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Study Protocol of CBT-AP Trial: A Randomized Controlled Trial of Cognitive Behavioral Therapy Integrated with Activity Pacing for Fatigued Breast Cancer Patients Undergoing Chemotherapy

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Abstract

Purpose: This paper reports the methodology for undertaking a randomized controlled trial to assess the combined effect of cognitive behavioral therapy (CBT) and activity pacing on fatigue experienced by breast cancer patients undergoing chemotherapy. **Method:** Fifty-eight patients experiencing severe fatigue will be randomized to a CBT group or usual care group. The intervention will be given for 6 sessions by a trained oncology nurse. Primary and secondary outcome measures will be assessed at baseline, the sixth week of intervention and at the third month post intervention. The primary outcome measure is fatigue (Brief Fatigue Inventory) and secondary outcome measures include depression (Patient Health Questionnaire) and quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire). The protocol is designed using the SPIRIT guidelines which is one of the EQUATOR checklists. **Discussion:** This is the first RCT that will determine the efficacy of CBT by integrating with activity pacing to reduce fatigue among breast cancer patients receiving chemotherapy. The intervention design is novel in addressing multiple precipitating and perpetuating factors of fatigue and integrated with activity pacing in CBT. **Conclusion:** If the intervention is effective, this therapeutic approach can be incorporated into a routine health care for breast cancer patients receiving chemotherapy.

Trial registration: The study have been registered in Pan-African Clinical Trial Registry (website) on August 24, 2020. The trial registration number is PACTR202008881026130.

Keywords

activity pacing, breast cancer, chemotherapy, cognitive behavioral therapy, fatigue, randomized controlled trial

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Background

Cancer is a major cause of death worldwide, accounting for an estimated 18.1 million new cases and 9.6 million deaths in 2018.[1] Globally, breast cancer is the most frequently diagnosed cancer and the leading cause for cancer death in women.[2,3] Similarly, breast cancer is a leading cause of death for women in Africa and sub-Saharan Africa, including Ethiopia.[4] The incidence of new cases of breast cancer in Ethiopia is increasing with an estimated 15 244 (22.6%) new cases and 5-years prevalence of 46.7%.[3] The trend of breast cancer from 1997 to 2012 had showed increasing the incidence of breast cancer.[5] Breast cancer is known to reduce quality of life (QoL) of patients. Quality of life is a dimension of practice which is an important endpoint in cancer treatment. It has been shown that quality of life

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assessment is helpful to predict treatment response and to identify common problems Interventions focused on quality of life among cancer patients could contribute to improved treatment and could be a prognostic factor for breast cancer patients. Anxiety, depression, pain, and fatigue are some of the most common problems that occur in breast cancer patients which negatively affect quality of life (QoL).[6,7]

Fatigue is one of the most common symptoms among cancer patients. About 1 in 4 breast cancer survivors suffers from severe fatigue.[8] Fatigue is associated with more advanced disease, chemotherapy, and receiving the combination of therapy.[8] Fatigue occurring secondary to chemotherapy and radiotherapy significantly affects QoL of cancer patients.[9,10] Fatigue that often comes with cancer is termed cancer related fatigue.[11,12] Fatigue was found to be the most common symptom and was the major factor that influenced the QoL of breast cancer patients in Ethiopia.[9,13]

Breast cancer patients develop psychological distress including anxiety, depression, reduced emotional functioning, and sleep disturbances during cancer detection, treatment, and post treatment periods that negatively influence QoL.[12,14]A recently conducted systematic review and meta-analysis showed depression occurs at higher rates in middle income countries than in high income countries.[15] About 1 in 4 (25%) of breast cancer patients had depression in Ethiopia. Depression impacts adherence to treatment, overall quality of life, and survival of the patient.[16,17]

Many studies have reported the effectiveness of cognitive behavioral therapy (CBT) on fatigue[18] anxiety, depression, and quality of life of breast cancer patients.[19] Behavioral intervention is the most common intervention for cancer related fatigue.[20] Social support, provision of education, awareness creation, and peer group support may be effective for symptoms that occur in breast cancer patients undergoing chemotherapy.[21]

CBT for fatigue in breast cancer patients is aimed to modify distorted thinking related to cancer related fatigue and to avoid its negative influence on behavior. CBT works using various strategies to modify dysfunctional thoughts by identifying unhelpful thoughts, and explaining about thought, belief, behavior, and fatigue. The strategies include goal setting, problem solving, coping mechanisms, activity scheduling, sleep hygiene, relaxation skills, and social communication skills.[22]

Cognitive behavioral therapy has 3 components which interact with each other. These are cognition (how we think), emotion (how we feel), and behavior (how we act). The individual's thoughts determine feelings and behavior.[23] CBT is effective in improving functioning and quality of life.[24] CBT will be used as an intervention to improve quality of life through CBT techniques such as: cognitive restructuring, coping skills, and problem solving. The goal of cognitive restructuring is to change maladaptive thought into more adaptive thought and undesirable behavior into more desirable behavior. The coping skills therapy will help breast cancer patients adapt to difficult situations. The problem-solving type of CBT is the broadest category in its scope which focuses on teaching the person about problem identification and generating solutions to the problem.

