


Managing Cancer and Living Meaningfully (CALM) Intervention on Chemotherapy-Related Cognitive Impairment in Breast Cancer Survivors

Integrative Cancer Therapies
Volume 19: 1–10
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1534735420938450
journals.sagepub.com/home/ict


Ke Ding, MD^{1*}, Xiuqing Zhang, MD^{1*}, Jingjing Zhao, MD¹,
He Zuo, MD¹, Ziran Bi, MD¹, and Huidong Cheng, MD, PhD^{1*}

Abstract

Objective: To evaluate the effectiveness and feasibility of Managing Cancer and Living Meaningfully (CALM), which is used to reduce chemotherapy-related cognitive impairment (CRCI), relieve psychological distress, and improve quality of life (QOL) in Chinese breast cancer survivors (BCs). **Methods:** Seventy-four BCs were enrolled in this study. All patients were randomly assigned to either the CALM group or the care as usual (CAU) group. All patients were evaluated by the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog), Distress Thermometer (DT), and the Functional Assessment of Cancer Therapy–Breast (FACT-B) before and after CALM or CAU application to BCs with CRCI. We compared the differences in all these scores between the CALM group and the control group and analyzed the correlation between cognitive function and QOL. **Results:** Compared with the CAU group, the performance of the CALM group on the FACT-Cog, DT, and FACT-B showed significant differences before and after CALM ($t = -18.909, -5.180, -32.421, P = .000, .000, .000$, respectively). Finally, there was a positive correlation between cognitive function and QOL in breast cancer patients before ($r = 0.579, P = .000$) and after ($r = 0.797, P = .000$) treatment. **Conclusions:** The present results indicated that CALM has salutary effects on the improvement of cognitive impairment and QOL and relieves psychological distress in breast cancer patients, which may be due to a positive correlation between psychological distress and cognitive function or QOL.

Keywords

breast cancer, chemotherapy, cognitive impairment, CALM

Submitted March 4, 2020; revised May 25, 2020; accepted June 10, 2020

Introduction

Breast cancer is the most common type of cancer in women worldwide.¹ With the improvement of breast cancer prevention and treatment, including surgical treatment, chemotherapy, radiation therapy, and endocrine therapy, the mortality rate has decreased.² Chemotherapy is one of the most basic treatments and can prolong patient survival. However, there is much evidence suggesting that chemotherapy can cause not only serious physical adverse reactions, such as nausea, vomiting, myelosuppression, and secondary infection, but also chemotherapy-related cognitive impairment (CRCI), which is also known as “chemo brain.”³ For the former, there are various effective treatments that can alleviate them. However, for the latter, there

is currently no universal method to treat it. The prevalence of cognitive impairment in cancer patients is as high as 75%, and this has been a hot research topic in recent years.^{4,5} CRCI is characterized as deficits in areas of cognition, including memory, attention, processing speed, and executive function, which seriously affect quality of life (QOL)

¹The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China

*These authors contributed equally to this work.

Corresponding Author:

Huidong Cheng, Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230601, China.
Email: chd1975ay@126.com



and work ability.⁶ These problems can be detected in up to 30% of patients prior to chemotherapy, and up to 75% of patients report some form of CRCI during treatment; moreover, CRCI is still present in up to 35% of patients many years following the completion of treatment.⁷ The exact mechanism of CRCI is unknown, although some researchers have tried to uncover the mechanism in several studies. Considering the negative impact of CRCI on the overall QOL experienced by patients, better designed and more targeted interventions are needed to manage CRCI.⁸ Some studies describe cognitive deficits that occur after chemotherapy and discuss cognitive behavioral interventions that are divided into pharmacological and nonpharmacological interventions and show that nonpharmacological interventions yield better benefits.⁹⁻¹²

In recent years, a type of psychological intervention proposed by Gary Rodin et al has achieved significant effects on symptom management in patients with advanced cancer, namely, Managing Cancer And Living Meaningfully (CALM).¹³ This is a novel, brief, manualized psychotherapeutic intervention designed both to relieve psychosocial distress and to promote psychological growth and development, a goal that has been regarded as achievable in the population.¹⁴ CALM addresses 4 main domains: symptom control and communication with health care providers; changes in self and relations with close others; spiritual well-being and sense of meaning and purpose; and preparing for the future, sustaining hope, and facing mortality.¹⁵ In pilot trials with patients with advanced cancer, researchers demonstrated that CALM was feasible and found evidence of improvement in depression, death-related anxiety, spiritual well-being, and attachment security.^{16,17}

Since CALM intervention has proven to be an effective psychological intervention, no studies have shown whether CALM treatment can effectively improve cognitive impairment in cancer patients. Therefore, we conducted a randomized controlled trial (RCT) to compare CALM with care as usual (CAU) in Chinese breast cancer survivors (BCs) assessed for CRCI. The primary outcome was cognitive impairment, including prospective memory (PM) and retrospective memory (RM), and secondary outcomes were QOL and the Distress Thermometer (DT).

Methods

Participants

This unblinded, parallel assignment RCT had 2 trial conditions: CALM intervention plus usual care versus CAU alone, with assessments at baseline and 1 month after treatment.

Seventy-four breast cancer patients with CRCI assessed by the Mini-Mental State Examination (MMSE) scale were enrolled in this study in the Department of Oncology of the

Affiliated Second Hospital of Anhui Medical University from August 2018 to September 2019. The patients were divided into 2 groups. The CALM intervention group was composed of 34 BCs, and the CAU group included 40 BCs. Assessments of CRCI (primary outcome), RM, PM, DT, and QOL were conducted at baseline and 1 month after CALM or CAU. All BCs were selected according to the following criteria:

1. Postoperative pathologic diagnosis of breast cancer, completion of at least 6 cycles of chemotherapy based on taxanes and anthracyclines, with no intolerable side effects
2. MMSE score <27, complaint of memory and attention problems following chemotherapy
3. Karnofsky performance status score ≥ 80
4. At least 18 years of age at diagnosis, with a primary school or higher level of education and a sufficient audiovisual ability to complete the necessary examinations for the study

Breast cancer patients were excluded if the following conditions were present:

1. History of central nervous system (CNS) disease
2. History of CNS radiation or CNS surgery
3. Previous use of drugs that improve cognitive function
4. Severe anxiety, depression, and other mental illnesses
5. Other physical and mental illnesses that can cause cognitive dysfunction

The study was approved by the Research Ethics Committee of the Affiliated Second Hospital of Anhui Medical University (Number of Ethical Approval: 2 012088), and all subjects provided their informed consent.

