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Sipjeondaebo-tang in patients with breast cancer with fatigue: a protocol for a pilot, randomised, double-blind, placebo-controlled, cross-over trial

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Abstract

Introduction

Cancer-related fatigue is a frequent symptom in patients with cancer and one of the most distressing symptoms in patients with breast cancer. Sipjeondaebo-tang (Juzen-taiho-to in Japanese or Shi-Quan-Da-Bu-Tang in Chinese) is a widely used herbal medicine for treatment of fatigue in Korea, China and Japan. The purpose of the present study is to evaluate the feasibility of Sipjeondaebo-tang for cancer-related fatigue.

Methods and analysis

The present study is a randomised, double-blind, placebo-controlled, cross-over study. Forty eight patients with breast cancer who are indicated for doxorubicin and cyclophosphamide will be recruited. The participants will receive 3 grams of Sipjeondaebo-tang or a placebo three times a day for 56 days. The primary outcome measurement is the change in the Brief Fatigue Inventory (BFI) scores. The secondary outcome measurements include the changes in the visual analogue scale (VAS) of fatigue, quality of life measured by the European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 and QLQ-BR23. The VAS of fatigue will be measured on every visit, and other outcomes will be measured on visit 2, 4, 6, and 7. The total study period is 14 weeks.

Ethics and dissemination

This study has been approved by the institutional review board of the Catholic Kwandong University International St. Mary's Hospital (reference IS16MNSI0011). Results will be published to a peer-reviewed journal and presented at scientific conference.

Trial registrations
ClinicalTrials.gov NCT02858856; Pre-results.

Strengths and limitations of this study

▪ This study is the first randomized controlled trial to evaluate the feasibility of Sipjeondaebo-tang for treatment of cancer-related fatigue.

▪ All participants receive identical chemotherapy.

▪ Limitations of this study is the relatively small number of participants and that it is conducted in single institution.

Introduction

Cancer-related fatigue has reported as frequently experienced symptom in patients with cancer regardless of tumour type, and one of the most distressing symptoms in patients with breast cancer.[1] National comprehensive cancer network (NCCN) defined cancer-related fatigue as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportionate to recent activity.[2] Fatigue is the most commonly reported side effect of various chemotherapy such as pain, nausea, and vomiting.[3] It has been reported that the prevalence of fatigue of patients with breast cancer receiving chemotherapy was more than 72%. [4 5] A previous study conducted at a hospital in south Korea reported that the prevalence of fatigue in cancer patients was 32.3% and that of women was 45.5%.[6]

Managing cancer-related fatigue is one of the main concerns of cancer patient management. Cancer-related fatigue lead to considerable socioeconomic costs for patients with cancer. Patients with cancer had difficulties in daily lives due to fatigue and missed 4.2 days of work per month on average. Primary caregiver of patient with cancer was also negatively influenced, and they missed 4.5 days of work per month on average.[7] Cancer-related fatigue

also compromise the quality of life and, in severe cases, it negatively affects the effectiveness of treatment by causing dose reductions or delaying anticancer therapy or reducing adherence to prescribed drugs.[8] Therefore management of cancer-related fatigue is very important. Though several factors have been identified that could contribute to the development of cancer-related fatigue, the pathological mechanisms involved are not well known.[9] The treatment of underlying pathologies of cancer-related fatigue such as hematopoietics or antidepressants are currently used, but it fails to treat fatigue produced by other etiologies or it only improves anemia or depression.[10] Furthermore cancer-related fatigue is not treated adequately compared to the needs of patients with cancer. More than half (61%) of patients with cancer answered that the fatigue have greater influences on their lives than pain, however only 27% of patients with cancer received specific recommendations for fatigue treatment. There is no definitive treatment for cancer-related fatigue, so only 9% of physicians prescribed drugs in response to fatigue.[7] Therefore, more research on evidence-based interventions for cancer-related fatigue is needed.

Sipjeondaebo-tang (SJDBT, Juzen-taiho-to in Japanese or Shi-Quan-Da-Bu-Tang in Chinese) has been the widely used herbal medicine in Korea, China and Japan, and in Korea, it is the third most commonly prescribed herbal medicine.[11] SJDBT treats syndrome of dual deficiency of qi and blood by balancing Yin and Yang in Korean medicine theory.[12] The efficacy of SJDBT approved by the Ministry of Food and Drug Safety (MFDS) is weakness after illness, anorexia, night sweats, cold hands and feet, and anemia.[13] Despite the frequent use of SJDBT for the treatment of fatigue, there were only clinical trials on hematotoxicity[14] and anemia of SJDBT,[15 16] and the scientific evidence for SJDBT on cancer-related fatigue is lacking. Therefore, the aim of the present study is to evaluate the feasibility of SJDBT for fatigue in patient with breast cancer receiving chemotherapy. For this, a randomised, double-blind, placebo-controlled, cross-over trial has been planned.

Methods and analysis

Study design

A randomised, double-blind, placebo-controlled, cross-over trial will be conducted at the Catholic Kwandong University International St. Mary's Hospital in Incheon, Republic of Korea. Any participants meeting the eligibility criteria will be enrolled. After enrolment, the participants will be randomly allocated to two groups: the group A and group B. Schematic flow of the study is shown in Figure 1. Both groups will receive 4 cycles of doxorubicin and cyclophosphamide chemotherapy, and each cycle will last 21 days. There is no expected protocol modification. However if it is happens, any modification in the protocol will be communicated to the entire investigators through a conference. The final manuscript for a submission will include all amendments.

Recruitment

Participant will be recruited as follows. Patients who visit the trial institution and fulfil the eligibility criteria will be recommended to participate in the study by the investigator in charge. The investigators will provide detailed trial information including study period, purpose, eligibility criteria, intervention and design.

Participants

Inclusion criteria

The inclusion criteria are as follows: men and women aged 20 to 65 years; patients who have histologically or cytologically confirmed breast cancer; patients who are indicated for

doxorubicin and cyclophosphamide; Eastern Cooperative Oncology Group (ECOG) performance status score 0 to 2; participant is willing and able to give informed consent for participation in the study

Exclusion criteria

The exclusion criteria are as follows: patient impossible to orally intake; patients who receive neoadjuvant chemotherapy; patient with mental illness such as dementia, delirium and depression; patients with hepatitis B, C or liver cirrhosis; patients with severe renal disability (2 times higher than the upper limit of normal for serum creatinine); patients with severe liver disability (3 times higher than the upper limit of normal for ALT, AST); patients with diabetes (HbA1c>8%) or hypertension (SBP > 160mmHg or DBP > 100mmHg) that is not controlled by diet or medication; patients with thyroid disease; severe systemic disease; use of other investigational products within the 30 days; known prior hypersensitivity to investigational product; individuals who are judged inappropriate for the study

Subject withdrawal criteria

The participants who meet the following criteria will be discontinued from the study. The participants who are withdrawn from study after allocation will be followed for outcomes as far as possible. The occurrence of a serious adverse event related to investigational product; investigator's decision that it is not appropriate to proceed the trial; participants who do not comply with investigator's instruction; occurrence of significant protocol violations; participant's withdrawal of consent or request to stop taking medication

Sample size

This study is a pilot study that examine the feasibility of conducting a large-scaled randomised clinical trial of SJDBT for treating cancer-related fatigue in patient with breast cancer. Thus, considering the sample size of other similar pilot studies, a total of 48 participants will be recruited for the present study.[17 18] Twenty four participants will be allocated to the group A and another twenty four to the group B.

Randomisation and allocation

The participants who meet the inclusion and exclusion criteria will be randomly allocated using random numbers generated by the Contract Research Organisation (CRO), Institute of Safety, Efficacy and Effectiveness Evaluation for Korean Medicine (ISEE). Block randomisation using R software with block size of four will be conducted. The enrolled participants will be assigned to one of two groups with the allocation ratio of 1:1. The randomisation table will be kept in the opaque and sealed envelope by the ISEE and it will be unclosed according to Standard Operating Procedures (SOPs).

Blinding

A researcher at ISEE will prepare computer generated random number and randomisation table. The Hanpoong Pharm and Foods CO., Ltd., the pharmaceutical company will produce and label the investigational product. The labelled investigational products will be provided to the study institution by the pharmaceutical company. Since ISEE is an independent centre from the trial institution, investigators involved in recruitment, treatment or outcome assessment will blind to the allocation.