Various studies have supported the effectiveness of CBT to improve the QoL of cancer patients. CBT reduces symptoms and improves cognitive and emotional functioning.[25,26] CBT effectively manages fatigue and improves QoL.[26-29] Therefore, effectively managing fatigue is very important to improve QoL.[30] Non-pharmacologic behavioral interventions like CBT are important to treat symptoms in breast cancer patients,[25] managing psychological symptoms like anxiety and depression.[19,30-33]

In this study, CBT will be integrated with activity pacing to help patients achieve a balance between activity and rest. Activity pacing enhances physical function and quality of life by monitoring energy, fatigue, and activity levels and then modifying daily activities that decrease fatigue and improve quality of life.[34] The essence of pacing is that the person with fatigue utilizes self-management of their level of activity in order to avoid exacerbations of symptoms and disability. It involves avoiding activities that exacerbate symptoms or interspersing activity with planned rest.

Activity pacing (AP) was based on the envelope theory of chronic fatigue syndrome. The envelope theory regards chronic fatigue syndrome as an organic disease process that results in a reduced amount of available energy which is not reversible by changes in behavior.[35,36] The disorder is associated with limited available energy, with fatigue exacerbations, and other related symptoms triggered by excessive activity resulting in prolonged inactive periods.[37] The aim of this therapy is to manage energy by assessing the relationship between activity and subsequent symptoms, and disability, and establishing baseline activity to avoid exacerbation of fatigue.[35,36] The AP intervention helps cancer patients to avoid exacerbations of symptoms by activity scheduling, and segmenting tasks into short time blocks.[37]

Activity pacing will be measured by an actigraph watch and logbooks to record daily and weekly activity and rest schedules and a priority list of activities to do in the week. Participants will wear the watch for 1 week (from Sunday evening to Saturday morning) and will be instructed to keep the watch on at all times except when swimming, bathing, or showering. During weekdays, participants enter responses into the watch about activity pacing, pain, and fatigue at pre-specified time points throughout the day.

This study is novel in combining CBT and activity pacing. In addition, this trial is innovative because it is the first study to assess the effect of a CBT intervention on fatigued breast cancer patients undergoing chemotherapy. CBT has been used to treat insomnia for cancer survivors[38,39] while another study applied CBT with a home-based exercise for ovarian cancer patients.[40] Moreover, CBT has also been used with breast cancer patients undergoing radiotherapy.[41,42]

Another study examined the effect of graded exercise therapy among cancer patients and cancer survivors.[37,43] However, no study has verified the effect of CBT in combination with activity pacing to avoid excessive activity which can result in prolonged inactive periods and exacerbation of fatigue in breast cancer patients undergoing chemotherapy.

In addition, no previous study has examined the impact of these therapies on cancer-related fatigue among breast cancer patients undergoing chemotherapy. Therefore, this effort is unique in assessing the effect of CBT-AP in a previously unstudied population. The findings of the study will be very helpful for health professionals to provide cognitive behavioral intervention for breast cancer patients. The results will also be helpful for policymakers to design new health policies on utilization of CBT for cancer patients as a part of routine care.

Cognitive behavior therapy effectively reduced post cancer fatigue. However, the effect of CBT on fatigue is not mediated by physical activity.[44] Therefore, this study will assess whether balance in activity and rest through CBT reduces fatigue.

The study hypothesized that fatigue severity will have a clinically significant difference in CBT group versus the usual care group.

Objectives

The objective of this study is to evaluate the combined effect of cognitive-behavioral therapy and activity pacing on cancer-related fatigue and QoL among breast cancer patients undergoing chemotherapy in Ethiopia.

Methods

Design

A randomized controlled trial (RCT) study design will be conducted to evaluate the efficacy of CBT compared to usual care (UC) for severely fatigued breast cancer patients receiving chemotherapy. Participants will be randomly allocated into 2 parallel groups in a 1:1 ratio: the cognitive behavioral therapy group, and the usual-care group. The intervention group will participate in cognitive behavioral therapy integrated with activity pacing and usual care, while the controlled group will receive only usual cancer care in accordance with the national guideline of cancer treatment. The usual care constitutes provision of chemotherapy, pain management, laboratory diagnostic assessment, and routine nursing care. The intervention will be given for 6 weeks (see Figure 1). The primary outcome measure is fatigue and secondary outcome measures are depression and QoL.