Procedure

Breast cancer survivors were identified through prescreening of outpatient oncology clinic data, and eligible patients were recruited during clinic appointments. Oncologists give a verbal experiment introduction to the patient and obtains the patient's informed consent. Then, the researchers evaluated the patient's ability to participate and performed baseline measurements. After the recruitment, the statistician randomly assigned patients to enter the trial. The CALM intervention is carried out in the conference room of the oncology department to ensure patient privacy. The research staff performed the CALM intervention on patients at their convenience during hospitalization. Finally, participants were contacted at 6 months to complete follow-up assessments, which were conducted by telephone, or patients came to the hospital for face-to-face evaluation if available.

Randomization

The statistician of our team, who did not participate in the implementation of the experiment, managed the randomization. Computer-generated randomization assignments were provided by the statistician after the participant's baseline assessment. Research staff were blinded to the sequence, which was written on cards and sealed in envelopes to be opened at assignment.

Intervention

CALM is a brief, manual, individual psychotherapy consisting of 4 main domains: symptom management and communication with health care providers, changes in self and relations with close others, sense of meaning and purpose, and concerns related to the future and mortality.¹³⁻¹⁷ In each CALM session, the patient decides which of these domains and to what extent each domain is covered depending on their current concerns and supportive care needs. During a period of 3 to 6 months, patients in the intervention group received up to 3 to 6 sessions of individual therapy, each lasting 30 minutes. Thus, our therapists aim to deliver a minimum of 3 sessions within 3 months, and participants are deemed compliant with intervention when they receive this number. It is best for the patient to complete a maximum of 6 courses within 6 months, when the patient has time available.

CALM is completed by 3 postgraduates, 1 psychologist, and 1 oncologist in the Department of Oncology, the Second Affiliated Hospital of Anhui Medical University, who are dedicated to the research of oncology psychology. Before conducting the study, CALM therapists received relevant training and continued supervision by clinical researchers. Our therapists were considered competent to provide CALM after receiving up to 4 hours of training and 2 cases of practical exercises. There is a group supervision meeting once a week for case formulation and discussion, which aims to ensure that treatment compliance, ability, and skill development are maintained throughout the treatment process. In order to ensure the treatment integrity of the intervention team, the therapist is monitored weekly and a case report is requested, and the therapist also records the conversation in a written report. In addition, senior clinicians are involved in evaluating the overall quality of intervention and discussions with each therapist to improve the efficiency of treatment.

Measures

The Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog)¹⁸ is a self-assessment scale specifically designed to evaluate the cognitive function of cancer patients through interviews with these patients; the tool is

used to assess the cognitive function of patients through a total of 37 items, including 4 dimensions: perceived cognitive impairments (CogPCI), comments from others (CogOth), perceived cognitive abilities (CogPCA), and impact of cognitive changes on QOL (CogQOL). Each item has a score of 0 to 4 points and 5 levels. The higher the total score, the better is the cognitive function. The English version has good reliability and validity. Research has proven that the Chinese version of FACT-Cog has good reliability and validity for breast cancer patients in China and can be used to evaluate the cognitive functional state of breast cancer patients in China.¹⁹

The MMSE was administered to assess general cognitive function, including memory, orientation, executive function, language, and visuospatial skills. In total, 30 questions are in the questionnaire, and each correct answer gets 1 point. If the assessed individual does not know the answer or gives the wrong answer to the question, he or she does not receive a score. The higher the score, the better is the cognitive function. A score of 27 to 30 indicates normal cognitive function, and a score below 27 indicates cognitive dysfunction.

Memory questionnaires include RM and PM²⁰; RM is the memory of past experiences or situations, and PM is the memory of future plans or intentions. The questionnaire contains 16 items, 8 of which test for PM barriers and 8 of which test for RM barriers. Patients are asked to rate their memory failure levels: 4, Very frequent; 3, Sometimes; 2, Very few; 1, Never. The total score of RM or PM is between 8 and 32. The higher the score, the greater is the memory impairment.

The DT is recommended by the National Comprehensive Cancer Center and has the advantages of being simple and easy to operate. It has become a popular tool for evaluating the psychological distress of cancer patients. DT is a visual analogue single-entry scale ranging from 0 to 10, with a total of 11 scores (0 = no trouble, 10 = extreme distress) to determine the patient's psychological distress level by the trouble score. The recommended threshold is 4 points. Patients with a score of 4 or more require further professional assessment and treatment.

The Functional Assessment of Cancer Therapy–Breast (FACT-B)²¹ questionnaire is a self-reported instrument designed to evaluate multidimensional QOL in BCs. The FACT-B consists of 5 subscales, physiological status, social/family status, emotional status, functional status, and additional attention, with higher scores indicating better QOL. The scoring method is set by a hierarchical entry with a total score of 0 to 4 (5 levels), as follows: “Not at all,” 0 points; “one point,” 1 point; “some,” 2 points; “equal,” 3 points; and “very,” 4 points. In addition to the physiological status GP1 to GP7, emotion GE1, GE3 to GE6, additional attention B1 to B3, B5 to B8, several items are positively scored. The positive entry counts

Table 1. Comparison of Demographic Characteristics and Clinical Data of Breast Cancer Between the CALM Group and the CAU Group^a.