Treatment protocol

The participants will receive SJDBT and placebo for total of 56 days. They will take 3 grams of investigational products orally with water three times a day after meals for 56 days. Administration periods of the investigational products will be for two weeks prior to visiting day for chemotherapy. Thus, the participants of group A will take SJDBT from day 1 to day 14 and from day 22 to day 35 and take placebo from day 43 to day 56 and from day 64 to day 77 of trial period. The participants of group B will take placebo from day 1 to day 14 and from day 22 to day 35 and take SJDBT from day 43 to day 56 and from day 64 to day 77 of trial period. The participants will be asked to return drug remains for the sake of calculating the compliance. During the clinical trial, the participants will be prohibited to get other treatment for fatigue.

Interventions

SJDBT is an herbal medicine which has been approved from the Korean ministry of food and drug safety (MFDS). It consists of 1.00 g Cinnamomi Cortex, 1.00g Paeoniae Radix, 1.00g Atractylodis Rhizoma Alba, 1.00g Ginseng Radix Alba, 1.00g Cnidii Rhizoma, 1.00g Astragali Radix, 1.00g Poria Sclerotium, 1.00g Rehmanniae Radix Preparata, 1.00g Angelicae Gigantis Radix and 0.5g Glycyrrhizae Radix. These raw materials and lactose hydrate and corn starch will be concentrated to single dose, 3 grams. The placebo consist of lactose, corn starch and caramel colouring, and it has an appearance, weight, colour and taste similar to SJDBT. Investigational products used in the present study is a dark brown-coloured granule, and are produced by Hanpoong Pharm and Foods Co., Ltd. in accordance with Korea Good Manufacturing Practice (KGMP) standards.

Primary outcome measurement

The primary outcome in the present study is the change in the Brief Fatigue Inventory (BFI) between the duration of the SJDBT administration and duration of placebo administration. BFI is an instrument for the rapid assessment of subjective fatigue status in patients with cancer.[19] The development of Korean version of the BFI was led by the national cancer center in Korea. Korean version of the BFI has now been validated.[20] The BFI consists of 9-item on 11-point rating scale and can be measured within 10 minutes. The BFI will be measured by a trained researcher at visit 2, 4, 6, and 7 according to SOPs.

Secondary outcome measurement

Secondary outcome measurements of the present study include the changes in the visual analogue scale (VAS) of fatigue, quality of life measured by the European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 and QLQ-BR23. EORTC-QLQ-C30 is a questionnaire developed to evaluate the quality of life in patients with cancer and QLQ-BR23 is a breast cancer specific module.[21] Korean version of the EORTC-QLQ-C30 and QLQ-BR23 have now been validated in Korean patient with cancer.[22 23] The study schedule according to The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) is detailed in Table 1.

Table 1 - Study schedule of the SJDBT trial (14 weeks)

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	Day -7 (V1)	Day 0 (V2)	Day 14 (V3)	Day 35 (V4)	Day 56 (V5)	Day 77 (V6)	Day 98 (V7)
Eligibility screen	X						

Informed consent	X						
Allocation		X					
Group A **SJDBT**		X*	X*				
Placebo				X*	X*		
Group B **SJDBT**				X*	X*		
Placebo		X*	X*				
Demographic characteristic	X						
Vital signs	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Laboratory test	X	X	X	X	X	X	X
Brief fatigue inventory		X		X		X	X
EORTC-QLQ-C30		X		X		X	X
EORTC-QLQ-BR23		X		X		X	X
VAS for fatigue		X	X	X	X	X	X

* The durations of administration are two weeks prior to the next visit.
(Day 1~14, day 22~35, day 43~56, day 64~77)

Safety outcomes

All safety related variables including vital signs, physical examination, hematologic test, biochemical test, urine test and adverse events will be recorded on the case report form (CRF) at every visit.

Statistical analysis

Efficacy assessment

The baseline characteristics will be analysed by either an independent two-sample t-test for continuous variables or the chi-square test for the categorical variables (Fisher's exact test will be used when the expected value is < 5). The continuous variables will be presented as the mean ± SD, and the categorical variables will be presented as the n (%). Statistical analyses for efficacy will be conducted for both the ITT (intention-to treat, all randomised participants who received at least one dose of study drug) and PP (per-protocol, subset of the participants completed the study without any major protocol deviations) data sets. ITT analyses will be considered as primary analyses and PP analysis will be considered as secondary analysis. The missing values will be imputed by the last-observation-carried-forward (LOCF) method. For the primary outcome measure, the mean differences of BFI between SJDBT administration period and placebo administration period will be compared using an independent two-sample t-test. If the normal distribution assumption is not satisfied for the continuous variables, Wilcoxon rank sum test will be conducted. For the secondary outcome measure, the mean differences of fatigue VAS, EORTC-QLQ-C30 and QLQ-BR23 between SJDBT administration period and placebo administration period will be compared using an independent two-sample t-test. The p-value of less than 0.05 will be regarded as statistically significant. The present study has not consider an interim analysis.

Safety assessment

The participants will be supposed to report any adverse events that may occur during the trial at every visit. Any identified adverse event will be recorded in the CRFs. If severe adverse event occur and is associated with the investigational product, the participant will be withdrawn from the study. Investigators will provide appropriate treatment to him or her. Any loss caused by the study will be compensated by insurance. The safety related variables

including laboratory test results and adverse events will be compared between SJDBT administration period and placebo administration period using the ITT dataset.

Data and safety monitoring

The ISEE will monitor the present study for quality control according to SOPs. The trial institution will be monitored while this study is ongoing. There is no plan for auditing. For data quality improvement, double data entry and range checks for data values will be conducted. Adverse reactions will be reported to IRB, and serious and unexpected adverse reactions will be reported to regulatory authorities. There will be no coordinating centre, steering committee, or endpoint adjudication committee in the present study.

Ethics and dissemination

This study has been approved by the IRB of the Catholic Kwandong University International St. Mary's Hospital (reference IS16MNSI0011). The current protocol version is 1.3. Obtaining a written informed consent will be conducted prior to study commencement from each participants by the investigator. The present study will be conducted in compliance with the Helsinki Declaration and Korean Good Clinical Practice (KGCP) published by the Ministry of Food and Drug Safety (MFDS). Any information obtained from participants will be handled confidentially. During the entire trial period, the data will be handled by the study identification number which is assigned to each participant at enrolment. All the records from the trial will be retained secure in a locked cabinet or password-protected files. Only investigators in charge will have authority to access to the data. The results of this study will be published in a scientific journal. Thus far, there is no plan for public release of the full protocol and individual datasets.

Discussion

The present study investigates the feasibility of SJDBT for cancer-related fatigue in patients with breast cancer. Although there are several published papers on whether SJDBT is effective in patients with cancer, the present study has its own significance. While previous studies focused on hematotoxicity,[14] quality of life,[24] anorexia,[25] and immunity[26] of patients with cancer, the present study evaluates the efficacy on cancer-related fatigue. The limitations of the present study includes the small sample size and single-centre trial. However, to the best of our knowledge, this is the first randomized controlled trial to evaluate the efficacy of the SJDBT for cancer-related fatigue. Furthermore, the present study reduces heterogeneity in participants by specifying not only cancer types but also types of chemotherapy. Besides, this study assesses quality of life to evaluate the effect of SJDBT on general health status of participant. Even though it has a few limitations, the present study would be meaningful in that it is a pilot study to plan further large-scale trials by evaluating not only cancer-related fatigue but also quality of life due to overall symptoms.

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Acknowledgements

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Authors' contributions

CC and SK have written the first manuscript for this trial and they will contribute to monitoring this trial. YK and MK have contributed to the development of the protocol. BHJ and YCS have edited the first manuscript. SGK has conducted all the procedures for this protocol. All authors have read and approved the final manuscript.

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Competing interests

None declared.

Patients consent

Obtained

Ethics approval

The Institutional Review Board of the Catholic Kwandong University International St. Mary's Hospital approved the study (reference IS16MNSI0011).

Provenance and peer review

Not commissioned; externally peer reviewed.

