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Original Article

Feasibility of a nurse-initiated brief cognitive behavioral strategy intervention program for symptom clusters experienced by patients with advanced non-small cell lung cancer

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ABSTRACT

Objective: To assess the feasibility of a nurse-initiated brief cognitive behavioral strategy (CBS) intervention program targeting pain and fatigue symptoms among the pain and fatigue/anorexia symptom clusters experienced by patients with advanced non-small cell lung cancer (NSCLC).

Methods: In this single-group, pre-post test study, 15 NSCLC outpatients undergoing medical treatment participated. After providing informed consent, participants completed a baseline questionnaire and received a booklet detailing brief cognitive-behavioral techniques (e.g., relaxation, symptom-management strategies), exercise therapy, and related tools. Follow-up calls were made five times over a 10-week period to monitor adherence and assess symptom severity changes.

Results: Ten participants (66.7%) completed the program. For pain management, 86.7% of participants chose deep breathing as a relaxation technique, and 80.0% used exercise to alleviate fatigue. Median symptom severities decreased from baseline to week 10 as follows: pain (2.00 to 1.00), sadness (1.00 to 0.00), and anxiety (1.00 to 0.50).

Conclusions: The naurse-initiated brief CBS intervention program is feasible and clinically relevant for patients with advanced NSCLC undergoing standard treatment in Japan.

Introduction

In the year 2020 there were 602,350 cancer deaths (23% lung cancer)[1] in the United States and 378,385 deaths[2] (20% lung cancer) in Japan, an East Asian country, Lung cancer is a leading cause of cancer deaths for both males and females worldwide,[3] and it is a health issue that must be addressed with urgency and priority. Non-small cell lung cancer (NSCLC), accounts for approximately 81% of all lung cancers.[4] Further, approximately 80% of patients with NSCLC are diagnosed when it is at an advanced, unresectable stage.[5] Advances in standard treatments such as chemotherapy, molecular targeted drug therapy, and immunotherapy have contributed to the survival of patients. However, it has been demonstrated that patients with advanced NSCLC experience multiple simultaneous symptoms that form symptom clusters, and that the burden of these clusters causes daily life interference and reduced quality of life (QOL).[6] In cancer nursing the concept of symptom clusters is relatively new. Nursing scientists have provided evidence of several basic symptom cluster characteristics.[7] They are groups of two or more symptoms that occur simultaneously, are interrelated, but are independent of other symptoms,[8] decreasing functional conditions, and deteriorating QOL.[8–11] Previous studies have reported that patients with lung cancer experience a number of symptoms simultaneously in the course of the disease and its treatment, forming clusters of symptoms that are related.[12–18] Two main symptom clusters were identified in the symptom experience of patients with advanced NSCLC undergoing standard treatment: a

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fatigue/anorexia cluster, which includes five symptoms (altered sense of taste, dry mouth, lack of appetite, drowsiness, and fatigue/tiredness) and a pain cluster, which includes three symptoms (anxiety, sadness, and pain).[6]

Examples of targeted interventions to address a specific symptom within a cluster are cognitive behavioral strategies (CBS). The broad category of CBS interventions including relaxation, guided imagery, distraction, and problem solving have been termed non-pharmacological therapies in the nursing and medical literature.[7,19–22] In psychology, CBS have been identified as "cognitive" and "behavioral" techniques and have developed to be termed parts of cognitive-behavioral theory (CBT).[7] Three principles of CBT are as follows:[23,24] 1) the situation perceived by patients influences their behavior and beliefs about their ability to control a situation, 2) patients can manipulate the ways they perceive specific situations (e.g., cognitive restructuring) and 3) the patient's ability to effectively control information application can be improved by changes in the assumptions they make.

Previous studies investigated the application of CBS interventions (relaxation, distraction) and exercise therapy focused relieving pain and fatigue/tiredness as individual symptoms.[23,25–27] Symptom severity of pain was reduced by relaxation and distraction.[23,25] Exercise therapy for a single symptom (fatigue/tiredness) was also found to benefit patients with lung cancer, in reducing symptom severity.[26]

The evidence for effective interventions focusing on symptom clusters among patients with cancer is still very limited,[19,20,25–30] and even more limited for advanced stage breast cancer. Two intervention methods focusing on symptom clusters in patients with lung cancer are known: Symptom management intervention using pharmacologic therapy, non-pharmacological interventions. These two categories were of 2–12 week durations and focused on theoretical symptom clusters (Table 1).[19,25,26,29,30]