	CALM (N = 34)	CAU (N = 40)	t/ χ	P
Age (years)	51.00 \pm 6.950	50.65 \pm 6.612	0.222	.825
Education (years)	8.53 \pm 2.048	9.13 \pm 2.244	-1.184	.240
Pathological type				
Invasive cancer	14	21	2.290	.514
Invasive ductal carcinoma	18	17		
Invasive basal carcinoma	2	1		
Invasive papillary carcinoma	0	1		
Tumor stage				
I	2	7	3.158	.206
II	21	18		
III	11	15		
KPS				
80	7	9	0.040	.842
90	27	31		

Abbreviations: CALM, Managing Cancer and Living Meaningfully; CAU, care as usual; SD, standard deviation; KPS, Karnofsky performance status.

^aData are presented as mean \pm SD.

directly from 0 to 4 points, and the reverse entry counts from 4 to 0 points. The psychometric properties, brevity, and relevance to patients' values make FACT-B suitable for the assessment of QOL.

Statistical Analysis

All data are expressed as the mean \pm standard deviation. Statistical analysis was performed using IBM SPSS Statistics 23.0 software. Baseline group differences on sample characteristics were examined using independent sample *t* tests and χ^2 tests. Scores between before and after intervention were analyzed by means of paired sample *t* tests. Scores between the CALM intervention group and CAU group were compared using 2 independent-sample *t* tests. The correlation analysis of cognitive function and QOL was based on the linear correlation analysis. All statistical tests were 2-tailed, with the level of significance set at $P < .05$.

Results

Table 1 shows that there were no significant differences in demographic information, including age ($t = 0.222$, $P = .825$), years of education ($t = -1.184$, $P = .240$), clinical information such as the Karnofsky performance status ($\chi = 0.040$, $P = .842$), pathological type ($\chi = 2.290$, $P = .514$), and tumor stage ($\chi = 3.158$, $P = .206$) between the CALM group and CAU group.

As illustrated in Table 2, we can see the performance of the BCs before and after CALM or CAU on the neuropsychological test, cognitive function test, memory questionnaires, DT, and QOL assessment scale. Compared with the

CAU group, the performance of the CALM group had significant changes in the total scores on the FACT-Cog ($t = -18.909$, $P = .000$), MMSE ($t = -5.171$, $P = .000$), RM ($t = -4.992$, $P = .000$), PM ($t = -5.067$, $P = .000$), DT ($t = -5.180$, $P = .000$), and FACT-B ($t = -32.421$, $P = .000$) before and after CALM, but for the CAU group, there were also significant differences in the total scores on the FACT-Cog ($t = -3.022$, $P = .004$), MMSE ($t = -3.830$, $P = .000$), DT ($t = -3.526$, $P = .000$), and FACT-B ($t = -5.523$, $P = .000$) before and after CAU, while no significant differences were found in RM ($t = -1.143$, $P = .253$) and PM ($t = -0.471$, $P = .638$). Considering these data together, although both groups' performance showed significant change, the magnitude of data changes in the CALM group was higher than in the CAU group.

Table 3 describes the differences between the 2 groups before and after CALM or CAU. At baseline, there were no statistically significant differences between the CALM group and the CAU group on any of the scale scores for the FACT-Cog ($t = -1.874$, $P = .065$), MMSE ($t = -0.323$, $P = .747$), RM ($t = -0.729$, $P = .466$), PM ($t = -1.565$, $P = .118$), DT ($t = -0.017$, $P = .986$), and FACT-B ($t = -0.305$, $P = .761$), which means that there was no significant difference between the 2 groups in the baseline period before the CALM or CAU. However, 1 month after the interventions, the 2 groups showed statistically significant differences: FACT-Cog ($t = 8.460$, $P = .000$), MMSE ($t = -3.095$, $P = .002$), RM ($t = -3.845$, $P = .000$), PM ($t = -3.989$, $P = .000$), DT ($t = -5.424$, $P = .000$), and FACT-B ($t = 14.739$, $P = .000$).

We can see from Figure 1 that 95 patients are eligible to participate between August 2018 and September 2019, 84

Table 2. Separate Comparison of Neuropsychological Tests, Cognitive Function Test, Memory Questionnaires, Distress Thermometer, and Quality of Life Assessment Scale in the 2 Groups of Breast Cancer Patients Before and After CALM or CAU^a.

Group	N	FACT-Cog	MMSE	RM	PM	DT	FACT-B
CALM group							
BCT	34	79.41 ± 7.063	22.21 ± 2.614	19.59 ± 1.598	21.47 ± 1.522	4.26 ± 0.994	72.76 ± 6.031
ACT	34	97.03 ± 7.280	24.85 ± 2.047	17.38 ± 1.477	19.41 ± 1.351	1.65 ± 0.849	104.47 ± 7.436
<i>t</i>		-18.909	-5.171	-4.992	-5.067	-5.180	-32.421
<i>P</i>		.000	.000	.000	.000	.000	.000
CAU group							
BCT	40	82.53 ± 7.172	22.47 ± 2.460	19.30 ± 1.436	20.85 ± 1.073	4.30 ± 0.992	73.17 ± 5.528
ACT	40	84.18 ± 5.477	23.30 ± 2.174	19.08 ± 1.760	20.98 ± 1.609	3.70 ± 0.758	82.38 ± 5.429
<i>t</i>		-3.022	-3.830	-1.143	-0.471	-3.526	-5.523
<i>P</i>		.004	.000	.253	.638	.000	.000

Abbreviations: CALM, Managing Cancer and Living Meaningfully; CAU, care as usual; FACT-Cog, Functional Assessment of Cancer Therapy–Cognitive Function; MMSE, Mini-Mental State Examination; RM, retrospective memory; PM, prospective memory; DT, Distress Thermometer; FACT-B, Functional Assessment of Cancer Therapy–Breast; BCT, before CALM/CAU treatment; ACT, after CALM/CAU treatment; SD, standard deviation.