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List of Figure

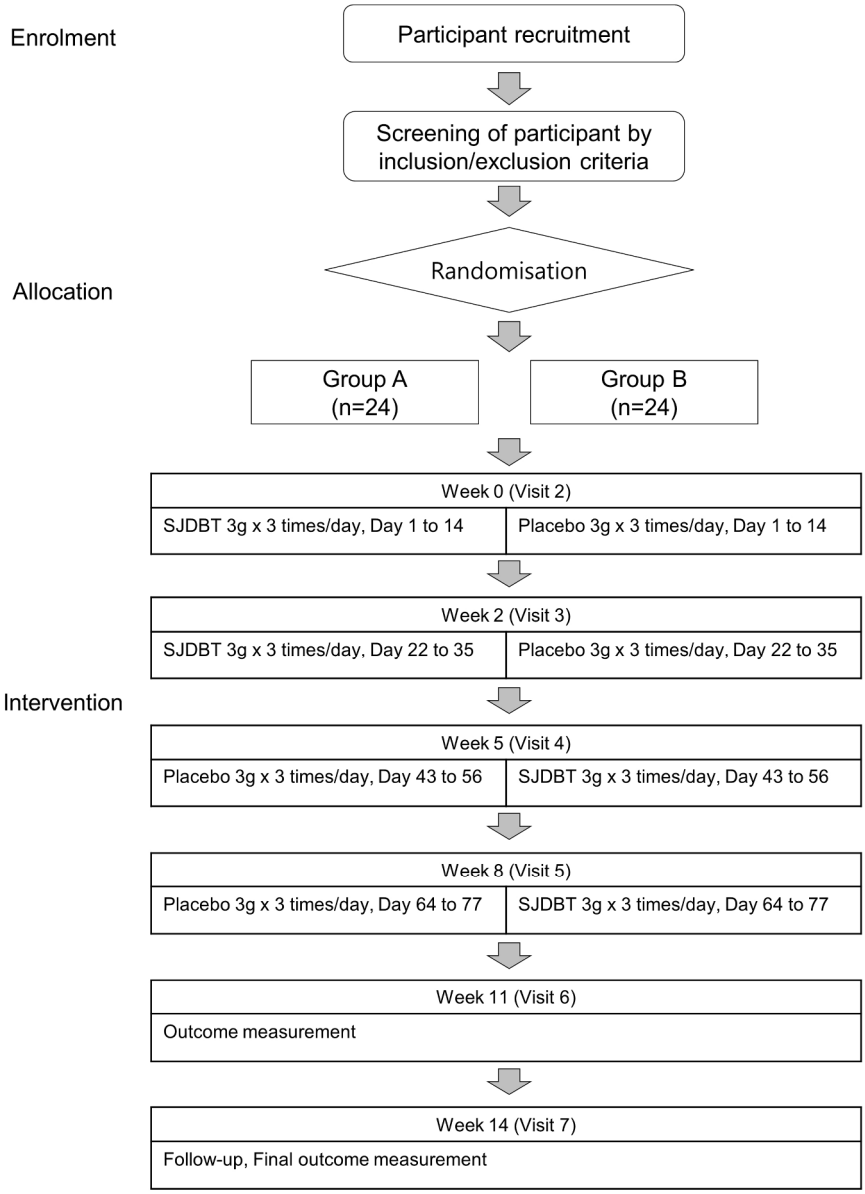

Figure 1. Study flow chart

190x254mm (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	2
	2b	All items from the World Health Organization Trial Registration Data Set	Appendix
Protocol version	3	Date and version identifier	12
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	14
	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	14
	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)	NA

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	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
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)	4
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	5
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)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	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)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	9
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)	9-10

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	6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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	8-9
	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	6

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	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	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	11
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	11-12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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

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Sipjeondaebo-tang in patients with breast cancer with fatigue: a protocol for a pilot, randomised, double-blind, placebo-controlled, cross-over trial

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Sipjeondaebo-tang in patients with breast cancer with fatigue: a protocol for a pilot, randomised, double-blind, placebo-controlled, cross-over trial

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Abstract

Introduction

Cancer-related fatigue is a frequent symptom in patients with cancer and one of the most distressing symptoms in patients with breast cancer. Sipjeondaebo-tang (Juzen-taiho-to in Japanese or Shi-Quan-Da-Bu-Tang in Chinese) is a widely used herbal medicine for treatment of fatigue in Korea, China, and Japan. The purpose of the present study is to evaluate the feasibility of Sipjeondaebo-tang for cancer-related fatigue.

Methods and analysis

The present study is a randomised, double-blind, placebo-controlled, cross-over study. Forty-eight patients with breast cancer who are indicated for doxorubicin and cyclophosphamide will be recruited. The participants will receive 3 g of Sipjeondaebo-tang or a placebo three times a day for 56 days. The primary outcome measurement is the change in the Brief Fatigue Inventory (BFI) scores. The secondary outcome measurements include the changes in the visual analogue scale (VAS) of fatigue, and quality of life measured by the European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 and QLQ-BR23. The VAS of fatigue will be measured on every visit, and other outcomes will be measured on visit 2, 4, 6, and 7. The total study period is 14 weeks.

Ethics and dissemination

This study has been approved by the institutional review board (IRB) of the Catholic Kwandong University International St. Mary's Hospital (reference IS16MNSI0011). The results of this study will be published in a peer-reviewed journal and presented at a scientific conference.

Trial registrations
ClinicalTrials.gov NCT02858856; Pre-results.

Strengths and limitations of this study

▪ This study is the first randomized controlled trial to evaluate the feasibility of Sipjeondaebo-tang for treatment of cancer-related fatigue.

▪ All participants receive identical chemotherapy regimens.

▪ The limitations of this study are its relatively small number of participants and the fact that it will be conducted in a single institution.

Introduction

Cancer-related fatigue is a frequently experienced symptom in patients with cancer regardless of tumour type, and one of the most distressing symptoms in patients with breast cancer.[1] The National Comprehensive Cancer Network (NCCN) defined cancer-related fatigue as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportionate to recent activity.[2] Fatigue is the most commonly reported side effect of chemotherapy, alongside pain, nausea, and vomiting.[3] In patients with breast cancer receiving chemotherapy, the prevalence of fatigue is greater than 72%.[4 5] In a study conducted at a hospital in South Korea, the prevalence of fatigue was 32.3% among patients with cancer and 45.5% among female patients with cancer.[6]

Managing cancer-related fatigue is one of the main concerns of cancer patient management. Cancer-related fatigue leads to considerable socioeconomic costs for patients with cancer. Patients with cancer face difficulties in their daily lives due to fatigue, and they miss an average of 4.2 days of work per month. The primary caregivers of patients with cancer are also negatively influenced, missing an average of 4.5 days of work per month.[7] Cancer-

related fatigue also compromises the quality of life and, in severe cases, it negatively affects the effectiveness of treatment by prompting dose reductions, delaying anticancer therapy, or reducing adherence to prescribed drugs.[8] Therefore, management of cancer-related fatigue is very important.

Several factors contribute to the development of cancer-related fatigue. However, the pathological mechanisms involved are not well known.[9] Currently, the underlying pathologies of cancer-related fatigue are treated with hematopoietic agents or antidepressants, but the treatment is not effective against fatigue produced by other aetiologies, or it only improves anaemia or depression.[10] Furthermore, cancer-related fatigue is not treated adequately to meet the needs of patients with cancer. More than half (61%) of patients with cancer answered that fatigue has greater influence on their lives than pain; however, only 27% of patients with cancer received specific recommendations for fatigue treatment. There is no definitive treatment for cancer-related fatigue, so only 9% of physicians prescribe drugs to treatfatigue.[7] Therefore, more research on evidence-based interventions for cancer-related fatigue is needed.

Sipjeondaebo-tang (SJDBT; Juzen-taiho-to in Japanese or Shi-Quan-Da-Bu-Tang in Chinese) is awidely used herbal medicine in Korea, China, and Japan. In Korea, it is the third most commonly prescribed herbal medicine.[11] According to Korean medicine theory, SJDBT treats the syndrome of dual deficiency of qi and blood by balancing Yin and Yang.[12] The Ministry of Food and Drug Safety (MFDS) has approved SJDBT to treat weakness after illness, anorexia, night sweats, cold hands and feet, and anaemia.[13] Despite the frequent use of SJDBT for the treatment of fatigue, there have only been clinical trials on hematotoxicity[14] and anaemia,[15 16] and scientific evidence for SJDBT on cancer-related fatigue is lacking. Therefore, the aim of the present study is to evaluate the feasibility of SJDBT for fatigue in

patients with breast cancer receiving chemotherapy. To achieve this aim, a randomised, double-blind, placebo-controlled, cross-over trial has been planned.