Specifically, among the interventions for specific symptom clusters in patients with advanced lung cancer, there is only one randomized controlled feasibility trial that conducted a non-pharmacological intervention using both multicomponent and follow-up (telephone contact) calls, aiming to manage the respiratory distress symptom cluster (breathlessness, cough, and fatigue) as a symptom cluster.[26]

One study has suggested that for patients with advanced cancer, intervention with brief CBS may be more practical than intervention with full-component, multi-session CBS.[25] Patients with advanced cancer experience multiple simultaneous symptoms as symptom clusters that may be due to disease progression or result from treatment, and few interventions have been developed and tested for patients with advanced cancer who have severe prognosis.[19] For this reason, Kwekkeboom[25] developed the brief CBS intervention consisting of a 20-min training session using the booklets as a nursing intervention for symptom management to reduce the burden on patients with advanced cancer who experience symptom clusters (pain, fatigue and sleep disturbance), and suggested that it provides a small therapeutic effect. The brief CBS is different from traditional multi-component CBS consisting of multiple sessions. Further, this randomized control trial (n = 164) focused on advanced cancer (heterogeneous), and conducted nine-week follow-ups. However, patients with cancer may be reluctant to talk about pain for fear that reporting pain will distract healthcare professionals from treatment and a sense of fatalism, or that pain due to cancer is inevitable.[31] In English-speaking countries, the etymology of the word "pain" includes the meanings of "penalty" and "punishment." However, in Japan, located in East Asia, the word "pain" (*Itami* in Japanese) means a condition of a degree to which somebody or something experiences distress, and is used to express extreme physical, material, or psychological conditions.[6] Originally, the word "*Itami*" does not include the meaning of "punishment".[32] Further, the Itami felt by patients with lung cancer is considered to suggest the "progress of the disease".[33] For this reason, Japanese patients with lung cancer may be less likely to complain about pain symptoms than those in Western countries.

In summary, in advanced cancers such as advanced NSCLC, few nursing intervention strategies are suitable to meet symptom cluster management and shorter life expectancy.[19] Specifically, there are no studies on non-pharmacological interventions using brief CBS and follow-up (telephone contact) calls that can be effective in symptom management, focusing on patients with advanced NSCLC (homogeneous, Stage IIIB, IV, recurrent) and on symptoms included in two symptoms clusters (Pain, Fatigue/anorexia) identified in this population, while considering reducing the burden on patients resulting from participating in the intervention. Further, most reports of CBS are based on research conducted in Europe and the United States, with no studies originating in the East Asian region including Japan.

If patients with advanced NSCLC undergoing standard treatment continue a brief CBS (problem solving strategy) with exercise therapy, which is expected to be effective for the pains in the Pain cluster (sadness, anxiety, and pain) and for the fatigue in the Fatigue/anorexia cluster (altered sense of taste, dry mouth, lack of appetite, drowsiness, and

Table 1
Intervention studies targeting a symptom cluster that included patients with lung cancer.

Author, Year	Design	n	% of patients with advanced stage lung cancer	Symptom clusters	Intervention
Molassiotis et al., 2021[29]	Randomized controlled single-blinded parallel group waitlist-controlled trial	156	97.4% NSCLC receiving Ct 41%, Ct and RT 38.5% Stage III 29.5%, Stage IV 61.5%	Fatigue, dyspnea and anxiety	**Qigong** 6- & 12-week follow-ups
Khamboon and Pakanta, 2021[20]	A quasi-experimental study using historical controls	80	Primary advanced NSCLC receiving Ct Stage III 5%, Stage IV 95%	Fatigue, loss of appetite and anxiety	**Symptom cluster management intervention based on symptom management theory** 1-, 2- & 4-week follow-ups
Kwekkeboom et al., 2018[25]	Randomized controlled trial	164	Advanced (metastatic or recurrent) cancer receiving Ct (LC 21%)	Pain, fatigue and sleep disturbance	**Brief cognitive-behavioral strategies intervention** 3-, 6- & 9-week follow-ups
Yorke et al., 2015[26]	Randomized controlled non-blinded parallel group feasibility trial	107	Primary LC, an expected prognosis of at least 3 months (no information about Stage)	**Respiratory distress symptom cluster** Breathlessness, cough and fatigue	**Non-pharmacological intervention** 12-week follow-up
Kwekkeboom et al., 2012[28]	A pilot randomized controlled trial	86	Advanced (metastatic or recurrent) cancer receiving Ct, RT (LC 29%)	**Pain, fatigue, sleep disturbance symptom cluster**	**Patient-controlled cognitive-behavioral intervention** 2-week follow-up
Chan et al., 2011[30]	Randomized controlled trial pre-post test	140	Advanced (stage III or IV) LC receiving palliative RT, concurrent treatment with Ct (18%) Distant metastasis 46%	Breathlessness, fatigue, anxiety	**Psychoeducational intervention** 3-, 6- & 12-week follow-ups

LC: lung cancer, NSCLC: non-small cell lung cancer, RT: radiation therapy, Ct: chemotherapy.

fatigue/tiredness), then with the assistance of follow-up calls by nurses, this may increase the likelihood of achieving palliative outcomes (reduction in symptom severity) of the patient symptoms, but may not lead to a decline in QOL.