^aData are presented as mean ± SD.

Table 3. Comparison of the Neuropsychological Tests, Cognitive Function Test, Memory Questionnaires, Distress Thermometer, and Quality of Life Assessment Scale Between the CALM Group and the CAU Group of Breast Cancer Patients Before and After CALM or CAU^a.

Group	N	FACT-Cog	MMSE	RM	PM	DT	FACT-B
Before CALM or CAU							
CALM	34	79.41 ± 7.063	22.21 ± 2.614	19.59 ± 1.598	21.47 ± 1.522	4.26 ± 0.994	72.76 ± 6.031
CAU	40	82.53 ± 7.172	22.47 ± 2.460	19.30 ± 1.436	20.85 ± 1.073	4.30 ± 0.992	73.17 ± 5.528
<i>t</i>		-1.874	-0.323	-0.729	-1.565	-0.017	-0.305
<i>P</i>		.065	.747	.466	.118	.986	.761
After CALM or CAU							
CALM	34	97.03 ± 7.280	24.85 ± 2.047	17.38 ± 1.477	19.41 ± 1.351	1.65 ± 0.849	104.47 ± 7.436
CAU	40	84.18 ± 5.477	23.30 ± 2.174	19.08 ± 1.760	20.98 ± 1.609	3.70 ± 0.758	82.38 ± 5.429
<i>t</i>		8.460	-3.095	-3.845	-3.989	-6.867	14.739
<i>P</i>		.000	.002	.000	.000	.000	.000

Abbreviations: CALM, Managing Cancer and Living Meaningfully; CAU, care as usual; FACT-Cog, Functional Assessment of Cancer Therapy–Cognitive Function; MMSE, Mini-Mental State Examination; RM, retrospective memory; PM, prospective memory; DT, Distress Thermometer; FACT-B, Functional Assessment of Cancer Therapy–Breast; SD, standard deviation.

^aData are presented as the mean ± SD.

of whom were randomly assigned to CALM ($n = 42$) and CAU ($n = 42$). However, 8 people did not complete the CALM intervention, and 2 people in the CAU group did not complete the final assessment. Finally, there were 34 people in the CALM group and 40 in the CAU group.

Figure 2 shows the results of the correlation analysis between FACT-Cog and FACT-B scores. Whether before or after CALM or CAU, there was a positive correlation between the 2 scores (before: $r = 0.579$, $P = .000$; after: $r = 0.797$, $P = .000$). These results indicate that the higher the cognitive function, the better was the QOL for breast cancer patients.

Through Figures 3 and 4, we see that cognitive function (before: $r = -0.602$, $P = .000$; after: $r = -0.806$, $P = .000$) and QOL (before: $r = -0.659$, $P = .000$; after: $r = -0.864$,

$P = .000$) have a negative correlation with psychological distress separately, which shows that the higher the psychological distress, the worse are the cognitive function and QOL.

In addition, we can see from the intuitive bar chart (supplementary file, available online), there were significant improvements in cognition, QOL, RM, PM, and psychological distress of the CALM group compared with the control group before and after treatment.

Discussion

The present study was a RCT to evaluate the CRCI in Chinese breast cancer patients with CALM treatment. Compared with the corresponding scores of the control