Methods and analysis

Study design

A randomised, double-blind, placebo-controlled, cross-over trial will be conducted at the Catholic Kwandong University International St. Mary's Hospital in Incheon, Republic of Korea. Any participants meeting the eligibility criteria will be enrolled. After enrolment, the participants will be randomly allocated to two groups: group A and group B. A schematic flow of the study is shown in Figure 1. Both groups will receive four cycles of doxorubicin and cyclophosphamide chemotherapy, and each cycle will last 21 days. There is no expected protocol modification. However, if it happens, any modification in the protocol will be communicated to the investigators via conference calls. The final manuscript for publication will include all the amendments.

Recruitment

Participants will be recruited as follows. Patients who visit the trial institution and fulfil the eligibility criteria will be invited to participate in the study by the investigator in charge. The investigators will provide detailed trial information including study period, purpose, eligibility criteria, intervention, and design.

Participants

Inclusion criteria

The inclusion criteria are as follows: men and women aged 20 to 65 years; patients who have histologically or cytologically confirmed breast cancer; patients who are indicated for doxorubicin and cyclophosphamide; Eastern Cooperative Oncology Group (ECOG) performance status score 0 to 2; and patients willing and able to give informed consent for participation in the study

Exclusion criteria

The exclusion criteria are as follows: patients who are unable to take drugs orally; patients receiving neoadjuvant chemotherapy; patients with mental illness such as dementia, delirium and depression; patients with hepatitis B, hepatitis C, or liver cirrhosis; patients with severe renal disability (two times higher than the upper limit of normal for serum creatinine); patients with severe liver disability (three times higher than the upper limit of normal for alanine transaminase [ALT], and aspartate transaminase [AST]); patients with diabetes (haemoglobin A1c [HbA1c] > 8%) or hypertension (systolic blood pressure [SBP] > 160 mmHg or diastolic blood pressure [DBP] > 100 mmHg) that is not controlled by diet or medication; patients with thyroid disease; patients with severe systemic disease; use of other investigational products within 30 days of the study period; patients with known prior hypersensitivity to the investigational product; and individuals who are judged inappropriate for the study

Subject withdrawal criteria

The participants who meet the following criteria will be discontinued from the study: the occurrence of a serious adverse event related to investigational product; investigator's decision that it is not appropriate to proceed the trial; participants who do not comply with investigator's instruction; occurrence of significant protocol violations; and participant's

withdrawal of consent or request to stop taking medication. The participants who are withdrawn from the study after allocation will be followed for outcomes as far as possible.

Sample size

This is a pilot study that examines the feasibility of conducting a large-scaled randomised clinical trial of SJDBT for treating cancer-related fatigue in patients with breast cancer. Considering that a sample size between 24 and 50 has been recommended for a pilot study,[17] [18] and the sample size of other similar pilot studies, a total of 48 participants will be recruited for the present study.[19] [20] Thus, 24 participants will be allocated to group A and another 24 to group B.

Randomisation and allocation

The participants who meet the inclusion and exclusion criteria will be randomly allocated using random numbers generated by the Contract Research Organisation (CRO), Institute of Safety, Efficacy and Effectiveness Evaluation for Korean Medicine (ISEE). Block randomisation using R software with block size of four will be conducted. The enrolled participants will be assigned to one of two groups with the allocation ratio of 1:1. The randomisation table will be kept in an opaque and sealed envelope by the ISEE and it will be unclosed according to Standard Operating Procedures (SOPs).

Blinding

A researcher at ISEE will prepare computer-generated random numbers and a randomisation table. Hanpoong Pharm and Foods Co., Ltd. will produce and label the investigational product in accordance with Korea Good Manufacturing Practice (KGMP) standards. The labelled investigational product will be provided to the study institution by the

pharmaceutical company. Since ISEE is an independent centre from the trial institution, investigators involved in recruitment, treatment, and outcome assessment will be blinded to the allocation.

Treatment protocol

The participants will receive SJDBT or placebo for a total of 56 days. They will take 3 g of the investigational product orally with water three times a day after meals. The administration periods of the investigational product will be two weeks prior to the visiting day for chemotherapy. The participants of group A will take SJDBT from day 1 to day 14 and from day 22 to day 35, and placebo from day 43 to day 56 and from day 64 to day 77 of the trial period. The participants of group B will take placebo from day 1 to day 14 and from day 22 to day 35, and SJDBT from day 43 to day 56 and from day 64 to day 77 of the trial period. The participants will be asked to return drug remains for the sake of calculating the compliance. During the clinical trial, the participants will be prohibited to get other treatment for fatigue.

Interventions

SJDBT is an herbal medicine that has been approved by the MFDS. It consists of 1.00 g Cinnamomi Cortex, 1.00g Paeoniae Radix, 1.00g Atractylodis Rhizoma Alba, 1.00g Ginseng Radix Alba, 1.00g Cnidii Rhizoma, 1.00g Astragali Radix, 1.00g Poria Sclerotium, 1.00g Rehmanniae Radix Preparata, 1.00g Angelicae Gigantis Radix and 0.5g Glycyrrhizae Radix. These raw materials, together with lactose hydrate and corn starch, will be concentrated to a single dose of 3 g. The placebo consists of lactose, corn starch, and caramel colouring, and it has an appearance, weight, colour, and taste similar to those of SJDBT. The investigational product used in the present study is a dark brown-coloured granule. The present study is an

investigator initiated trial (IIT) funded by the government, and the role of pharmaceutical company is limited to provide the investigational product.

Primary outcome measurement

The primary outcome is the change in the usual fatigue severity of the Brief Fatigue Inventory (BFI) between the duration of the SJDBT administration and the duration of placebo administration. BFI is an instrument for the rapid assessment of subjective fatigue status in patients with cancer. Its reliability and sensitivity has been validated.[21] The development of the Korean version of the BFI was led by the National Cancer Center in Korea. The Korean version of the BFI has now been validated.[22] The usual fatigue severity of BFI has been validated as a sensitive and reliable clinical indicator in Korean patients with cancer,[23] and the clinical implication of the worst fatigue severity of BFI has also been validated.[21] The BFI consists of 9 items on an 11-point rating scale and can be measured within 10 minutes. The BFI will be measured by a trained researcher at visit 2, 4, 6, and 7 according to SOPs.

Secondary outcome measurements

Secondary outcome measurements include the global BFI score, worst fatigue severity of BFI, changes in the visual analogue scale (VAS) of fatigue, and quality of life measured by the European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 and QLQ-BR23. EORTC-QLQ-C30 is a questionnaire developed to evaluate the quality of life in patients with cancer and QLQ-BR23 is a breast cancer specific module.[24] Although some limitations have been reported, three fatigue questions on EORTC-QLQ-C30 have been independently validated as a measure of fatigue.[25 26] The Korean version of the EORTC-QLQ-C30 and QLQ-BR23 has now been validated in Korean patients with cancer.[27 28] The

study schedule according to The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) is detailed in Table 1.

Table 1 - Study schedule of the SJDBT trial (14 weeks)

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	Day -7 (V1)	Day 0 (V2)	Day 14 (V3)	Day 35 (V4)	Day 56 (V5)	Day 77 (V6)	Day 98 (V7)
Eligibility screen	X						
Informed consent	X						
Allocation		X					
SJDBT Group A		X*	X*				
Placebo				X*	X*		
SJDBT Group B				X*	X*		
Placebo		X*	X*				
Demographic characteristic	X						
Vital signs	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Laboratory test	X	X	X	X	X	X	X
Brief fatigue inventory		X		X		X	X
EORTC-QLQ-C30		X		X		X	X
EORTC-QLQ-BR23		X		X		X	X
VAS for fatigue		X	X	X	X	X	X

* The durations of administration are two weeks prior to the next visit. (Day 1~14, day 22~35, day 43~56, day 64~77)

Safety outcomes

All safety-related variables including vital signs, physical examination, hematologic test, biochemical test, urine test and adverse events will be recorded on the case report form (CRF) at every visit. Adverse events will be evaluated using the National Cancer Institute (NCI; Bethesda, MD USA) common terminology criteria for adverse events (CTCAE) v4.03.[29] The adverse events will be assessed by a trained investigator at every visit and if any participant wishes to consult a doctor for any reason, including the occurrence of an adverse event, they can contact the investigator in charge at any time, or visit the trial institution for examination, and all of this will be recorded on the CRF.

