15-16
	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	16
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	17
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)	6, Table1, Figure1
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	19-20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	9

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		9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions		9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how		9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		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		9-10
	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		16
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		18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)		18
	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	10
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	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
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)	20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8,10
	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	23-24
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
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	24
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	16
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	24
	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	20
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

Phase III, international, multi-centre, double-blind, dose increment, parallel-arm, randomised controlled trial of duloxetine versus pregabalin for opioid-unresponsive neuropathic cancer pain: A JORTC-PAL16 Trial Protocol

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Primary Subject Heading:	Palliative care
Secondary Subject Heading:	Palliative care
Keywords:	Adult palliative care < PALLIATIVE CARE, Cancer pain < ONCOLOGY, Clinical trials < THERAPEUTICS

STUDY PROTOCOL

Phase III, international, multi-centre, double-blind, dose increment, parallel-arm, randomised controlled trial of duloxetine versus pregabalin for opioid-unresponsive neuropathic cancer pain: A JORTC-PAL16 Trial Protocol

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Abstract

Introduction: Management of neuropathic cancer pain (NCP) refractory to regular opioids remains an important challenge. The efficacy of pregabalin for NCP except chemotherapy-induced peripheral neuropathy (CIPN) has already been confirmed in two randomised controlled trials (RCTs) compared with placebo. Duloxetine offers the potential of analgesia in opioid refractory NCP. However, there are no RCT of duloxetine for the management of opioid-refractory NCP as a first line treatment. Both classes of drugs have the potential to reduce NCP, but there has been no head-to-head comparison for the efficacy and safety, especially given differing side-effect profiles.

Methods and analysis: An international, multi-centre, double-blind, dose increment, parallel-arm, RCT is planned. Inclusion criteria include: adults with cancer experiencing NCP refractory to opioids; Brief Pain Inventory (BPI)-item 3 (worst pain) of ≥4; Neuropathic Pain on the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS) of ≥12 despite of an adequate trial of regular opioid medication (≥60mg/day oral morphine equivalent dose). Patients with CIPN are excluded.

The study will recruit from palliative care teams (both inpatients and outpatients) in Japan and Australia. Participants will be randomised (1:1 allocation ratio) to duloxetine or pregabalin arm. Dose escalation is until day 14 and from day 14 to 21 is a dose de-

escalation period to avoid withdrawal effects. The primary endpoint is defined as the mean difference in BPI item 3 for worst pain intensity over the previous 24 hours at day 14 between groups. A sample size of 160 patients will be enrolled between February 2020 and March 2023.

Ethics and Dissemination: Ethics approval was obtained at Osaka City University Hospital Certified Review Board and South Western Sydney Local Health District Human Research Ethics Committee. The results of this study will be submitted for publication in international journals and the key findings presented at international conferences.

Trial registration number: jRCTs051190097, Date of registration: 27 January 2020. ACTRN12620000656932, Date of registration: 5 June 2020.

Keywords: duloxetine, pregabalin, randomised controlled trial, neuropathic cancer pain, palliative care.

Strengths and limitation of this study

■This is the first study to compare the analgesic efficacy and safety of duloxetine with pregabalin in patients experiencing neuropathic cancer pain refractory to opioids, not induced by chemotherapy. The results of the trial will clarify the first-line standard of care for neuropathic cancer pain.

■A high-quality double blind multicentre RCT study design adequately powered to provide a clinically meaningful outcome, and enable the safety and tolerability following intervention to be prospectively and systematically evaluated.

■ This study includes heterogenous causes of neuropathic cancer pain not related to chemotherapy to determine the pharmacological effects of pregabalin and duloxetine in sparsely studied but clinically relevant populations.

■The primary endpoint is not average pain intensity over the past 24 hours but the difference in worst pain intensity score, which has shown the highest degree of internal consistency for assessing a pain-reduction treatment effect.

■Recommendations for maximum dosing of adjuvant analgesics will be followed, and the results of this RCT will be the first to evaluate the efficacy of pharmacological treatment on well-defined NCP.

Introduction

Management of patients with cancer experiencing opioid-refractory neuropathic pain remains an important challenge. Neuropathic pain requires multi-pharmacological therapy, with adjuvant analgesics such as anticonvulsants and antidepressants, added to opioids; however strong evidence for their efficacy in neuropathic cancer pain (NCP) is limited [1].