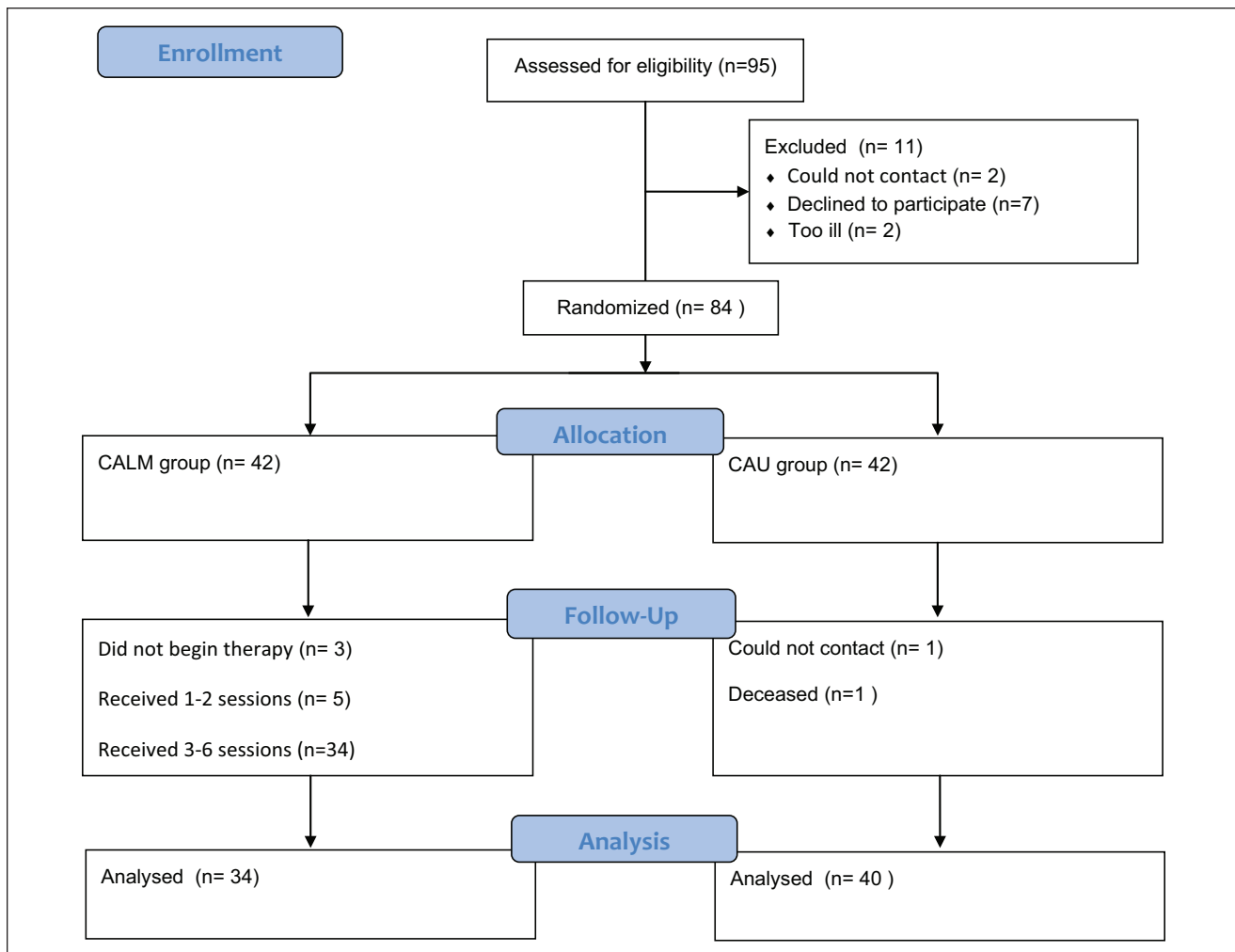


Figure 1. CONSORT flow diagram.

group, there were great improvements in cognitive function, including RM and PM, psychological distress, and QOL, in 34 BCs who completed a brief CALM intervention aimed at managing cognitive symptoms associated with chemotherapy. Participants rated CALM as helpful with regard to such problems and reported high treatment satisfaction. The present results indicated that CALM is a feasible and effective cognitive behavioral, nonpharmacologic management strategy for common problems faced by many cancer survivors. Moreover, this study is a controlled investigation that suggests the effectiveness of CALM in the treatment of cognitive impairment in BCs. Another result of the present study is that there was a positive correlation between cognition and QOL, which is consistent with previous evidence.²² We also found that there was a negative correlation between psychological distress and cognitive function or QOL.

At present, interventions for BCs with CRCI can be broadly classified into 4 categories: (1) cognitive training

interventions, (2) compensatory strategies with cognitive training interventions, (3) pharmacological interventions, and (4) integrative medicine interventions.¹² All these interventions may contribute to treatment effectiveness directly through learning via positive neuroplasticity or indirectly through stress reduction methods that people can learn. Cognitive training interventions are methods for restoring cognitive function through repeated practice using cognitive exercises domains such as memory, attention, speed of processing, or executive functioning.²³ Kesler and colleagues¹⁰ studied the efficacy of a home-based computerized cognitive training, which focuses on training memory, executive functions, speed of processing, and cognitive flexibility. The results showed that participants receiving cognitive training showed significant improvements in these aspects. Compensatory strategies are used to support function in areas of cognitive deficits, which allows patients to rely on other techniques that can gradually transition from external support (such as mnemonics, external prompts) to internal

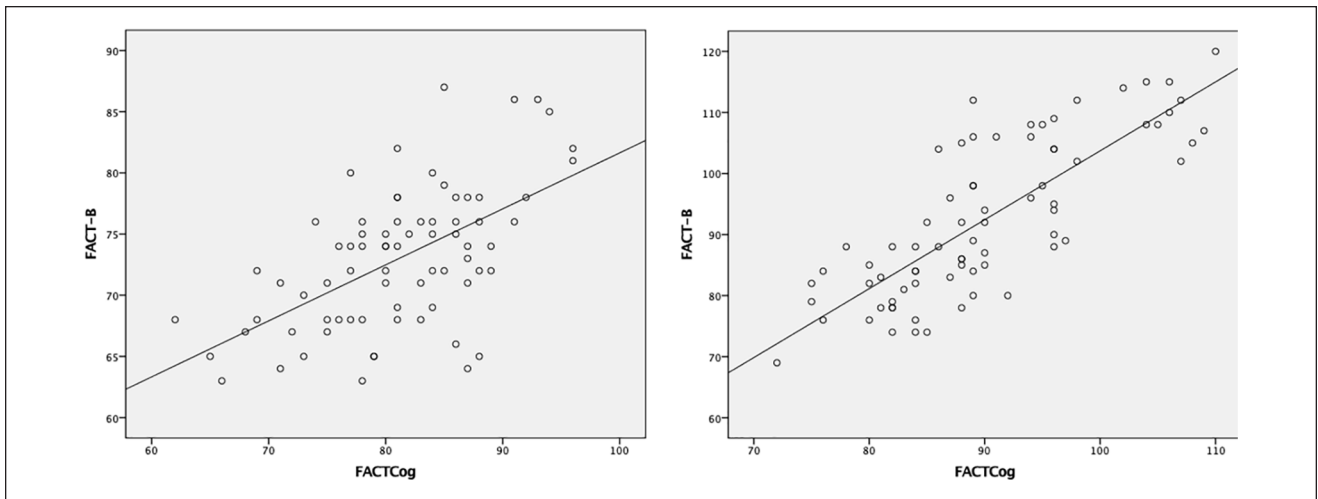


Figure 2. Correlation analysis between cognitive function and quality of life before and after Managing Cancer and Living Meaningfully (CALM) or care as usual (CAU).

There is a positive correlation between Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) and Functional Assessment of Cancer Therapy–Breast (FACT-B) scores whether it is before or after CALM or CAU (before: $r = 0.579$, $P = .000$; after: $r = 0.797$, $P = .000$).