Statistical analysis

Efficacy assessment

The baseline characteristics will be analysed by an independent two-sample t-test for continuous variables or the chi-square test for the categorical variables (Fisher's exact test will be used when the expected value is < 5). Alternatively, if the normality assumption is not satisfied, Wilcoxon rank sum test will be conducted for the continuous variables. The normality assumption will be assessed by the Shapiro-Wilk test. The continuous variables will be presented as the mean ± standard deviation (SD) or median and range, and the categorical variables will be presented as the n (%) or the absolute and relative frequencies. Statistical analyses for efficacy will be conducted for both the ITT (intention-to treat, all randomised participants who receive at least one dose of the study drug) and PP (per-protocol, a subset of the participants who complete the study without any major protocol deviations) data sets. ITT analyses will be considered as primary analyses and PP analysis will be considered as secondary analysis. The missing values will be imputed by multiple imputation.

For the primary outcome measure, the mean differences of BFI between the SJDBT administration period and the placebo administration period will be compared using an independent two-sample t-test. If the normal distribution assumption is not satisfied for the continuous variables, Wilcoxon rank sum test will be conducted. For the secondary outcome measure, the mean differences of fatigue VAS, EORTC-QLQ-C30, and QLQ-BR23 between the SJDBT administration period and the placebo administration period will be compared using an independent two-sample t-test or Wilcoxon rank sum test. A p-value of less than 0.05 will be regarded as statistically significant. The present study does not consider an interim analysis.

Safety assessment

The participants will be asked to report any adverse events that may occur during the trial at every visit. Any identified adverse event will be recorded in the CRFs. If a severe adverse event occurs and is associated with the investigational product, the participant will be withdrawn from the study and receive appropriate treatment. Any loss caused by the study will be compensated by insurance. Safety-related variables, including laboratory test results and adverse events, will be compared between the SJDBT administration period and the placebo administration period using the ITT dataset.

Data and safety monitoring

The ISEE will monitor the present study for quality control according to SOPs. The trial institution will be monitored while this study is ongoing. There is no plan for auditing. For data quality improvement, double data entry and range checks for data values will be conducted. Adverse reactions will be reported to the institutional review board (IRB), and serious and unexpected adverse reactions will be reported to regulatory authorities. There will

be no coordinating centre, steering committee, or endpoint adjudication committee in the present study.

Ethics and dissemination

This study has been approved by the IRB of the Catholic Kwandong University International St. Mary's Hospital (reference IS16MNSI0011). The current protocol version is 1.3. Written informed consent will be obtained prior to study commencement from each participant by the investigator. The present study will be conducted in compliance with the Helsinki Declaration and Korean Good Clinical Practice (KGCP) published by the Ministry of Food and Drug Safety (MFDS). Any information obtained from the participants will be handled confidentially. During the entire trial period, the data will be handled by the study identification number, which is assigned to each participant at enrolment. All the records from the trial will be retained secure in a locked cabinet or password-protected files. Only investigators in charge will have authority to access the data. The results of this study will be published in a scientific journal. Thus far, there is no plan for public release of the full protocol and individual datasets.

Patient and public involvement

There was no patients or public involvement in the design of the present study, and there is no planned patient or public involvement to recruitment to and conduct the study.

Discussion

The present study investigates the feasibility of SJDBT for cancer-related fatigue in patients with breast cancer. SJDBT is a widely used herbal medicine in Korea, China, and Japan and

its pharmacological efficacy has been partly reported. In preclinical studies on cancer, SJDBT has been shown to inhibit melanoma metastasis by inducing natural killer (NK) cell activity and suppressing vascularization,[30 31] alleviate cancer-induced anorexia and cachexia,[32] and protect against anticancer drug-induced myelosuppression.[33] It also exhibits anti-angiogenic and immunomodulatory effects in malignant glioma[34] and preventive effects in endometrial carcinogenesis.[35] A case report suggested that SJDBT combined with gemcitabine enhances the antitumor effects in advanced biliary tract cancer.[36] Furthermore, SJDBT protects against carbon tetrachloride-induced anorexia and hepatotoxicity,[37] protects the gastric mucosa by exerting antioxidant effects,[38] inhibits retinal neovascularization by inhibiting angiogenesis,[39] and restraint stress.[40] Its potential therapeutic effect on Alzheimer's disease has also reported.[41] Altogether, these studies suggest the use of SJDBT on various diseases as well as further studies. Although there are several published papers on the efficacy of SJDBT in patients with cancer, the present study has its own significance. While previous studies focused on hematotoxicity,[14] quality of life,[42] anorexia,[43] and immunity[44] of patients with cancer, the present study focuses on cancer-related fatigue. The limitations of the present study include its small sample size and single-centre design. The sample size of the present study is quite small compared to that of studies that evaluated the efficacy of American ginseng for cancer-related fatigue.[45 46] However, to the best of our knowledge, this is the first randomized controlled trial to evaluate the efficacy of SJDBT for cancer-related fatigue. So far, most studies on patients with cancer using traditional Korean medicine conducted in Korea are small-scale studies. Similar to other small pilot studies on sleep disturbance,[47] anorexia,[43] fatigue,[48] and pain[49] in patients with cancer conducted in Korea, which provided evidence for further study, we hope that the present study will also promote further studies and the use of herbal medicines in patients with cancer. The present study may be regarded as a study that investigates preventive effect of SJDBT in fatigue during chemotherapy.

However, one of the limitations of the present study is the difficulty to define clearly whether the fatigue is due to chemotherapy, surgery, or breast cancer. Based on the results of this study, a further, large scale study to investigate the efficacy of SJDBT in patients with significant fatigue during the first cycle of chemotherapy is needed. Furthermore, the present study reduces patient heterogeneity by specifying not only cancer types but also types of chemotherapy. Besides, this study assesses quality of life to evaluate the effect of SJDBT on general health status. Even though it has a few limitations, the present study would be meaningful in that it is a pilot study to plan further large-scale trials by evaluating not only cancer-related fatigue but also quality of life due to overall symptoms.

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Authors' contributions

CC and SK have written the first manuscript for this trial and they will contribute to monitoring this trial. YK and MK have contributed to the development of the protocol. BHJ

and YCS have edited the first manuscript. SGK has conducted all the procedures for this protocol. All authors have read and approved the final manuscript.

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Competing interests

None declared.

Patients consent

Obtained

Ethics approval

The Institutional Review Board of the Catholic Kwandong University International St. Mary's Hospital approved the study (reference IS16MNSI0011).

Provenance and peer review

Not commissioned; externally peer reviewed.

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List of Figure

Figure 1. Study flow chart

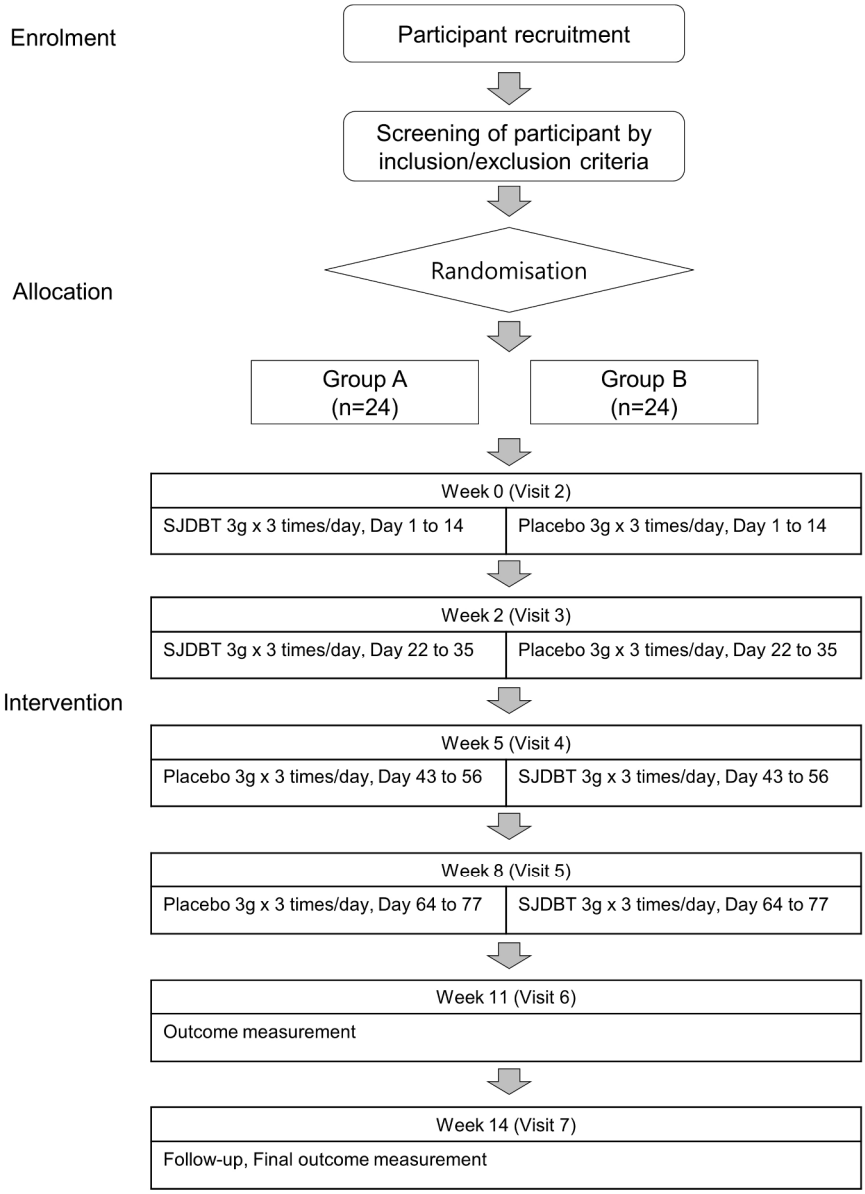

Figure 1. Study flow chart

190x254mm (300 x 300 DPI)