Participant's Intervention and Outcome

Study setting. The study will be conducted in Tikur Anbessa Specialized Hospital (TASH). TASH is a teaching hospital located in Addis Ababa, the capital city of Ethiopia, and it provides both teaching and clinical care services in different fields. It is also a major referral center from all corners of the country, especially for cancer patients. The hospital is the only cancer center in the country providing radiotherapy. Therefore, the distance of the hospital might result higher dropout rate of participants from the study.

Eligibility Criteria

Patients will be recruited after diagnosis of breast cancer and prior to the completion of chemotherapy.

Inclusion Criteria

- Female breast cancer patients aged 18 years and above.
- Non-relapsed breast cancer patients in any stage of the disease undergoing chemotherapy.
- Patients experiencing severe fatigue (overall rating 7 or more out of 10)[45] on a fatigue severity scale of Brief Fatigue Inventory (BFI).

Exclusion Criteria

- Patients who can't speak Amharic.
- Patients with psychiatric illness or uncontrolled medical illness will be screened by oncologist.
- Various types of clinically relevant systematic diseases or somatic causes that can result fatigue (eg, anemia, malnutrition, hemoglobin level, hypothyroidism, and other physical comorbidities). If the fatigue has a somatic cause or systemic disease that is confirmed by the oncologist, the patient will not participate in the study.[26]
- Laboratory diagnosis is made by the hospital as usual care service. If the patient is presented with other cause of fatigue during chemotherapy it will be managed by their own physician. If an emergency case occurs during the intervention session the physician and nurses involved in the research team will manage it.
- Patients who have previously taken or currently undergoing CBT for cancer-related fatigue, depression, or quality of life of breast cancer patients.

Outcomes. The time points for outcome measurement and data collection is mentioned in Table 1. Primary and secondary outcomes will be measured at the baseline (T_0), at the sixth week of intervention (T_1); and third-month post-intervention (T_2). (see Table 1).

Primary outcome

Fatigue. It will be measured by a Brief Fatigue Inventory Amharic version (BFI-Amh). BFI consists of 9