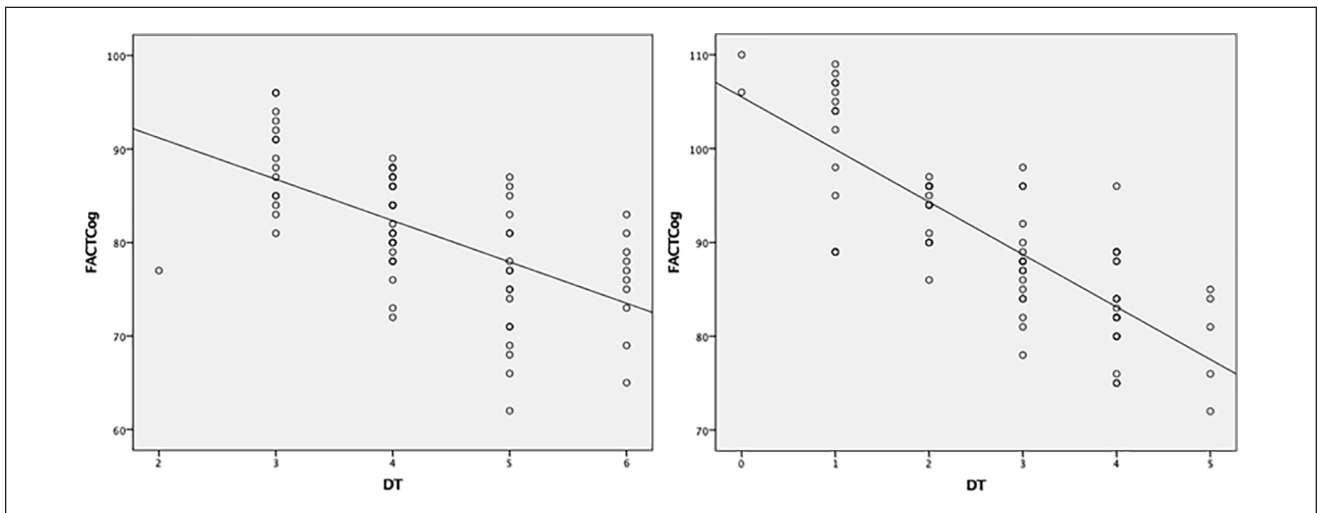


Figure 3. Correlation analysis between psychological distress and cognitive function before and after Managing Cancer and Living Meaningfully (CALM) or care as usual (CAU).

There is a negative correlation between Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) and Distress Thermometer (DT) scores whether it is before or after CALM or CAU (before: $r = -0.602$, $P = .000$; after: $r = -0.806$, $P = .000$).

cognitive processes over time.²⁴ Ferguson et al's⁹ research confirmed that psychological education strategies to compensate for cognitive deficits can improve some cognitive measures and improve QOL. Drugs in the pharmacological intervention include methylphenidate, modafinil, epoetin, and so on.^{25,26} These drugs may improve cognition by reducing fatigue or increasing sobriety or by increasing unknown mechanisms of positive neuroplasticity. However, previous studies found that pharmacological intervention has little or no effect.^{27,28} Integrative medicine interventions consists of

a group of varied treatments and practices that are complementary to standard care for symptom relief.²⁹ Such interventions include meditation, tai chi, qigong, yoga, exercise, and biofeedback.^{30,31} These are focused on meditation and other forms of mindfulness to control breathing, thus achieving relaxation and stress control, and related studies have achieved the expected results.

All in all, the remaining psychological interventions other than pharmacological interventions have a significant effect on improving cognition, and do not have the

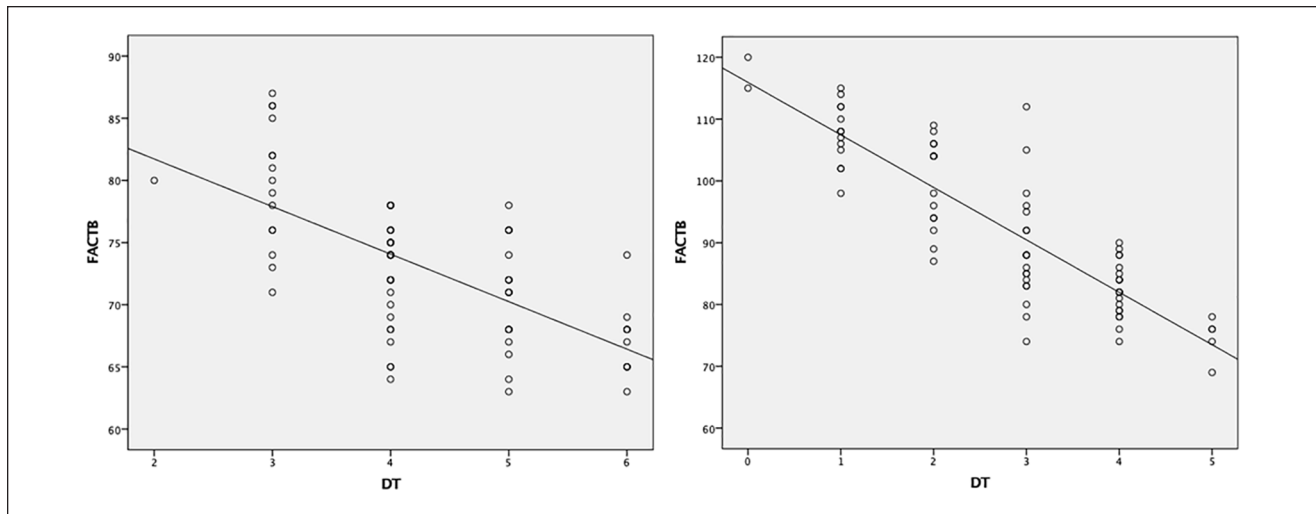


Figure 4. Correlation analysis between psychological distress and quality of life before and after Managing Cancer and Living Meaningfully (CALM) or care as usual (CAU).

There is a negative correlation between Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) and Functional Assessment of Cancer Therapy–Breast (FACT-B) scores whether it is before or after CALM or CAU (before: $r = -0.659$, $P = .000$; after: $r = -0.864$, $P = .000$).

bothersome side effects of drugs. Therefore, psychological interventions have become the most appropriate and feasible treatment for improving CRCI, which promotes the conduct of this study.