According to numerous guidelines, gabapentinoids (pregabalin, gabapentin), tricyclic antidepressants (TCA) including amitriptyline and selective serotonin noradrenalin reuptake inhibitor (SNRI) including duloxetine are recommended with careful titration as first-line drugs [2-7]. Among them, the efficacy of gabapentinoids for this population has already been demonstrated in three randomised controlled trials (RCTs) compared with placebo, arguably making this a standard of care [8-10]. Data support gabapentinoids as promising, safe agents in this setting, warranting further evaluation in robust randomised controlled trials compared with other candidates (e.g., SNRIs and TCAs). The results of two RCTs targeting NCP [10,11], found the effect of TCA is limited and even in small dose (e.g., amitriptyline; 30-50mg/day), many adverse events (AEs) occurred. Pregabalin was superior in terms of analgesic effect and opioid reducing effect in comparisons among pregabalin, gabapentin, amitriptyline, and placebo[10].

Duloxetine has been reported to be effective in the management of chemotherapy-induced peripheral neuropathy (CIPN) [12], but no randomised trials have examined its effects on opioid-refractory NCP. Although there is no standard first line treatment for NCP, a systematic review and meta-analysis suggested gabapentinoids be used first [13]. Although there are few reports of duloxetine in NCP, Matsuoka et al. have conducted a feasibility pre- and post-test [14] and an RCT [15,16], which have shown the benefit of duloxetine (number needed to treat; NNT = 3.4) [15] and superiority for tingling pain[16]. However, there are no RCT of oral duloxetine for the management of opioid-refractory NCP.

In the double-blind RCT described here, we will evaluate the efficacy and safety of duloxetine and pregabalin for opioid-refractory NCP. Both classes of drug have the potential to reduce NCP, but there has been no head-to-head comparison for the efficacy and safety especially given differing side-effect profiles. The results of this RCT may help to clarify the first-line standard treatment for NCP.

Methods and analysis

Study design

The SPIRIT (Standard Protocol Items for Randomised Trials) statement and its

checklist were followed in preparing the protocol. This international, multi-centre, randomised, double-blind, two-parallel arm, dose-increment study will be performed to compare the efficacy and safety of duloxetine and pregabalin for NCP (Figure 1). This study will also have a qualitative sub-study in which patient experience of the intervention will be explored if additional consent is provided.

Study Settings and Participants

Participants will be recruited from adult palliative care sites across Japan and Australia (both inpatients and outpatients). The inclusion and exclusion criteria are summarised in Box 1.

Box 1. Inclusion and exclusion criteria

Inclusion Criteria

- Inpatients and outpatients with diagnoses of cancer and neuropathic pain who, in the opinion of the site investigator, are candidates for therapy with duloxetine or pregabalin
- Insufficient response (defined as pain related to cancer with a worst pain score of ≥4 or greater on BPI item 3 (worst pain intensity) score in the past 24 hours) to an adequate opioid medication (defined as the maximum tolerated dose or titration to at least 60mg/day oral morphine equivalent dose for 24 hours unless contra-indicated or further escalation is deemed unnecessary or inappropriate in the opinion of the clinical investigator).
- Age 18 years or older (Japan 20 years or older)
- AKPS ≥50.

• Taking stable regular analgesics (opioids, paracetamol, non-steroidal anti-inflammatory drugs) and any type of regular adjuvant analgesic (e.g. antidepressants, anticonvulsants, antiarrhythmic agents, N-methyl-D-aspartate receptor antagonists, and steroids) within 72 hours before commencing on the study. Short acting and rapid onset breakthrough-opioids as needed may be used ≤4 doses/day and still be considered "stable".
Exclusion Criteria
• Chemotherapy-Induced Peripheral Neuropathy (glove and stocking distribution and prior use of a therapy known to cause this) • Spinal cord compression • Contraindication for duloxetine or pregabalin. • Taking gabapentioids or duloxetine for any reason within the previous two weeks. • Taking SSRI or SNRI for any reason. • Taking a monoamine oxidase inhibitor. • Participants who have participated in a clinical trial involving a new chemical entity within four weeks prior to study entry. • Starting a new chemotherapy regimen within 14 days of baseline. • Patients with renal failure defined as eGFR ≤30ml/min/1.73m2 calculated according to the GFR-EPI equation. • Patients with hepatic failure (Child Pugh B or C). • Patients who have a recent history of drug misuse. • 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 will be adults experiencing cancer pain (neuropathic or mixed) refractory to opioids. Diagnosis of NCP is based on the International Association for the Study of Pain (IASP) criteria, in which a diagnosis of NCP 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 NCP is graded as definite NCP (1 to 4 present) and probable NP (1 to 3) [17]. Definite and probable NCP will be considered to indicate NCP and patients with these conditions will be eligible as subjects. Patients with a worst numerical rating scale (NRS) pain score (BPI-item 3) in the preceding 24-hour period ≥4 [18] and those with LANSS scores ≥12 will be included [19]. The exclusion criteria will be patients with: CIPN (glove and stocking); spinal cord compression; contraindications for duloxetine or pregabalin; or impaired cognitive function.