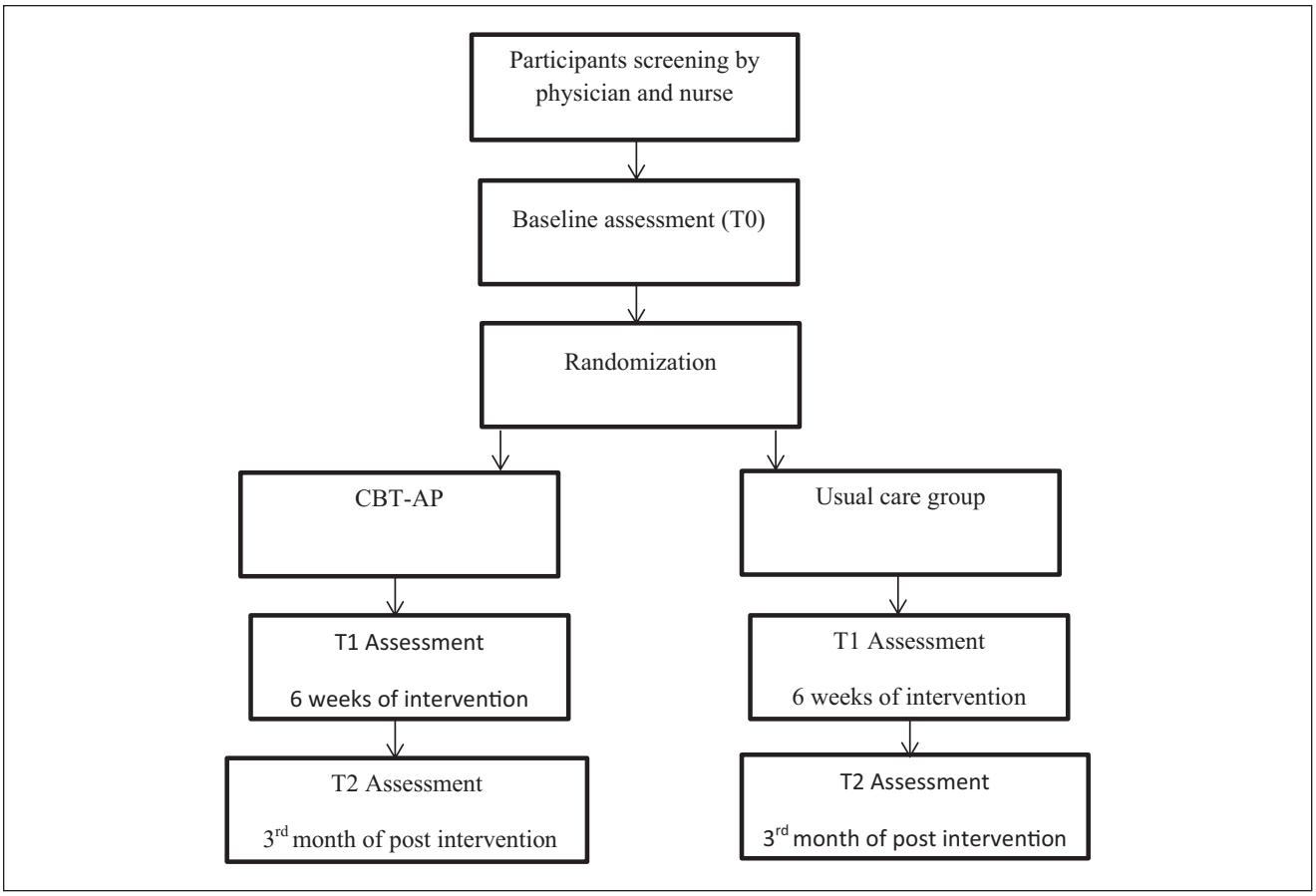

Figure 1. Study flowchart of CBT-AP trial.

Table 1. Data Collection Time for Measurement of Outcome and Patient Characteristics.

			Time points for measurement		
	Enrollment	Allocation	T_0	T_1	T_2
Eligibility screen	×				
Informed consent	×				
Randomization	×				
Allocation		×			
Intervention					
CBT			—	—	—
Assessment			×		
Socio demographic Characteristics			×		
Clinical characteristics			×		
Patient medical chart					
Fatigue			×	×	×
Brief fatigue Inventory(BFI-9)					
Quality of life					
EORTC QLQ C-30			×	×	×
EORTC QLQ BR-45			×	×	×
Depression					
PHQ-9			×	×	×

Baseline (T_0), sixth week of intervention (T_1), and third month of post intervention (T_2).

items asking patients if the participant felt unusually fatigued in the last week. The questionnaire has shown good acceptability, internal reliability of ($\alpha = .97$), construct, and concurrent validity.[46] The first 3 items measure the severity of fatigue at its worst, usual, and now during the past 24 hours, with each item score 0 indicates (no fatigue) and 10 indicate (fatigue as bad as you can imagine). The other 6 items evaluate the extent that fatigue has interfered with various aspects of the patient's life. The interference of items will be measured on 0 to 10 scale, with 0 being does not interfere and 10 being completely interfere. Its use of simple, single word designations of fatigue severity levels and functional domains make it very easy to understand.[45]

Secondary Outcomes

Quality of life. It is measured by EORTC QLQ C-30 and EORTC QLQ BR-45. EORTC QLQ C-30 is a reliable and valid measure of the quality of life of cancer patients consisting of 30 items arranged with 5 functional scales, 3 symptom scales, and global health and quality of life scale. After scoring procedures of QLQ C-30, all scales will be transformed to 0 to 100 scales. Higher scores represent a better level of functioning of functional and single-item scales. A higher score of symptom scales represents a higher level of symptoms for the symptom scales.[47]

EORTC QLQ BR-45 is the updated version of EORTC QLQ BR-23 that incorporates an additional 22 items that contain the target symptom scale and satisfaction scale.[48]

Depression. Depression will be measured by the patient health questioinnarie-9 (PHQ-9) which is a short instrument used to assess major depressive disorder. The Amharic version of the PHQ-9 demonstrated good internal reliability ($\alpha = .81$), test-retest reliability ($\alpha = .92$), and validity.[49] The score of each item is from 0 (not at all) to 3 (nearly every day). The total score ranges from 0 to 27.[50]

Interventions. The intervention consists of 6 treatment sessions. All patients will start by setting goals and finish by realizing goals. Goals will be defined using the SMART criteria—specific, measurable, and achievable and time bound. Patients will set their own short and long term goals. Then goals will be measured according to what was set, how far, how long for and how often? Realizing goals means the overall treatment session will be evaluated as to whether goals are achieved according to what is set initially. The intervention protocol was prepared by reviewing different literature,[26,28,51] protocols,[52,53] and manuals.[54-56] The precipitating and perpetuating factors of fatigue are considered during the preparation of the protocol. These factors include deregulation of the sleep-wake pattern, dysfunctional cognition, poor coping with the experience of cancer and its treatment, excessive fear of disease recurrence, lack of social support, and negative social interactions.