We have not identified any studies conducted in Eastern Asia, particularly Japan, that have explored the following: Can a combination of a brief CBS, which is relatively unfamiliar in Japanese clinical practice, and exercise therapy be understood and accepted by Japanese patients with advanced NSCLC undergoing standard treatment for stages IIIB or IV, including recurrent cases? Which specific components of CBS and exercise therapy would be tolerable for patients with advanced-stage NSCLC, particularly those who have already experienced symptom clusters, without being perceived as burdensome? Furthermore, if patients are able to continue with the CBS, is there evidence to suggest that they might experience initial benefits from this nurse-initiated brief CBS intervention?

With this background, the present study aims to evaluate the feasibility of this first Japanese clinical trial of the application of a nurse-initiated brief CBS intervention directed at pain and fatigue/tiredness for patients with advanced NSCLC undergoing standard treatment.

This study will apply a nurse-initiated brief CBS (involving relaxation, distraction, exercise and other therapies) intervention focused on pain and fatigue/tiredness symptoms among the Pain and Fatigue/anorexia symptom clusters, and evaluate the acceptability among Japanese patients with advanced lung cancer. Second, this study will evaluate the beginning efficacy of this intervention on symptom clusters found among Japanese patients with advanced stage lung cancer among the clinical practices in Japan.

Methods

The study was approved by the Ethics Committee of the medical university the authors belong to and the Ethics Committee of the institutions where the study was conducted (IRB No. 16185).

Study design and participants

This study employed a one-group pretest-posttest design, and reports a feasibility test conducted the first time in clinical settings in Japan. Referring to a previous feasibility study for similar CBS interventions among patients with cancer ($n = 30$),[7] and the results reported by Julious,[34] we recruited 15 patients diagnosed with advanced (Stage IIIB or IV, recurrent) stage NSCLC as a convenience sample. This sample size ($n = 15$) was assumed to be an achievable number based on two elements: one is that the similar feasibility study by Kwekkeboom et al.[7] in the USA had a sample size of 30, and $n = 10$ is an achievable number in Japan if we take into account a population ratio of 3:1 between the USA and Japan; and the other one is that the present study was conducted in the same two facilities as the previous study ($n = 60$) by the authors[6] that focused on patients with advanced NSCLC. In that study the recruitment ratio of two facilities (a respiratory medicine department at a university hospital in the north Kanto region ($n = 40$) and a respiratory center at a general hospital in the Tokyo metropolitan area ($n = 20$)) was 2:1. Assuming that the number of outpatients has remained at about the same level, the present study used the same recruitment ratio as the previous, 2:1, and enrolled 10 outpatients from the university hospital in the north Kanto region and 5 from the Tokyo metropolitan area, resulting in the sample size of 15. We considered this size an achievable number based on the sample size of the study by Kwekkeboom et al.[7]

Eligibility criteria included the criteria: adult patients who were diagnosed with advanced stage lung cancer, undergoing standard treatment, who have not been diagnosed with another cancer within the past year, and who were determined by their physicians to be cognitively able to participate in the study. Eligibility included patients who rated ≥ 1 any symptoms on a 0–10 scale, included in the Pain cluster (sadness, anxiety, and pain), or Fatigue/anorexia cluster (altered sense of taste, dry mouth, lack of appetite, drowsiness, and fatigue/tiredness) in the past 24 hours. Exclusion criteria were for patients who had been diagnosed with another cancer in the previous year, those who had unbearable physical or mental distress, and those who were considered to be incapable of understanding and responding to the questions by their physicians.

After the patients signed an informed consent form that contained explanation about the study outline and participation conditions, they completed questionnaires, including a symptom assessment form and a QOL assessment form at the pretest (baseline). Using the booklet to introduce CBS content and exercise therapy for symptom management of pain and fatigue/tiredness in the two symptom clusters, a research nurse provided a 30-min educational session intervention. The session educated eligible patients about their choices regarding CBS and exercise therapy. These interventions were to be conducted at a time and date based on their preferences.