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 and informed consent will be obtained.

Randomisation

Physicians will introduce the trial to patients after screening for eligibility by nurse or staff. Upon enrollment, patients will be randomly allocated to duloxetine or pregabalin 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[20] to avoid a large bias: (1) worst pain intensity measured by the NRS in the last 24 h (≤6, ≥7) [2,21]; (2) dose of opioid (≥90mg oral morphine equivalent dose, 60-90mg, <60mg) [22,23]; (3) Hospital Anxiety and Depression Score (HADS) total score (≤10, ≥11) [24]; (4) body weight (≥80kg or <80kg) [25]; (5) race (Australian (Asian descent; e.g.; China, India, Vietnam, Philippines, etc.) [25], Australian (partial or no Asian descent), Japanese, others (e.g.; Italy South, Africa, etc.)), and (6) study site[25,26].

Masking

Patients and clinicians responsible for treatment will be blinded to administration of duloxetine or pregabalin. Both the duloxetine and the pregabalin capsules will be indistinguishable by encapsulation and only unblinded pharmacists at each site will

know the allocation result of each patient. Duloxetine (Cymbalta®) and pregabalin (Lyrica®) will be administered with a change in dosage form: the capsules will be covered with a No. 1 capsule (length 19mm) of the same material to make an over-capsule.

Data management, central monitoring, and audit

Evaluations will be performed at eight time points: eligibility, the day before the start of treatment (day 0; the time of randomisation), day 3, day 4, day 7, day8, day 14, and day 21 after initiation of treatment. The timing and details of evaluations are given in Table 1.

Table 1. Times and Events Schedule

	Eligibility* Baseline/D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D 9-13**	**D 14/ET**	**D 15-20**	**D 21 (EOS)**
Investigations												
Consent Randomisation	○*											
Liver function, eGFR	○*									○		
Study Drug Administration	○	○	○	○	○	○	○	○	○	○	○	○
Medical file review												
Demographics, Diagnosis	○*											

	Eligibility* Baseline/D1	D2	D3	D4	D5	D6	D7	D8	D 9-13	D 14/ET	D 15-20	D 21 (EOS)
Selected medications (e.g., opioid)	○	○	○	○	○	○	○	○	○	○	○	○
Breakthrough medications	○	○	○	○	○	○	○	○	○	○	○	○
Patient assessed (PRO assessments)												
Daily Diary	○	○	○	○	○	○	○	○	○	○	○	○
BPI-SF	○									○		
Worst pain (BPI-item 3)	○*	○	○	○	○	○	○	○	○		○	○
Average pain (BPI-item 5)	○*	○	○	○	○	○	○	○	○		○	○
SF-MPQ-2	○									○		
EORTC-QLQ-PAL-C15	○									○		
HADS	○*									○		
Global impression of change				○				○		○		○
Pain expectation	○											
PRO-CTCAE	○							○		○		○
Clinician assessed												
Medical assessment	○*											
Height and Weight	○											
Vital signs	○									○		○

	Eligibility* Baseline/D1	D2	D3	D4	D5	D6	D7	D8	D 9-13	D 14/ET	D 15-20	D 21 (EOS)
AKPS	○*		○				○			○		
LANSS	○*											
Personalised pain goal	○											
Adverse events (CTCAE)	○		○				○			○		○
Substudies (if consented)												
Qualitative patient interview										○		

BPI-SF: Brief Pain Inventory-Short Form, SF-MPQ2: Short-Form McGill Pain Questionnaire-2, EORTC-QLQ-PAL-C15: The European Organisation for Research and Treatment of Cancer quality of life core 15 palliative questionnaire, HADS: Hospital Anxiety and Depression Scale, PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, AKPS: Australia-modified Karnofsky Performance Status, LANSS: the Leeds Assessment of Neuropathic Symptoms and Signs, CTCAE: Common Terminology Criteria for Adverse Events, EoS: End of Study, ET: Early Termination.