The intervention protocols include different CBT strategies that modify dysfunctional thoughts such as; coping strategies, goal setting, activity scheduling, sleep hygiene, relaxation skills, and social communication skills.[22]

The intervention includes activity pacing which is alternating planned periods of activity with regular rest period. The activity pacing is derived from the envelope theory[57] that suggests fatigue is associated with limited available energy, with exacerbations in fatigue that is triggered by excessive activity resulting in prolonged inactive periods. Elements of pacing include planning activities in advance, establish baseline activities, taking regular rest breaks, choosing activities based on available energy and prioritizing activities, managing energy, ergonomics, and activity stations.[58]

The intervention will be given for 6 consecutive weeks. Three sessions will be delivered by face to face (first, fourth, and sixth sessions) and the other 3 session will be delivered by telephone (second, third, and fifth session). Face to face sessions will be given for 2 hours and telephone session will be given for 20 minutes.

Various studies showed the effectiveness of CBT delivered for a total duration of 5 to 6 weeks.[28,51,59,60] Therefore, provision of CBT for 6 weeks will save time and be cost effective. It can also reduce patient dropout rate due to long therapeutic session.

The intervention combines individual and group-based cognitive behavioral therapy. Group therapy is important to share an individual's concern with others to help each other; members will realize that one is not alone in having real problems. Individual therapy is also important for identifying the specific patient problem and managing it accordingly. The group session will be conducted according to the COVID-19 guidelines to prevent transmission. There will be 5 participants per 1 group and the accommodation room for the therapy will be wide enough for social distancing among participants; it is well ventilated to prevent COVID-19 transmission. The intervention will be provided by an oncology nurse and clinical psychologist. The nurse will be trained by a clinical psychologist who is certified on CBT. The training will be given for 2 days, with 6 hours. of training per day. The skill of the trained nurse will be examined by a standardized checklist. The nurse and the clinical psychologist should be clinical staff who have a clinical experience of 3 or more years on cancer care, and CBT respectively.

The content of the intervention session is mentioned as follows:

Session 1

Introductory lesson about breast cancer and relaxation exercise. This session will start with an introduction of the