CALM therapy is a brief psychotherapeutic intervention that Rodin et al have developed to alleviate distress and to promote psychological health in cancer patients. This supportive-expressive therapy is rooted in several theoretical foundations, including relational theory, attachment theory, and existential psychotherapy, which provides a reflective space for the processing of thoughts and emotions and facilitates the solution of practical and existential questions that face cancer patients with mental distress. It shares the function of manualized supportive-expressive,³²⁻³⁴ cognitive-existential,^{35,36} and meaning-centred³⁷ group psychotherapies intended for patients with advanced disease. There are 5 benefits of this intervention: (1) a safe place to address the experience of advanced cancer; (2) permission to talk about death and dying; (3) assistance in managing disease and navigating health care systems; (4) resolution of relational tensions; and (5) an opportunity to “be seen as a whole person” within the health care system.¹³

Cancer patients usually experience a number of challenges, including physical symptoms and progressive deterioration. Disease burden and other factors might trigger depression, psychological distress, death anxiety, and the loss of hope and meaning in life.^{38,39} Recently, CALM as one kind of psychotherapy has proven to be a useful treatment that provides a systematic approach to alleviating distress in cancer patients.¹³ The possible mechanism may contain the following points: First, the positive influence of CALM was a benefit from the opportunity it gave the participants for

communication and reflection, for assistance with problem-solving in practice, and for the support in solving the distressing issues that the cancer caused to themselves and their families. Second, a time and a safe place was provided to talk about disturbing and potentially frightening problems (such as death) related to their disease, which could contribute to emotional relief, and patients were thereby encouraged to discuss with their families or good friends issues that they had previously found difficult to solve. Third, the sense of meaning and hope in life was rekindled through this individual psychotherapy, promoting patients to begin rightly to face the rest of life. Overall, CALM addresses these issues to change what we have termed an ultimate common pathway of disturbances that leads to depression, anxiety, and other psychological distress in this population. In addition, previous evidence has indicated that anxiety, depression, and overall psychological distress are closely associated with CRCI.⁴⁰ Moreover, in the present study, we found a negative correlation between psychological distress and either cognitive function or QOL. Therefore, the mechanisms by which CALM exerts its effects of improving cognition and QOL may be related to the relief of psychological distress, including anxiety and depression caused by diseases. Further studies are needed to clarify possible mechanism of CALM intervention on CRCI in breast cancer patients.

The main limitation of this study is the small sample size, which may not represent the actual differences in improvement between CALM group and CAU group. Hence, in future research, there is a need to recruit larger sample sizes and use longer term follow-up to replicate these results, and to confirm the effectiveness of CALM treatment. In addition, there is a potential bias due to the

different period and different amount of sessions patients have received as therapy. However, in CALM therapy, participants are typically deemed compliant with intervention when they receive a minimum of 3 sessions within 3 months, so this bias has no significant effect on our experimental results. This experiment uses self-assessment scales and questionnaires to evaluate the effectiveness of treatment, which is subjective in itself, which may bias the true effect of the results. Finally, this trial was not registered because it was a preliminary exploratory study of a small sample and it is not a pharmacological experiment.

Conclusion

CALM is expected to serve as a brief intervention to improve cognitive function and promote QOL and psychological health in BCs. The present study revealed that there are further encouraging and supportive investigations evaluating the effectiveness of CALM treatment in improving cognitive impairment in Chinese breast cancer patients, and this intervention needs to be promoted and implemented in clinical oncology practice.

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.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Natural Science Foundation of China (Nos. 81872504; 81372487).

ORCID iDs

Ke Ding  <https://orcid.org/0000-0002-9682-4957>

Xiuqing Zhang  <https://orcid.org/0000-0002-1953-3910>

Supplemental Material

Supplemental material for this article is available online.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J Clin*. 2015;65:123-138.
3. Hermelink K. Chemotherapy and cognitive function in breast cancer patients: the so-called chemo brain. *J Natl Cancer Inst Monogr*. 2015;2015:67-69.
4. Miao H, Li J, Hu S, et al. Long-term cognitive impairment of breast cancer patients after chemotherapy: a functional MRI study. *Eur J Radiol*. 2016;85:1053-1057.
5. Schmidt JE, Beckjord E, Bovbjerg DH, et al. Prevalence of perceived cognitive dysfunction in survivors of a wide range of cancers: results from the 2010 LIVESTRONG survey. *J Cancer Surviv*. 2016;10:302-311.
6. Myers JS. Chemotherapy-related cognitive impairment: the breast cancer experience. *Oncol Nurs Forum*. 2012;39:E31-E40.
7. Janelins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry*. 2014;26:102-113.
8. Lange M, Joly F. How to identify and manage cognitive dysfunction after breast cancer treatment. *J Oncol Pract*. 2017;13:784-790.
9. Ferguson RJ, McDonald BC, Rocque MA, et al. Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial. *Psychooncology*. 2012;21:176-186.
10. Kesler S, Hosseini SMH, Heckler C, et al. Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. *Clin Breast Cancer*. 2013;13:299-306.
11. Morean DF, O'Dwyer L, Cherney LR. Therapies for cognitive deficits associated with chemotherapy for breast cancer: a systematic review of objective outcomes. *Arch Phys Med Rehabil*. 2015;96:1880-1897.
12. Vance DE, Frank JS, Bail J, et al. Interventions for cognitive deficits in breast cancer survivors treated with chemotherapy. *Cancer Nurs*. 2017;40:E11-E27.
13. Nissim R, Freeman E, Lo C, et al. Managing Cancer and Living Meaningfully (CALM): a qualitative study of a brief individual psychotherapy for individuals with advanced cancer. *Palliat Med*. 2012;26:713-721.
14. Lo C, Hales S, Jung J, et al. Managing Cancer and Living Meaningfully (CALM): phase 2 trial of a brief individual psychotherapy for patients with advanced cancer. *Palliat Med*. 2014;28:234-242.
15. Lo C, Hales S, Rydall A, et al. Managing Cancer and Living Meaningfully: study protocol for a randomized controlled trial. *Trials*. 2015;16:391.
16. Lo C, Hales S, Chiu A, et al. Managing Cancer and Living Meaningfully (CALM): randomised feasibility trial in patients with advanced cancer. *BMJ Support Palliat Care*. 2019;9:209-218.
17. Rodin G, Lo C, Rydall A, et al. Managing Cancer and Living Meaningfully (CALM): a randomized controlled trial of a psychological intervention for patients with advanced cancer. *J Clin Oncol*. 2018;36:2422-2432.
18. Van Dyk K, Hunter AM, Ercoli L, Petersen L, Leuchter AF, Ganz PA. Evaluating cognitive complaints in breast cancer survivors with the FACT-Cog and quantitative electroencephalography. *Breast Cancer Res Treat*. 2017;166:157-166.
19. Cheung YT, Lim SR, Shwe M, Tan YP, Chan A. Psychometric properties and measurement equivalence of the English and Chinese versions of the functional assessment of cancer therapy-cognitive in Asian patients with breast cancer. *Value Health*. 2013;16:1001-1013.