Once a patient is enrolled or randomised, the study site will make every 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, 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 site will maintain individual records for each patient as source data, which will include a signed 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 Japanese Organisation for Research and Treatment of Cancer (JORTC) Data Center (Japan) and the Improving Palliative Care through Clinical Trials (IMPACCT) Trials Coordination Centre (Australia) will oversee the intra-study data sharing process in each country. The clinical data entry, data management and central monitoring will be performed using the electric data capture system VIEDOC 4 (PCG Solutions, Sweden) in Japan and REDCap (Vanderbilt University, USA) in Australia. An interim analysis will not be performed. Audit may take place by JORTC Audit Committee in Japan and by an external agency in Australia.

Safety assessments

Investigators must record all AEs in the medical records and web systems. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE Ver.4.0) [27,28] will be used to grade each AE. All AEs are to be followed up continually during their course. All serious adverse events (SAEs) must be reported to Osaka City University Hospital Certified Review Board (CRB) and a Medical Monitor within Australia, with annual safety reporting to the Human Research Ethics Committee (HREC), and to investigators in all sites. Participants that are enrolled into the study

will be treated by health care providers properly.

Assessment tools

All the appropriate permissions were obtained for the use for the assessment instruments.

Brief Pain Inventory-Short Form (BPI-SF)

The Brief Pain Inventory – Short Form will be used as it is a brief and easy tool for the assessment of pain within both the clinical and research settings. It has been validated in both the chronic pain and cancer settings. The numerical rating scale of 0 to 10 is simple for participants to use and reflects common clinical assessment of pain [29].

Global Impression of Change

The Global Impression of Change is a participant-rated 7- point scale (1-7) that provides information about the participants' perception of their overall change in pain since commencing the study. This will allow the investigators to compare the pain rating using the NRS with participant perception of improvement. The results of this scale over the study period will assist to determine the clinical significance of any

improvement seen [30].

Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)

The LANSS estimates the probability that neuropathic mechanisms contribute to the chronic pain experience in each participant. It has 85% sensitivity for detecting neuropathic pain. It is a seven-item scale including sensory description and examination. A score of ≥12 indicates that neuropathic mechanisms are likely to contribute to the participant's pain. It will be used to define a population with neuropathic pain [31]. The LANSS will be collected to determine eligibility.

Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2)

The Short Form McGill Pain Questionnaire 2 (SF-MPQ-2) [32] will be used to examine differences in effects due to pain mechanisms. The SF-MPQ-2 and its Japanese version have been validated in cancer neuropathic pain [33]. It is a 22-item questionnaire covering the domains of superficial and deep spontaneous pain, paroxysmal pain, evoked pain and paresthesia/dysaesthesia. We also used this tool in the pilot study that underpins the current trial [15,16] and consider the possibility of effective pain types. This time it will be used to make a comparison for that verification.

Personalised pain goal

The personalised pain goal [34] is a tool used to tailor pain management to individual needs. "Participants are asked to describe on a 0-10 scale, the level/intensity of pain that will allow the patient to achieve comfort in physical, functional, and psychosocial domains" [34] This will be asked by the research nurse or staff at baseline, and may include explanation of terminology. Zero will represent no pain and ten will represent worst pain. This is not a validated tool. We use this scale because some argued that neither between-group difference in mean values nor changes in pain intensity (e.g., absolute or relative values) correctly evaluated the patient's discomfort.

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

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL will be used for evaluation of patient quality of life. The reliability and validity of the original version [35] and Japanese version [36] have been confirmed.

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) [37] 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 [37,38].

Patient Expectation

Patient's expectation of a decrease in pain of each patient will be examined as one study has shown the effect of expectation of pain decrease influenced pain prognosis in cancer pain [39].

Australia-modified Karnofsky Performance Status (AKPS)

The Australia-modified Karnofsky Performance Status (AKPS) [40] will be used to assess performance status. The AKPS is a useful modification of the Karnofsky Performance Status (KPS) [41] and validated as an appropriate tool for palliative medicine.

CTCAE/PRO-CTCAE

Any new or worse AEs will be evaluated and classified according to CTCAE criteria [27,28] and the Patient-Reported Outcomes version of the Common Terminology Criteria

for Adverse Events (PRO-CTCAE) [42]. PRO-CTCAE was developed by the National Cancer Institute (NCI) as an AE assessment system to evaluate patients' subjective symptoms. Its content validity and psychometric validity have been verified in the original English version [42,43]. Japanese version of the PRO-CTCAE had acceptable reliability and linguistic [44] and psychometric [45] validity for common and clinically important symptoms.