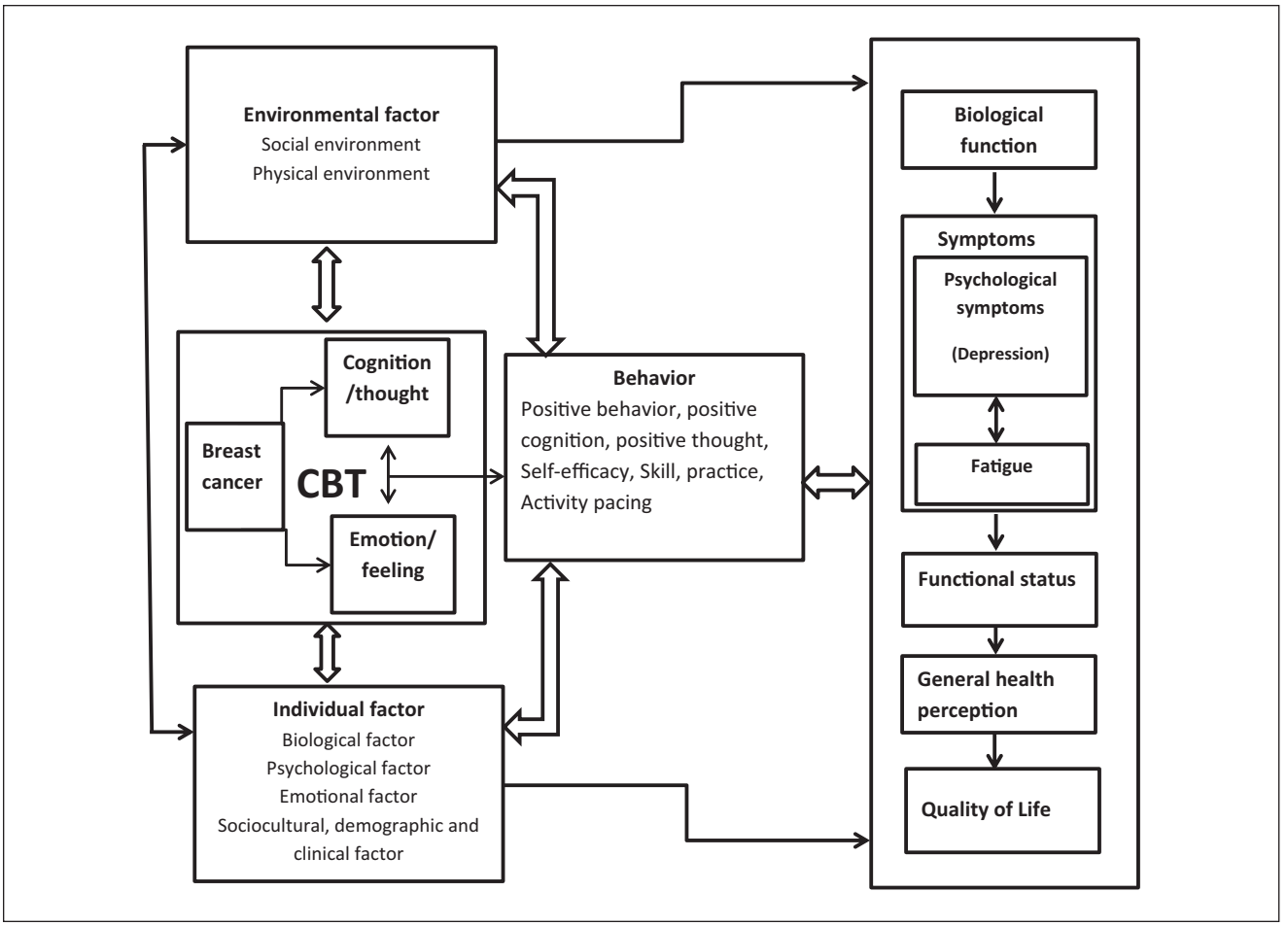

Figure 2. Conceptual frameworks for the effect of CBT on fatigue and QoL of breast cancer patients undergoing chemotherapy.

therapist participants and setting ground rules. The therapist will describe breast cancer, chemotherapy, fatigue, and CBT framework.

The conceptual frame work is developed from cognitive adaptation theory, social cognitive theory, cognitive behavioral theory, Wilson and Cleary model, health promotion model, and energy envelope theory. The framework of practice includes 4 major components: that is, situation/event, cognition/thought, emotion/feeling, and behavior/response (see Figure 2).

Relaxation is the other technique of CBT that helps patients to relax whenever they feel tense or anxious. This technique was effectively used by various studies.[27,28,61] Relaxation training is a simple, effective, and quick method of controlling anxiety symptoms. Two forms of relaxation will be demonstrated to the study participants: progressive muscle relaxation and deep breathing exercises (abdominal breathing).

Session 2

Goal setting and activity pacing. In this session, the participants will set reliable treatment goals. Activity pacing is alternating planned periods of activity with a regular rest period. It encourages participants to avoid exacerbations of fatigue and other symptoms by planning daily and weekly schedules of activities and resting time.[57]

Session 3

Management of sleep disturbance and dysfunctional thought. An irregular sleep-wake rhythm which disturbs sleeping pattern can be restored by maintaining sleep hygiene; adherence to fixed bedtimes and wake-up times and avoid sleeping during the day and unbroken regimented night-time sleep routine.[26,37,53,59] In this session, dysfunctional thoughts about breast cancer, and its treatment will be assessed. Participants will identify their own positive and negative thoughts, their subsequent emotion, behavior, and consequences.

Session 4

Cognitive restructuring and coping mechanisms. In this session, the participant will learn strategies for increasing positive thoughts and decreasing unhealthy or dysfunctional negative

thoughts, and thus decreasing fatigue. The participants identified unhelpful dysfunctional thoughts will be disputed and replaced by more helpful ways of thinking. Another part of this session is learning about coping mechanisms to decrease stress, anxiety, depression, and treatment side effects.[52]

Session 5

Individual dysfunctional thought management and improving social support. In this session, the participant will learn how to adopt more realistic expectations. The participants will also learn how to be more assertive. The therapist will dispute the participant's dysfunctional thoughts and cognition about the social environment and expectations to replace it with more positive thoughts.[52]

Session 6

Realizing goals. The overall treatment session will be reviewed. The participants will start realizing the treatment goals they set in the first session. The participants will prepare an action plan to maintain cognitive and behavioral changes in the future.

Adherence to the Intervention

Adherence will be measured by evaluating attendance of each session and by reviewing the completion of homework diaries in the workbook given to the participant. Each session has goals and a worksheet to be completed by the patient. Therefore, the therapist will assess participant's adherence to the intervention by evaluating whether goals are met and homework diaries are completed at the beginning of every session using a logbook and worksheet for each goal.

Intervention Fidelity

All group and individual sessions will be audio recorded after getting consent from participants, then 10% will be randomly selected (with a computer-generated random number sequence). An independent psychiatrist nurse (who is not involved in the study and who is experienced in CBT) for cancer patients will rate their adherence to the intervention manual using a standardized fidelity checklist.