20. Crawford JR, Smith G, Maylor EA, Sala SD, Logie RH. The Prospective and Retrospective Memory Questionnaire (PRMQ): normative data and latent structure in a large non-clinical sample. *Memory*. 2003;11:261-275.
21. Ng R, Lee CF, Wong NS, et al. Measurement properties of the English and Chinese versions of the Functional Assessment of Cancer Therapy-Breast (FACT-B) in Asian breast cancer patients. *Breast Cancer Res Treat*. 2012;131:619-625.
22. Dwek MR, Rixon L, Hurt C, Simon A, Newman S. Is there a relationship between objectively measured cognitive changes in patients with solid tumours undergoing chemotherapy treatment and their health-related quality of life outcomes? A systematic review. *Psychooncology*. 2017;26:1422-1432.
23. Von Ah D, Jansen CE, Allen DH. Evidence-based interventions for cancer- and treatment-related cognitive impairment. *Clin J Oncol Nurs*. 2014;18(suppl):17-25.
24. Reuter-Lorenz PA, Park DC. Human neuroscience and the aging mind: a new look at old problems. *J Gerontol B Psychol Sci Soc Sci*. 2010;65:405-415.
25. Lower EE, Fleishman S, Cooper A, et al. Efficacy of dexamethylphenidate for the treatment of fatigue after cancer chemotherapy: a randomized clinical trial. *J Pain Symptom Manage*. 2009;38:650-662.
26. Fan HG, Park A, Xu W, et al. The influence of erythropoietin on cognitive function in women following chemotherapy for breast cancer. *Psychooncology*. 2009;18:156-161.
27. Fan HGM, Clemons M, Xu W, et al. A randomised, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. *Support Care Cancer*. 2008;16:577-583.
28. Escalante CP, Meyers C, Reuben JM, et al. A randomized, double-blind, 2-period, placebo-controlled crossover trial of a sustained-release methylphenidate in the treatment of fatigue in cancer patients. *Cancer J*. 2014;20:8-14.
29. Fouladbakhsh JM, Stommel M. Gender, symptom experience, and use of complementary and alternative medicine practices among cancer survivors in the US cancer population. *Oncol Nurs Forum*. 2010;37:E7-E15.
30. Milbury K, Chaoul A, Biegler K, et al. Tibetan sound meditation for cognitive dysfunction: results of a randomized controlled pilot trial. *Psychooncology*. 2013;22:2354-2363.
31. Miki E, Kataoka T, Okamura H. Feasibility and efficacy of speed-feedback therapy with a bicycle ergometer on cognitive function in elderly cancer patients in Japan. *Psychooncology*. 2014;23:906-913.
32. Bordeleau L, Szalai JP, Ennis M, et al. Quality of life in a randomized trial of group psychosocial support in metastatic breast cancer: overall effects of the intervention and an exploration of missing data. *J Clin Oncol*. 2003;21:1944-1951.
33. Classen C, Butler LD, Koopman C, et al. Supportive-expressive group therapy and distress in patients with metastatic breast cancer: a randomized clinical intervention trial. *Arch Gen Psychiatry*. 2001;58:494-501.
34. Giese-Davis J, Koopman C, Butler LD, et al. Change in emotion-regulation strategy for women with metastatic breast cancer following supportive-expressive group therapy. *J Consult Clin Psychol*. 2002;70:916-925.
35. Kissane DW, Bloch S, Smith GC, et al. Cognitive-existential group psychotherapy for women with primary breast cancer: a randomised controlled trial. *Psychooncology*. 2003;12:532-546.
36. Kissane DW, Love A, Hatton A, et al. Effect of cognitive-existential group therapy on survival in early-stage breast cancer. *J Clin Oncol*. 2004;22:4255-4260.
37. Breitbart W, Gibson C, Poppito SR, Berg A. Psychotherapeutic interventions at the end of life: a focus on meaning and spirituality. *Can J Psychiatry*. 2004;49:366-372.
38. Rodin G, Lo C, Mikulincer M, Donner A, Gagliese L, Zimmermann C. Pathways to distress: the multiple determinants of depression, hopelessness, and the desire for hastened death in metastatic cancer patients. *Soc Sci Med*. 2009;68:562-569.
39. Lo C, Zimmermann C, Gagliese L, Li M, Rodin G. Sources of spiritual well-being in advanced cancer. *BMJ Support Palliat Care*. 2011;1:149-153.
40. Yang Y, Hendrix CC. Cancer-related cognitive impairment in breast cancer patients: influences of psychological variables. *Asia Pac J Oncol Nurs*. 2018;5:296-306.