Interventions

All participants will take blinded opaque capsules each morning after breakfast and bedtime for 14 days. Dose escalation is until day 14 and from day 14 to 21 is a dose de-escalation period to avoid withdrawal effects. Participants will increase the study drugs to stage 2 on day 4 and to stage 3 on day 8. Participants will be assessed for AEs during the study period. If a person experiences mild, moderate, or severe AEs, as classified by the NCI Criteria, they will be treated symptomatically. If symptoms persist, participants will continue the previous dose prior to adverse symptoms being noted (or if on the amount of stage 1 will exit the study). If participants experience unacceptable AEs on: days 1 - 3 on the stage 1 drug (30mg duloxetine or 50mg pregabalin daily dose) they will be withdrawn from the study; days 4 - 7 on the stage 2 drug (30mg duloxetine or

150mg pregabalin daily dose) they will continue in the study to day 14 on stage 1 drug (30mg duloxetine or 50mg pregabalin daily dose); days 8 - 14 on the stage 3 drug (60 mg duloxetine or 300mg pregabalin daily dose) they will continue in the study to day 14 on stage 2 drug (30mg duloxetine or 150mg pregabalin daily dose) . Assessments to determine net clinical effect will be conducted on day 14. The dose will be tapered down until the amount of stage 1 (stage 3→2→1 or stage 2→1) and the medication will be stopped to avoid a discontinuation syndrome, mirroring the schedule for initial upwards titration (i.e. duloxetine 30mg/pregabalin 150 mg for 4 days, 30mg/50mg for 3 days then cease <from stage 3; days 15-21> or duloxetine 30mg/pregabalin 50mg for 3 days then cease < from stage 2; days 15-17 >). Rescue opioids will be available on an 'as needed' basis, up to eight doses of currently prescribed breakthrough opioid in any 24-hour period. Following cessation of study medications, participants will be reviewed by their treating clinician regarding any future open label prescribing of the study medications. If pain is present or re-occurs during the downward titration phase, the treating clinician should determine the most appropriate pain medication according to the local standard of care and monitor the patient closely.

Concomitant therapy

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. New analgesics will not be started. If nausea occurs during the treatment period, use of an antiemetic will be permitted.

Study endpoints

Primary endpoint

The primary endpoint is a mean difference between study arms of worst pain intensity over the previous 24 hours at day 14 measured using the BPI items 3.

Secondary endpoints

Efficacy will be assessed using the following secondary endpoints: the average pain intensity (BPI items 5) at days 14 and 21; the worst pain intensity (BPI items 3) at day 21; the SF-MPQ-2 scores; EORTC QLQ-C15-PAL scores; changes in HADS score; and daily opioid dose (on each day). AEs will also be assessed using NCI CTCAE and PRO-CTCAE.

Additionally we will calculate percentage of participants with a reduction (BPI-I items 3) of 1 point; 2 point; > 2 points; 30% and 50% pain decrease from the baseline on day3, day7 and day14, percentage of participants in whom increase to the maximum dose is achieved, percentage of participants in whom can achieve personal pain goal, percentage of participants in whom need to adjust baseline opioids and adjuvant analgesics, the completion rate of the study medication and procedures, total daily dose of adjuvant analgesics use (on each day), prospectively sought AEs with the likelihood of relationship to intervention (toxicity), and health service utilisation-planned and unplanned contact, investigations, hospitalisations.

Statistical considerations

All statistical procedures will be detailed in the statistical analysis plan through a blinded data review before data fixation, including the handling of missing values and necessity of sensitivity analysis. For the primary endpoint, the current policy is to employ observed case analysis when the number of missing observations is very small, and to employ multiple imputation when there are a certain number of missing observations and the missing mechanism is considered to be missing at random.

Statistical hypothesis

Comparison of the primary endpoint of the worst pain intensity (BPI items 3) at day 14 between duloxetine groups and pregabalin groups will be conducted using a two-sided Student's t-test at a significance level of 5% according to the intention-to-treat principle. Point estimates and 95% CIs for the difference between two group means will be calculated.

The secondary endpoints of efficacy (BPI items 5, SF-MPQ-2, EORTC QLQ-C15-PAL, HADS, daily opioid dose, and group comparison of worst pain on the BPI-item3 in the previous 24 hours) will be evaluated similarly to the primary endpoint.