The intervention provider will be scored on 5 scales from 0 (poor) to 6 (excellent) based on (1) how they address immediate concern, (2) how they explain the outline of the session, (3) how they discuss outcomes, (4) their adherence in providing the intervention, and (5) their competency in delivering each session.

Sample Size Calculation

Sample size was calculated using G-power by priori power analysis. An effect size of 0.83 will be used from a previous study conducted on cancer-related fatigue.[41] For 80% power at a significance level of 0.05 (2-tailed), the sample size needed is 48. The dropout rate was taken from a previous study done on the effect of CBT among breast cancer patients which is 10.5%.[41] In this study, participants might have financial difficulties to cover transportation costs and patients are also coming from all parts of the country. Therefore, the drop-out rate in the current RCT is estimated to be 20%. Therefore, the total number of participants in this trial will be 58.

Recruitment

Patients will be recruited by physicians and nurses in an oncology unit. They will introduce the study to eligible patients during a regular follow-up in the outpatient clinic at the hospital. Clinicians will also give the patients leaflets and information packs about the study. Patients who are interested to participate in the study will be sent patient information sheets.

Randomization. A computer-generated sequence will be employed to randomize study participants into the intervention or control groups. Larger block size reduces the future likelihood of predictability. Blocking restricts randomization by assigning participants to blocks. Longer block size will help to protect against predicting the treatment sequence.[62] Therefore, block randomization will be used with a block size of 6 in this study. An independent statistician who will not participate in any other parts of the study will generate the random sequence. The statistician will keep the list with him/herself throughout the study period. Therefore, the random list will be concealed to the other members of the research team.

After study participants are recruited by the researcher, the patient's information (name, age, gender) will be sent to the statistician. The statistician will assign study participants in to the treatment group labels according to the generated random sequence at a ratio of 1:1 and will send it back to the interventionist by email. The interventionist will inform participants of their treatment allocation. The statistician (random-list keeper) will be blinded to the treatment group label.

Blinding. In order to minimize bias, the data collector and statisticians will be blinded. Intervention sessions will take place in a separate private room away from other research team members and clinical staff; outcome data will not be collected by the interventionist or other research team members. However, it's not possible to blind participants[41] and intervention providers[63] for the psychological treatment.[52]

Data Collection

Data will be collected by trained clinical nurses with Bachelors of Science degree. The data collectors will be

given 1-day of training about the questionnaires and the data collection process by the principal investigator. The questionnaires will be prepared in hard copy format. Data collectors will be blinded for intervention allocation.

Informed consent will be obtained from eligible patients who agreed to participate in the study. The participants will answer 4 sets of Amharic version questionnaires as a baseline assessment (EORTC QLQ-C30, EORTC QLQ-BR45, BFI-9, and PHQ-9). Data collectors will record the patient's socio-demographic and clinical characteristics from the patient's medical record.

Statistical Analysis

The data analyst will be blinded to intervention allocation. Chi-square test and ANOVA will be used to analyze the categorical and continuous data respectively to compare the significance between the 2 groups. Repeated measurements analysis of variance, hierarchical models (multilevel models), and generalized estimating equations (GEE) for the repeated measurement data will be conducted.[64] Analysis stratified by the stage of disease will also be conducted. ANOVA will be used among 2 groups; the post hoc Tukey test will be applied to assess differences in 2-group comparisons.

We will compare study groups at baseline, after 6 weeks and 3 months of intervention, using intention to treat with multiple imputations, assuming that data were missing at random. All statistical tests will be 2-tailed.

Handling of Missing Data

Missing data will be estimated within the GEE without replacement, based on the assumption that the missing data were random or not associated with the independent factors (ie, group and time) of the study. If missed data was not at random or associated with the dependent factors (ie, groups and time points), it will be replaced by multiple imputation before being entered into the GEE analysis. If the missing data was at random, an incomplete set of data will be used and the missing data will be estimated within the GEE model.[65]

Data Management and Confidentiality

All study participants will have a random identification number which will be used to link data from the different assessments. Confidentiality will be maintained by coding all participant data with a unique identification number. The study participant identification information data set will be the participant tracking system used to follow-up women. All other datasets will label participant records with a unique study number. The participant's clinical information will not be mentioned in the participant identifier. The data storage security will be kept in locked files or password-protected data files.

Sensitivity Analysis

Based on compliance of intervention, study participants will be classified into a complier group and a non-complier group. The 2 groups will be analyzed separately according to compliance of intervention using modified intention-to-treat (mITT) and per-protocol (PP) analysis.