Next, we gave the enrolled participants the same set of symptom assessment at baseline, and three posttests (1st week (Wk1), 2nd week (Wk2), and 10th week (Wk10)) after the educational session intervention. Because patients with advanced NSCLC (Stage IIIB or IV, recurrent) undergo treatment such as chemotherapy, molecular targeted drug therapy, and /or immunotherapy, we timed the follow up data collection around these therapies for patient convenance. Timepoint Wk2 includes careful physical monitoring and every Wk3-6 during treatment.[35,36] Previous studies have identified the following advantages: in the first week of an intervention, early symptom changes under treatment;[20] and in the second week, effects of the symptom intervention.[28] Further, using after deciding the baseline timepoint, we decided the follow-up time points as Wk1 (confirmation of understanding of the particulars of the intervention, request for completing a symptom assessment form and a QOL assessment form), Wk2 (confirmation of the ongoing understanding of the particulars of the intervention, request for completing the symptom assessment form and the QOL assessment form), and Wk10 (confirmation of continued understanding of the particulars of the intervention, and a request for completing the symptom assessment form and the QOL assessment form). We also decided these three time points carefully by referring to the previous study (Table 1). This is the first feasibility study targeting only patients with advanced NSCLC in real clinical practice. We considered that patients would suffer treatment side effects over time and that at Wk1 and Wk2 we could conduct follow-ups by taking into account the burden on the patients, we concluded that 10-week follow-up length may yield a sufficient effect of the intervention.

These three follow-up time points (Wk1, Wk2, Wk10) were customized for Japanese patients with advanced lung cancer, based on previous CBS intervention studies for patients with advanced cancer.[7,23,25] We set these timepoints to allow for the following considerations: At Wk1: to improve the understanding of cognitive behavioral intervention (CBI) and encourage participants to start CBI by clarifying any uncertainties about CBS and answering any questions the participants could have; to adjust CBS to make it more effective by sharing the progress of CBS with the participants and research nurses in the case that the assessments of the brief CBS at Wk2 and in this study would suggest the effectiveness CBS to be insufficient; and at Wk10, to empower participants to continue the CBS by asking the participants about the progress of CBS and confirming their awareness of the CBS effectiveness.

We also asked the participants about their preferred schedule for five follow-up calls. Participants were requested to complete and mail the questionnaires in the evaluation day evening or within one week of the evaluation day.

Intervention

The intervention research nurse held master's degree and five years or longer experience in oncology nursing. The research nurse coordinated study procedures. Prior to the intervention, the PI provided training (one hour) and guidance about the study for the research nurse in charge of

the intervention: Background, Objectives, Characteristics and content of the brief CBS, and the use of the booklet to provide the brief CBS, role play and overview of all content were included in the training.

The PI ensured the fidelity of the intervention by the research nurse, with the following steps: (1) Sharing the research objectives and methods with the research nurse, (2) Ensuring and sharing the research nurse understanding of the contents of the booklet, (3) Having patients read the CBS strategy information in the booklet, and choose a strategy with understanding when providing brief CBS interventions, (4) Monitoring that the intervention was delivered and that appropriate communication was made by being present at the first CBS strategy and follow-up calls. The time spent on this intervention program is about 30 min per patient including the explanation of the intervention booklet and responses to individual questions.

Instruments

For the demographic data, participants were asked to complete a questionnaire asking about their marital status, the presence or absence of persons living together with them, and their educational history. The name of the cancer diagnosis, duration (in days) since the diagnosis, history of the treatment to date, presence of comorbidities, their use of pain medications, and history of emergency department visits (Wk1, Wk2 and Wk10) were collected by the research nurse from the medical charts.

The symptom assessment questionnaire including 13 items of a Japanese version of the MD Anderson Symptom Inventory[37] (MDASI-J),[38] which assesses cancer-related symptoms common to cancer patients, and the Advanced NSCLC symptom modules, consisting of 9 advanced NSCLC typical additional symptoms (altered sense of taste, weight loss, leg weakness, cough, rash, impaired concentration, irritability, anxiety and depression), which was used in the previous study[6] by the authors of the present study.

The MDASI rates the symptoms over the previous 24-h period on a 10-point scale of 0 (not present) to 10 (as bad as can be imagined). The Advanced NSCLC symptom modules rate the symptoms in a similar manner. The higher the score, the more severe (stronger) the symptom severity. Daily life interference caused by the symptoms were assessed with the MDASI-J daily life interference (6 items arranged in the same order as in the MDASI). The higher the score, the more severe (stronger) the difficulties.