Longitudinal changes in BPI-item 3 and BPI-item 5 will be evaluated using mean scores and 95% CIs. The distribution of grades of AEs (NCI CTCAE and PRO-CTCAE) and the incidence of AEs of Grade 3 or higher and of Grade 4 will be determined. Sub-group analyses will be performed to evaluate the difference among various types of peripheral NCP.

Sample size calculation

The difference between group BPI-item 3 on day 14 is assumed to be one point and the standard deviation of the NRS is taken to be 2.0 points [16, 46, 47]. As there was no consensus

about the minimal clinically important differences in NCP at the planning stage of the study, we decided to adopt 1-point difference compared to pregabalin as the clinical significant difference, according to the recommendation of interpreting the clinical importance of group differences in chronic pain clinical trials [46].

Based on our primary outcome, which is worst pain intensity (BPI-item 3) at day 14, we will estimate 64 participants per group would detect a mean difference of 1.0 (SD 2.0; 80% power with a two-sided significance level of 0.05 for comparison).

Considering withdrawal and drop-out of 20%, we plan to recruit 160 participants into the study.

Ethical issues

All patients will be required to provide written informed consent. The study will be performed in accordance with the Declaration of Helsinki, the Australian Good Clinical Practice, and the Japan's Clinical Trials Act. The protocol was approved by the Osaka City University Hospital CRB and the Scientific Advisory Committee (Palliative Care Clinical Studies Collaborative (PaCCSC)) within Australia with annual safety reporting to the approving HRECs. This trial has been registered with the clinical trials registries within both Japan and Australia. Modifications in the study protocol will be

communicated to approving CRB (Japan) and HRECs (Australia). Each Ethics Committee or Institutional Review Board will review informed consent materials given to participants and adapt according to their own institution's guidelines.

Discussion

To our knowledge, the results of the recent systematic review [48] has shown the low quality of currently available evidence on the effectiveness of adjuvant analgesics in the treatment of cancer pain and our subsequent clinical trial [16] shows the low-quality evidence of adjuvant analgesics for opioid refractory NCP as well. There has been no RCT of the analgesic efficacy of oral duloxetine for the management of opioid refractory NCP as a first line treatment.

In our planned trial, the use of a randomised, double-blind, two-parallel arm design, 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, especially in this population [49], namely; the treatment might have carryover effects and alter the response to subsequent treatments; and palliative patients may not be in a comparable condition

at the start of the crossover trial treatment period.

Several issues related to the content of the trial require discussion. There will be five major concerns: (i) the heterogeneity of causes of NCP, (ii) risk of drug-drug interactions and masking/confounding of the true effect of the study intervention, (iii) the choice of the primary endpoint, (iv) necessity of a placebo group, and (v) the dose schedule of each drugs.

First, to address the heterogeneous causes of NCP, we excluded patients with CIPN and central NP, and targeted patients with NCP non-responsive or intolerant to opioid therapy, but the trial might still be criticised due to combination of various peripheral NCPs in one study. Narrower criteria are theoretically possible, but accrual of patients who meet these criteria is likely to be difficult. Furthermore, in palliative care field, a framework for classifying research subpopulations to which the research findings are being applied by clinicians, health planners, and funders in real-world settings has been suggested [50]. We thus decided to include various types of peripheral NCP in the study, and sub-group analyses will be performed.

Second, although drugs with major drug-drug interactions with duloxetine or pregabalin (e.g., contraindicated) will be excluded, continuation of the other adjuvant analgesics might cause the risk of moderate-minor drug-drug interactions. The

possibility of masking/confounding of the true effect of the study intervention cannot be completely ruled out, however, randomisation will allow for some degree of balance between the groups.

Third, the primary endpoint is the difference in worst pain intensity score at day 14 between two groups. Although we had acknowledged that the average pain intensity is adopted by many clinical trials about NCP [51], including three RCTs [8,9,16] in patients with NCP, some authors recommend worst pain intensity in the last 24 hours as primary endpoints because it satisfies most key recommendations in the draft guidance [18]. Furthermore, to evaluate chronic pain, especially considering the nature of NCP in this setting, we concluded that it is better to use the "worst pain intensity in the last 24 hours" as the primary endpoint after discussion among the members of the study's steering committee.

Fourth, although we discussed the need for a placebo arm, gabapentinoids (gabapentin and pregabalin) are one of the most widely used treatments for NCP (not for just cancer pain, nor CIPN). Phase III studies [8,10] revealed moderate analgesic effects of gabapentinoids (gabapentin and pregabalin) compared with placebo in combination with opioids for NCP (not for just cancer pain, nor CIPN). From the results of these 2 RCTs [8,10], we concluded that it was no longer ethical to use a placebo arm.