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	2
	2b	All items from the World Health Organization Trial Registration Data Set	Appendix
Protocol version	3	Date and version identifier	12
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	14
	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	14
	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)	NA

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	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
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)	4
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	5
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)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	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)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	9
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)	9-10

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	6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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	8-9
	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	6

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	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	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	11
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	11-12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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

BMJ Open

Sipjeondaebo-tang in patients with breast cancer with fatigue: a protocol for a pilot, randomised, double-blind, placebo-controlled, cross-over trial

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Sipjeondaebo-tang in patients with breast cancer with fatigue: a protocol for a pilot, randomised, double-blind, placebo-controlled, cross-over trial

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Abstract

Introduction

Cancer-related fatigue is a frequent symptom in patients with cancer and one of the most distressing symptoms in patients with breast cancer. Sipjeondaebo-tang (Juzen-taiho-to in Japanese or Shi-Quan-Da-Bu-Tang in Chinese) is a widely used herbal medicine for treatment of fatigue in Korea, China, and Japan. The purpose of the present study is to evaluate the feasibility of Sipjeondaebo-tang for cancer-related fatigue.

Methods and analysis

The present study is a randomised, double-blind, placebo-controlled, cross-over study. Forty-eight patients with breast cancer who are indicated for doxorubicin and cyclophosphamide will be recruited. The participants will receive 3 g of Sipjeondaebo-tang or a placebo three times a day for 56 days. The primary outcome measurement is the change in the Brief Fatigue Inventory (BFI) scores. The secondary outcome measurements include the changes in the visual analogue scale (VAS) of fatigue, and quality of life measured by the European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 and QLQ-BR23. The VAS of fatigue will be measured on every visit, and other outcomes will be measured on visit 2, 4, 6, and 7. The total study period is 14 weeks.

Ethics and dissemination

This study has been approved by the institutional review board (IRB) of the Catholic Kwandong University International St. Mary's Hospital (reference IS16MNSI0011). The results of this study will be published in a peer-reviewed journal and presented at a scientific conference.

Trial registrations
ClinicalTrials.gov NCT02858856; Pre-results.

Strengths and limitations of this study

- This study is the first randomized controlled trial to evaluate the feasibility of Sipjeondaebo-tang for treatment of cancer-related fatigue.
- All participants receive identical chemotherapy regimens.
- The limitations of this study are its relatively small number of participants and the fact that it will be conducted in a single institution.

Introduction

Cancer-related fatigue is a frequently experienced symptom in patients with cancer regardless of tumour type, and one of the most distressing symptoms in patients with breast cancer.[1] The National Comprehensive Cancer Network (NCCN) defined cancer-related fatigue as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportionate to recent activity.[2] Fatigue is the most commonly reported side effect of chemotherapy, alongside pain, nausea, and vomiting.[3] In patients with breast cancer receiving chemotherapy, the prevalence of fatigue is greater than 72%.[4 5] In a study conducted at a hospital in South Korea, the prevalence of fatigue was 32.3% among patients with cancer and 45.5% among female patients with cancer.[6]

Managing cancer-related fatigue is one of the main concerns of cancer patient management. Cancer-related fatigue leads to considerable socioeconomic costs for patients with cancer. Patients with cancer face difficulties in their daily lives due to fatigue, and they miss an average of 4.2 days of work per month. The primary caregivers of patients with cancer are also negatively influenced, missing an average of 4.5 days of work per month.[7] Cancer-

related fatigue also compromises the quality of life and, in severe cases, it negatively affects the effectiveness of treatment by prompting dose reductions, delaying anticancer therapy, or reducing adherence to prescribed drugs.[8] Therefore, management of cancer-related fatigue is very important.

Several factors contribute to the development of cancer-related fatigue. However, the pathological mechanisms involved are not well known.[9] Currently, the underlying pathologies of cancer-related fatigue are treated with hematopoietic agents or antidepressants, but the treatment is not effective against fatigue produced by other aetiologies, or it only improves anaemia or depression.[10] Furthermore, cancer-related fatigue is not treated adequately to meet the needs of patients with cancer. More than half (61%) of patients with cancer answered that fatigue has greater influence on their lives than pain; however, only 27% of patients with cancer received specific recommendations for fatigue treatment. There is no definitive treatment for cancer-related fatigue, so only 9% of physicians prescribe drugs to treatfatigue.[7] Therefore, more research on evidence-based interventions for cancer-related fatigue is needed.

Sipjeondaebo-tang (SJDBT; Juzen-taiho-to in Japanese or Shi-Quan-Da-Bu-Tang in Chinese) is awidely used herbal medicine in Korea, China, and Japan. In Korea, it is the third most commonly prescribed herbal medicine.[11] According to Korean medicine theory, SJDBT treats the syndrome of dual deficiency of qi and blood by balancing Yin and Yang.[12] The Ministry of Food and Drug Safety (MFDS) has approved SJDBT to treat weakness after illness, anorexia, night sweats, cold hands and feet, and anaemia.[13] Despite the frequent use of SJDBT for the treatment of fatigue, there have only been clinical trials on hematotoxicity[14] and anaemia,[15 16] and scientific evidence for SJDBT on cancer-related fatigue is lacking. Therefore, the aim of the present study is to evaluate the feasibility of SJDBT for fatigue in

patients with breast cancer receiving chemotherapy. To achieve this aim, a randomised, double-blind, placebo-controlled, cross-over trial has been planned.

Methods and analysis

Study design

A randomised, double-blind, placebo-controlled, cross-over trial will be conducted at the Catholic Kwandong University International St. Mary's Hospital in Incheon, Republic of Korea. Any participants meeting the eligibility criteria will be enrolled. After enrolment, the participants will be randomly allocated to two groups: group A and group B. A schematic flow of the study is shown in Figure 1. Both groups will receive four cycles of doxorubicin and cyclophosphamide chemotherapy, and each cycle will last 21 days. There is no expected protocol modification. However, if it happens, any modification in the protocol will be communicated to the investigators via conference calls. The final manuscript for publication will include all the amendments.

Recruitment

Participants will be recruited as follows. Patients who visit the trial institution and fulfil the eligibility criteria will be invited to participate in the study by the investigator in charge. The investigators will provide detailed trial information including study period, purpose, eligibility criteria, intervention, and design.

Participants

Inclusion criteria

The inclusion criteria are as follows: men and women aged 20 to 65 years; patients who have histologically or cytologically confirmed breast cancer; patients who are indicated for doxorubicin and cyclophosphamide; Eastern Cooperative Oncology Group (ECOG) performance status score 0 to 2; and patients willing and able to give informed consent for participation in the study

Exclusion criteria

The exclusion criteria are as follows: patients who are unable to take drugs orally; patients receiving neoadjuvant chemotherapy; patients with mental illness such as dementia, delirium and depression; patients with hepatitis B, hepatitis C, or liver cirrhosis; patients with severe renal disability (two times higher than the upper limit of normal for serum creatinine); patients with severe liver disability (three times higher than the upper limit of normal for alanine transaminase [ALT], and aspartate transaminase [AST]); patients with diabetes (haemoglobin A1c [HbA1c] > 8%) or hypertension (systolic blood pressure [SBP] > 160 mmHg or diastolic blood pressure [DBP] > 100 mmHg) that is not controlled by diet or medication; patients with thyroid disease; patients with severe systemic disease; use of other investigational products within 30 days of the study period; patients with known prior hypersensitivity to the investigational product; and individuals who are judged inappropriate for the study

Subject withdrawal criteria

The participants who meet the following criteria will be discontinued from the study: the occurrence of a serious adverse event related to investigational product; investigator's decision that it is not appropriate to proceed the trial; participants who do not comply with investigator's instruction; occurrence of significant protocol violations; and participant's

withdrawal of consent or request to stop taking medication. The participants who are withdrawn from the study after allocation will be followed for outcomes as far as possible.