Intention-to-treat analysis includes patients randomized to the group regardless of treatment compliance, regardless of the treatment they actually received, and regardless of deviation from the protocol.[66] Sensitivity tests will be done to compare differences in the interpretation of results between the mITT and PP analysis. The aim of analyzing mITT and PP separately will provide information about the effect of the intervention.[67]

Data Monitoring

The trial will be monitored by Data Monitoring Committee (DMC). The DMC comprises 2 independent researchers, a consumer representative, and 1 member of the study investigator team. The DMC will be responsible for monitoring participant safety, adherence to protocol, and data quality. If any of the participants reports a severe problem, the therapist will refer the participant to the clinic immediately. Any women with previously undiagnosed mental health problems identified during screening will also be informed and recommended to seek a referral to a mental health specialist. No serious harm is expected as a result of the trial. However, if harm does occur, the participant will be referred to clinic.

Ethical Approval

The study protocol has been reviewed and approved by the Institutional Review Board of Zhengzhou University, (IRB approval number: ZZURIB 2020-10; Date; 18/06/2020) and Addis University, College of Health Science teaching hospital (IRB approval number: 101/20/Onco; Date: 28/10/2020). Participant's information will be used for research and analysis only, and are strictly confidential without permission. Any protocol modifications will be submitted to the university and the hospital research ethics committee, and the trial registry by the study team.

The participants will be informed that they are free to drop out of the study at any time without any consequences. Recruitment of study participants will be carried out after the written informed consent is obtained. If CBT-AP is effective, the participants in the usual-care group, will receive CBT after the trial

Trial Status

The trial was registered in Pan African Clinical Trial Registry (PACTR202008881026130, August 24, 2020). Recruitment will be started on April, 2021 and will be completed on June 2021. This protocol is designed based on SPIRIT guidelines for reporting parallel group randomized trials (see Supplemental File 1).

Dissemination of the finding. The results of this study will be disseminated through publication in peer-reviewed journals and presentations at national and international conferences. Feedback will be sent to the hospital so that any participants are able to access the result through their clinician. Two publications are anticipated: 1 paper reporting the feasibility analysis of CBT for breast cancer patients and a second paper focuses on the efficacy of CBT.

Discussion

Fatigue is found to be the most common symptom scale that decreases quality of life of breast cancer patients undergoing chemotherapy. Sometimes this fatigue may cause depression, nausea, vomiting, or pain.[68] Many studies reported the effectiveness of CBT on fatigue. The National Comprehensive Cancer Network (NCCN) has recommended cognitive behavioral therapy to intervene fatigue in cancer patients.[69]

Cognitive behavioral therapy is effective to reduce fatigue, anxiety, and depression. Breast cancer patients who received CBT had an improvement of Quality of Life compared to the control group.[70,71] CBT will be integrated with activity pacing that can help patients to achieve a balance between activity and rest. AP intervention helps cancer patients to avoid exacerbations of symptoms by activity scheduling, and segmenting tasks into short time blocks. It enhances physical function and quality of life by monitoring energy and activity levels and then modifying daily activities that decrease fatigue and improve quality of life.[37]

To our knowledge, this study will be the first RCT determining the efficacy of CBT that integrates activity pacing compared to a usual care group in reducing fatigue and improving QoL of breast cancer patients receiving chemotherapy. The intervention design is unique and was carefully considered to address multiple precipitating and perpetuating factors of fatigue and integrated CBT with activity pacing in breast cancer patients.

Study Limitation

This protocol has mentioned participants and interventionists cannot be blinded because, this is not possible in psychological treatment. There is no sham intervention in the usual care group, and further studies are needed.

Relevance to Clinical Practice

Most previous intervention studies have been carried out in advanced breast cancer survivors. However, there are few studies in the earlier treatment period. The earlier treatment of fatigue symptom during chemotherapy is very important. (1) It can reduce fatigue in breast cancer patients during cancer treatment. (2) It provides women with evidence-based strategies during their earlier treatment trajectory which they can continue to use after cancer treatment and into survivorship. This study will verify the feasibility and efficiency of the CBT-AP when it is provided by trained nurses. Then, CBT-AP will be recommended to be incorporated into a routine health care for breast cancer patients undergoing chemotherapy.

Conclusion

If the effectiveness of CBT-AP is confirmed, it will be an integral part of supportive care for breast cancer patients undergoing chemotherapy.

Further study would be warranted with a larger sample size to compare the efficacy of individual versus group CBT and to determine mediating or moderating factors of intervention.

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Author Contributions

MAG has contributed to study conception and design. CBT-AP intervention was designed by MAG, CC, and WP. The first draft of the manuscript was written by MAG and all authors commented on previous versions of the manuscript. EY, ES, and CP have been involved in revising the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

All procedures performed in studies involving human participants will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Supplemental Material

Supplemental material for this article is available online.

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