Finally, the following dose titration schedule has been devised to maximize the likelihood of benefit while minimising the risk of AEs. The participant will commence duloxetine or pregabalin at 30mg and 50mg respectively and will be titrated according to response in increments of cessation to a maximum of 60mg (duloxetine) and 300mg (pregabalin). As the starting dose differs between Australia and Japan, it was necessary to determine a uniform dose for the international study. The starting dose of duloxetine in Japan is 20 mg in the setting for palliative care [52], while in the West it is usually 30 mg or 60 mg. We chose 30 mg for the starting dose of duloxetine because we assumed that it was also tolerable for Japanese patients. In the same setting, the starting dose of pregabalin in Japan is 50 mg [52], while in the West it is usually 25-100mg from the results of recent systematic review and meta-analysis [13]. Taking these results into consideration, we assume that starting 150 mg pregabalin is not tolerable and 50 mg is safe for patients in both countries. Dworkin et al. conducted a systematic review of pharmacologic management of NCP and made the recommendations for maximum dosing [53] and according to the National Comprehensive Cancer Network (NCCN) guideline of adult cancer pain [2] we have defined initiation dose and maximum dose of both drugs.

Moreover, we set a dose decrement titration periods instead of doing key open to

avoid a discontinuation syndrome of each drug and to keep scientific reliability. Therefore, the planned international double-blind multi-centre RCT will be the first to evaluate the efficacy and safety of duloxetine and pregabalin treatment in patients suffering from well-defined NCP refractory to opioids, and the results of the trial will help to clarify the first-line standard treatment for NCP.

Trial status

The trial opened in January 2020. At the time of manuscript submission (February 2021), twenty-one patients have been randomised. We expect to complete the recruitment by September 2022 and to finish this trial by March 2023.

Confidentially

Data will be retained in accordance with the Japanese Clinical Research Act and the Australian regulations for Good Clinical Practice. 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 15 years after study completion and then destroyed by

the data centre.

Dissemination

The results of this trial 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

Immediately after the publication of the primary results, de-identified individual participant data that underlie the results reported in the article(s) and other documents (study protocol and statistical analysis plan) will be available for any purpose, only if approved by JORTC Independent Data Monitoring Committee (IDMC) and the Cancer Symptom Trials (CST) Scientific Advisory 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

The protocol was approved by the Osaka City University Hospital Certified Review Board and South Western Sydney Local Health District Human Research Ethics Committee (Australia). Informed consent for participation in the trial will be obtained from all patients.

Patient and Public Involvement

The invaluable contribution of patients and caregivers are recognised by ensuring that all research undertaken considers patients and caregivers experience and perspectives. Patients and caregivers' representatives were actively involved in all aspects of our research including the design, implementation, evaluation, and dissemination of this randomised control clinical trial. As a member of the protocol investigator team, the patients and caregivers' representative ensure that the physical and emotional wellbeing of patients and caregivers were taken into consideration when planning this clinical trial and implementing the result findings into practice.

Competing interests

The authors declare that they have no competing interests.

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Sponsor detail

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Abbreviations

NCP: Neuropathic cancer pain; RCTs: randomized controlled trials; BPI: Brief pain inventory; LANSS: the Leeds assessment of neuropathic symptoms and signs; CIPN: Chemotherapy-Induced Peripheral Neuropathy; TCA: Tricyclic Antidepressant; SNRI: Serotonin & Norepinephrine Reuptake Inhibitors; AE: Adverse event; NNT: number needed to treat; AKPS: Australia-modified Karnofsky Performance Status; KPS: Karnofsky Performance Status; IASP: International Association for the Study of Pain; NRS: Numerical Rating Scale; HADS: Hospital Anxiety and Depression Scale; JORTC: Japanese Organization for Research and Treatment of Cancer; IMPACCT: The Improving Palliative Care through Clinical Trials; AE: Adverse event; CTCAE:

Common Terminology Criteria for Adverse Events; SAEs: Serious adverse events; CRB: Certified Review Board; HREC: Human Research Ethics Committee: BPI-SF: Brief Pain Inventory-Short Form; SF-MPQ: Short-Form McGill Pain Questionnaire; EORTC: European Organization for Research and Treatment; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events ; NCI: National Cancer Institute; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NMDA: N-methyl-D-aspartate; PaCCSC: Palliative Care Clinical Studies Collaborative; NCCN: National Comprehensive Cancer Network; IDMC: Independent Data Monitoring Committee; CST: Cancer Symptom Trials; AMED: Japan Agency for Medical Research and Development; NHMRC: Australian Government National Health and Medical Research Council; UTS: University of Technology Sydney

Authors' contributions

HM, KC, BF, LB, HI, YM, HH, KA, JL, BL, PA, SK, NF, TM, ML, MA, ES, SI, JP, AK, and DC participated in the design of the study. SO, TY, 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 group or the pregabalin group.