Sample size

This is a pilot study that examines the feasibility of conducting a large-scaled randomised clinical trial of SJDBT for treating cancer-related fatigue in patients with breast cancer. Considering that a sample size between 24 and 50 has been recommended for a pilot study,[17] [18] and the sample size of other similar pilot studies, a total of 48 participants will be recruited for the present study.[19] [20] Thus, 24 participants will be allocated to group A and another 24 to group B.

Randomisation and allocation

The participants who meet the inclusion and exclusion criteria will be randomly allocated using random numbers generated by the Contract Research Organisation (CRO), Institute of Safety, Efficacy and Effectiveness Evaluation for Korean Medicine (ISEE). Block randomisation using R software with block size of four will be conducted. The enrolled participants will be assigned to one of two groups with the allocation ratio of 1:1. The randomisation table will be kept in an opaque and sealed envelope by the ISEE and it will be unclosed according to Standard Operating Procedures (SOPs).

Blinding

A researcher at ISEE will prepare computer-generated random numbers and a randomisation table. Hanpoong Pharm and Foods Co., Ltd. will produce and label the investigational product in accordance with Korea Good Manufacturing Practice (KGMP) standards. The labelled investigational product will be provided to the study institution by the

pharmaceutical company. Since ISEE is an independent centre from the trial institution, investigators involved in recruitment, treatment, and outcome assessment will be blinded to the allocation.

Treatment protocol

The participants will receive SJDBT or placebo for a total of 56 days. They will take 3 g of the investigational product orally with water three times a day after meals. The administration periods of the investigational product will be two weeks prior to the visiting day for chemotherapy. The participants of group A will take SJDBT from day 1 to day 14 and from day 22 to day 35, and placebo from day 43 to day 56 and from day 64 to day 77 of the trial period. The participants of group B will take placebo from day 1 to day 14 and from day 22 to day 35, and SJDBT from day 43 to day 56 and from day 64 to day 77 of the trial period. The participants will be asked to return drug remains for the sake of calculating the compliance. During the clinical trial, the participants will be prohibited to get other treatment for fatigue.

Interventions

SJDBT is an herbal medicine that has been approved by the MFDS. It consists of 1.00 g Cinnamomi Cortex, 1.00g Paeoniae Radix, 1.00g Atractylodis Rhizoma Alba, 1.00g Ginseng Radix Alba, 1.00g Cnidii Rhizoma, 1.00g Astragali Radix, 1.00g Poria Sclerotium, 1.00g Rehmanniae Radix Preparata, 1.00g Angelicae Gigantis Radix and 0.5g Glycyrrhizae Radix. These raw materials, together with lactose hydrate and corn starch, will be concentrated to a single dose of 3 g. The placebo consists of lactose, corn starch, and caramel colouring, and it has an appearance, weight, colour, and taste similar to those of SJDBT. The investigational product used in the present study is a dark brown-coloured granule. The present study is an

investigator initiated trial (IIT) funded by the government, and the role of pharmaceutical company is limited to provide the investigational product.

Primary outcome measurement

The primary outcome is the change in the usual fatigue severity of the Brief Fatigue Inventory (BFI) between the duration of the SJDBT administration and the duration of placebo administration. BFI is an instrument for the rapid assessment of subjective fatigue status in patients with cancer. Its reliability and sensitivity has been validated.[21] The development of the Korean version of the BFI was led by the National Cancer Center in Korea. The Korean version of the BFI has now been validated.[22] The usual fatigue severity of BFI has been validated as a sensitive and reliable clinical indicator in Korean patients with cancer,[23] and the clinical implication of the worst fatigue severity of BFI has also been validated.[21] The BFI consists of 9 items on an 11-point rating scale and can be measured within 10 minutes. The BFI will be measured by a trained researcher at visit 2, 4, 6, and 7 according to SOPs.

Secondary outcome measurements

Secondary outcome measurements include the global BFI score, worst fatigue severity of BFI, changes in the visual analogue scale (VAS) of fatigue, and quality of life measured by the European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 and QLQ-BR23. EORTC-QLQ-C30 is a questionnaire developed to evaluate the quality of life in patients with cancer and QLQ-BR23 is a breast cancer specific module.[24] Although some limitations have been reported, three fatigue questions on EORTC-QLQ-C30 have been independently validated as a measure of fatigue.[25 26] The Korean version of the EORTC-QLQ-C30 and QLQ-BR23 has now been validated in Korean patients with cancer.[27 28] The

study schedule according to The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) is detailed in Table 1.

Table 1 - Study schedule of the SJDBT trial (14 weeks)

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	Day -7 (V1)	Day 0 (V2)	Day 14 (V3)	Day 35 (V4)	Day 56 (V5)	Day 77 (V6)	Day 98 (V7)
Eligibility screen	X						
Informed consent	X						
Allocation		X					
SJDBT Group A		X*	X*				
Placebo				X*	X*		
SJDBT Group B				X*	X*		
Placebo		X*	X*				
Demographic characteristic	X						
Vital signs	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Laboratory test	X	X	X	X	X	X	X
Brief fatigue inventory		X		X		X	X
EORTC-QLQ-C30		X		X		X	X
EORTC-QLQ-BR23		X		X		X	X
VAS for fatigue		X	X	X	X	X	X

* The durations of administration are two weeks prior to the next visit. (Day 1~14, day 22~35, day 43~56, day 64~77)

Safety outcomes

All safety-related variables including vital signs, physical examination, hematologic test, biochemical test, urine test and adverse events will be recorded on the case report form (CRF) at every visit. Haemoglobin, haematocrit, red blood cell indices, white blood cell differential count, platelet, etc. will be measured in the blood and nitrite, albumin, bilirubin, ketone, protein, etc. will be measured in the urine. Adverse events will be evaluated using the National Cancer Institute (NCI; Bethesda, MD USA) common terminology criteria for adverse events (CTCAE) v4.03.[29] The adverse events will be assessed by a trained investigator at every visit and if any participant wishes to consult a doctor for any reason, including the occurrence of an adverse event, they can contact the investigator in charge at any time, or visit the trial institution for examination, and all of this will be recorded on the CRF. A serious adverse event will be considered to be an event with the following outcomes: death, life-threatening condition, hospitalization or prolongation of hospitalization, disability or permanent damage.

Statistical analysis

Efficacy assessment

The baseline characteristics will be analysed by an independent two-sample t-test for continuous variables or the chi-square test for the categorical variables (Fisher's exact test will be used when the expected value is < 5). Alternatively, if the normality assumption is not satisfied, Wilcoxon rank sum test will be conducted for the continuous variables. The normality assumption will be assessed by the Shapiro-Wilk test. The continuous variables will be presented as the mean ± standard deviation (SD) or median and range, and the categorical variables will be presented as the n (%) or the absolute and relative frequencies.

Statistical analyses for efficacy will be conducted for both the ITT (intention-to treat, all randomised participants who receive at least one dose of the study drug) and PP (per-protocol, a subset of the participants who complete the study without any major protocol deviations) data sets. ITT analyses will be considered as primary analyses and PP analysis will be considered as secondary analysis. The missing values will be imputed by multiple imputation. For the primary outcome measure, the mean differences of BFI between the SJDBT administration period and the placebo administration period will be compared using an independent two-sample t-test. If the normal distribution assumption is not satisfied for the continuous variables, Wilcoxon rank sum test will be conducted. For the secondary outcome measure, the mean differences of fatigue VAS, EORTC-QLQ-C30, and QLQ-BR23 between the SJDBT administration period and the placebo administration period will be compared using an independent two-sample t-test or Wilcoxon rank sum test. A p-value of less than 0.05 will be regarded as statistically significant. The present study does not consider an interim analysis.

Safety assessment

The participants will be asked to report any adverse events that may occur during the trial at every visit. Any identified adverse event will be recorded in the CRFs. If a severe adverse event occurs and is associated with the investigational product, the participant will be withdrawn from the study and receive appropriate treatment. Any loss caused by the study will be compensated by insurance. Safety-related variables, including laboratory test results and adverse events, will be compared between the SJDBT administration period and the placebo administration period using the ITT dataset.