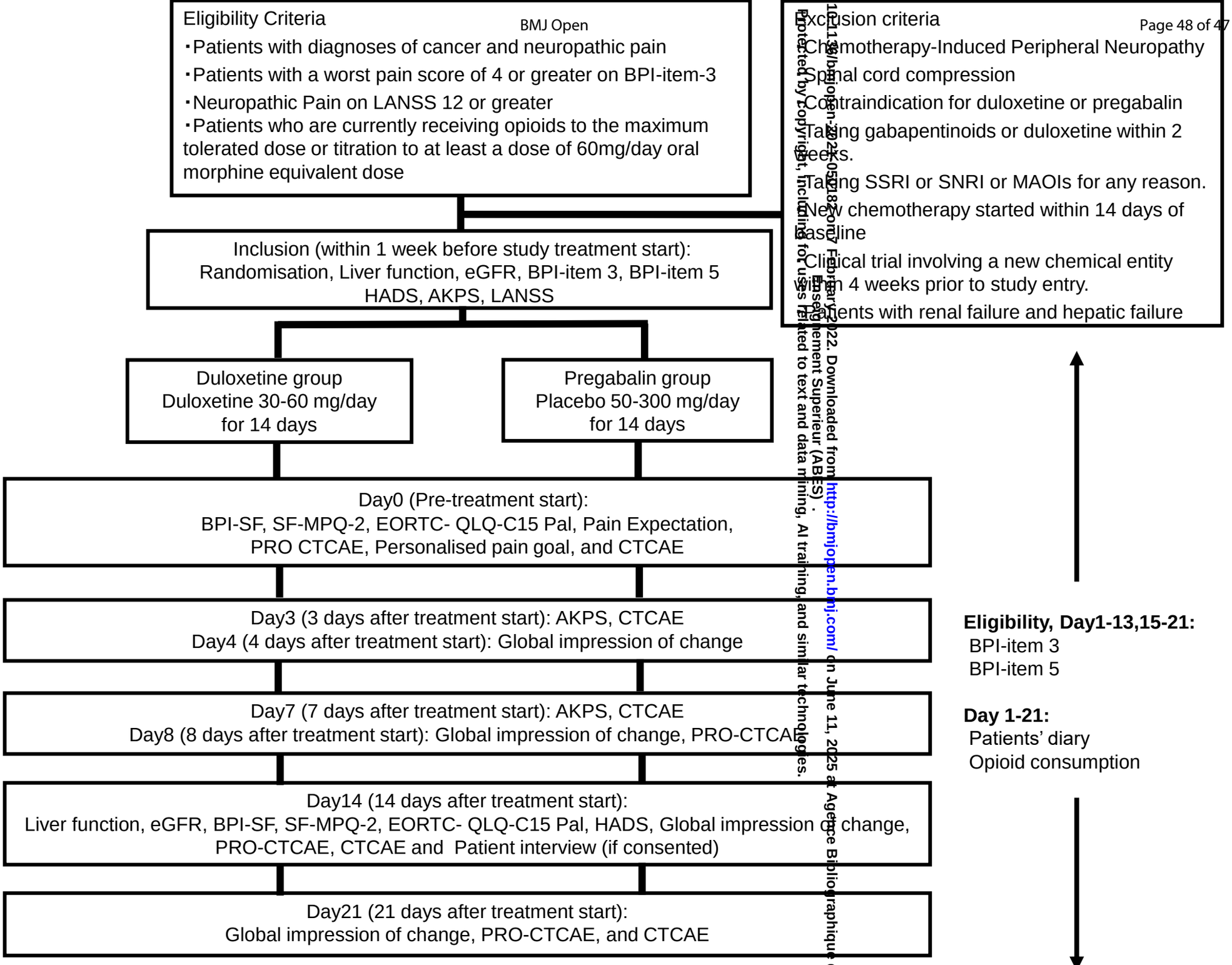

Fig.1. Flow chart of the procedures in the study