Data and safety monitoring

The ISEE will monitor the present study for quality control according to SOPs. The trial institution will be monitored while this study is ongoing. There is no plan for auditing. For data quality improvement, double data entry and range checks for data values will be conducted. Adverse reactions will be reported to the institutional review board (IRB), and serious and unexpected adverse reactions will be reported to regulatory authorities. There will be no coordinating centre, steering committee, or endpoint adjudication committee in the present study.

Ethics and dissemination

This study has been approved by the IRB of the Catholic Kwandong University International St. Mary's Hospital (reference IS16MNSI0011). The current protocol version is 1.3. Written informed consent will be obtained prior to study commencement from each participant by the investigator. The present study will be conducted in compliance with the Helsinki Declaration and Korean Good Clinical Practice (KGCP) published by the Ministry of Food and Drug Safety (MFDS). Any information obtained from the participants will be handled confidentially. During the entire trial period, the data will be handled by the study identification number, which is assigned to each participant at enrolment. All the records from the trial will be retained secure in a locked cabinet or password-protected files. Only investigators in charge will have authority to access the data. The results of this study will be published in a scientific journal. Thus far, there is no plan for public release of the full protocol and individual datasets.

Patient and public involvement

There was no patients or public involvement in the design of the present study, and there is no planned patient or public involvement to recruitment to and conduct the study.

Discussion

The present study investigates the feasibility of SJDBT for cancer-related fatigue in patients with breast cancer. SJDBT is a widely used herbal medicine in Korea, China, and Japan and its pharmacological efficacy has been partly reported. In preclinical studies on cancer, SJDBT has been shown to inhibit melanoma metastasis by inducing natural killer (NK) cell activity and suppressing vascularization,[30 31] alleviate cancer-induced anorexia and cachexia,[32] and protect against anticancer drug-induced myelosuppression.[33] It also exhibits anti-angiogenic and immunomodulatory effects in malignant glioma[34] and preventive effects in endometrial carcinogenesis.[35] A case report suggested that SJDBT combined with gemcitabine enhances the antitumor effects in advanced biliary tract cancer.[36] Furthermore, SJDBT protects against carbon tetrachloride-induced anorexia and hepatotoxicity,[37] protects the gastric mucosa by exerting antioxidant effects,[38] inhibits retinal neovascularization by inhibiting angiogenesis,[39] and restraint stress.[40] Its potential therapeutic effect on Alzheimer's disease has also reported.[41] Altogether, these studies suggest the use of SJDBT on various diseases as well as further studies. Although there are several published papers on the efficacy of SJDBT in patients with cancer, the present study has its own significance. While previous studies focused on hematotoxicity,[14] quality of life,[42] anorexia,[43] and immunity[44] of patients with cancer, the present study focuses on cancer-related fatigue. The limitations of the present study include its small sample size and single-centre design. The sample size of the present study is quite small compared to that of studies that evaluated the efficacy of American ginseng for cancer-related fatigue.[45 46] However, to the best of our knowledge, this is the first randomized controlled trial to evaluate the efficacy of SJDBT for cancer-related fatigue. So far, most studies on patients with cancer using traditional Korean medicine conducted in

Korea are small-scale studies. Similar to other small pilot studies on sleep disturbance,[47] anorexia,[43] fatigue,[48] and pain[49] in patients with cancer conducted in Korea, which provided evidence for further study, we hope that the present study will also promote further studies and the use of herbal medicines in patients with cancer. The present study may be regarded as a study that investigates preventive effect of SJDBT in fatigue during chemotherapy. However, one of the limitations of the present study is the difficulty to define clearly whether the fatigue is due to chemotherapy, surgery, or breast cancer. Based on the results of this study, a further, large scale study to investigate the efficacy of SJDBT in patients with significant fatigue during the first cycle of chemotherapy is needed. Furthermore, the present study reduces patient heterogeneity by specifying not only cancer types but also types of chemotherapy. Besides, this study assesses quality of life to evaluate the effect of SJDBT on general health status. Even though it has a few limitations, the present study would be meaningful in that it is a pilot study to plan further large-scale trials by evaluating not only cancer-related fatigue but also quality of life due to overall symptoms.

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Authors' contributions

CC and SK have written the first manuscript for this trial and they will contribute to monitoring this trial. YK and MK have contributed to the development of the protocol. BHJ and YCS have edited the first manuscript. SGK has conducted all the procedures for this protocol. All authors have read and approved the final manuscript.

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Competing interests

None declared.

Patients consent

Obtained

Ethics approval

The Institutional Review Board of the Catholic Kwandong University International St. Mary's Hospital approved the study (reference IS16MNSI0011).

Provenance and peer review

Not commissioned; externally peer reviewed.

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List of Figure

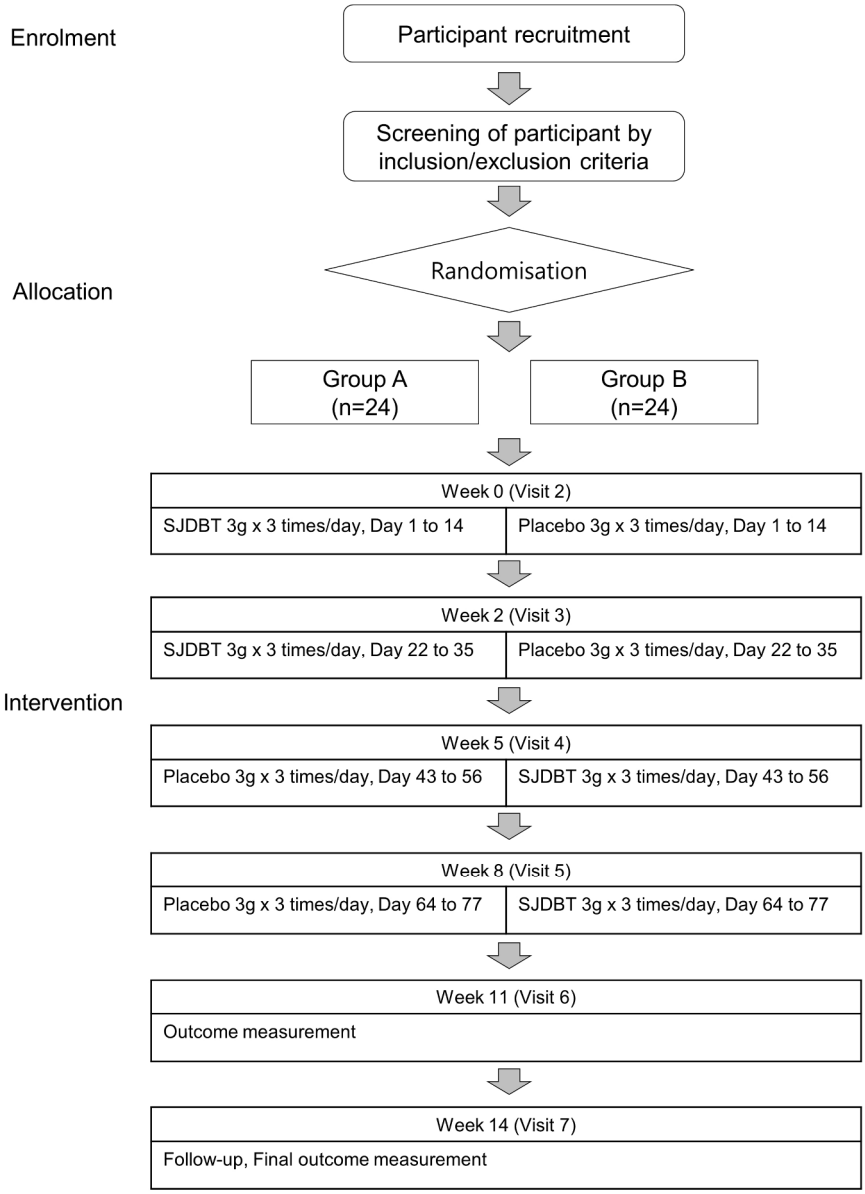

Figure 1. Study flow chart

190x254mm (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	2
	2b	All items from the World Health Organization Trial Registration Data Set	Appendix
Protocol version	3	Date and version identifier	12
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	14
	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	14
	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)	NA

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	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
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)	4
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	5
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)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	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)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	9
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)	9-10

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	6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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	8-9
	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	6

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	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	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	11
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	11-12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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