Quality of life was assessed using a Japanese version of the Core QOL Questionnaire (QLQ-C30), consisting of 30 items, and the Japanese version of LC13, consisting of 13 items specific to patients with lung cancer used with permission from the European Organization for Research and Treatment of Cancer (EORTC).[39,40] The EORTC-QLQ-C30 is a questionnaire that assesses the core contents of QOL in patients with cancer on a standard score of 0–100. The higher the score, the better the QOL. This paper reports on EORTC-QLQ-C30.

The reliability and validity of these MDASI, MDASI-J, NSCLC symptom modules, and EORTC-QLQ-C30 have been reported.[6,37–40] Cronbach alpha coefficients in the present study sample were $\alpha = 0.77\text{-}0.92$ and $\alpha = 0.91\text{-}0.95$, $\alpha = 0.84\text{-}0.93$, and $\alpha = 0.77\text{-}0.85$ for daily life interference in the MDASI-J, NSCLC symptom modules, and EORTC-QLQ-C30, respectively.

Intervention procedure

After the baseline symptom assessment, we explained the nurse-initiated brief CBS intervention based on the 15-page booklet (Table 2), and details of CBS related to pain and fatigue/tiredness for symptom clusters and their management. This guidance was provided in a face-to-face manner.

The booklet contains the following sections: Symptom clusters (Pain, Fatigue/anorexia), definitions of pain, fatigue and loss of appetite (anorexia); and introduction of pain alleviation strategies: relaxation (deep breathing, music, other), imagery, and adoption of preferred methods; for fatigue and anorexia relief: exercise (at least 2000 steps/day), relaxation (same as Pain), afternoon nap, constant food intake and supplements, and adoption of preferred methods. Next, we asked the participants to select an alleviation strategy for each of pain, fatigue, and anorexia that met their preferences. We ended the 30-min session by explaining the strategy to the participants. The research nurse conducted follow-up calls at 5 timepoints starting from this intervention date (beginning of Wk1: during Wk1; beginning of Wk2: during 2Wk; and during Wk10). At the Wk1, we verified the participant understanding of CBS, and from the second week onward we asked them about the status of implementation of symptom alleviation strategies, and gave them advice and encouragement to continue the strategies.

At the end of three of these follow-up calls (Wk1, Wk2, and Wk10), we asked participants to self-report on the MDASI-J and advanced NSCLC symptom scales, EORTC-QLQ-C30 and LC13, and evaluated the responses. For patients with advanced cancer, it is difficult to completely avoid Missing Not At Random (MNAR) data, which is caused by difficulty in completing a questionnaire as the disease progresses and the patient condition worsens.[41,42] At present, no standard method has been established for cases where MNAR has occurred.[39,41] As an imputation method for missing values that are common in QOL assessments among patients with advanced cancers, replacement by mean method is introduced to utilize the valuable data from these patients.[39] For this reason, we used the mean imputation method, which is an approach in which data are supplemented with missing values for analysis.[41]

SPSS 27.0 (IBM® SPSS®) was used for the descriptive statistics and statistical analysis. We conducted descriptive statistics for background data, symptom severity and the EORTC-QLQ-LC30 at the pretest and posttests (Wk1, Wk2, and Wk10), intervention (deep breathing frequency/day) and exercise therapy (steps/day). For the feasibility of the study participants: (1) acceptability was evaluated by calculating the retention rate of participants from recruitment and for the study period, and (2) the efficacy of the nurse-initiated brief CBS intervention was assessed and evaluated by changes in symptom severity at pretest (baseline) and posttests (Wk1, Wk2, and Wk10). Changes in the 5 functions of QOL and Global QOL were also evaluated by descriptive statistics. The significance level was set at 5%.

Table 2
Overview of booklet.

Page	Contents
3	**Introduction**
4–5	Follow-up call schedule: (1) first half Wk1, (2) last half Wk1, (3) first half Wk2, (4) last half Wk2, (5) Wk10
7	Symptom clusters
8	Pain cluster
9	What is pain?
10	Pain alleviation strategies: Choose one or more of the options below • Take deep breaths and relax. • Listen to music to relax. • Guided imagery therapy (the researcher (nurse) will explain how to do this). ▪ Imagine waves. ▪ Imagine a forest. • Include your preferred methods ( ).
11	Fatigue/anorexia cluster
12	What are fatigue and anorexia?
14	Fatigue and anorexia alleviation strategies: Choose one or more options as below • Keep a daily step count (mobile phone, pedometer, etc.) and continue the walking till the target number of steps (equivalent to about 20 minutes of walking) (about 2000 steps). • Try relaxation methods such as music as described in the Pain alleviation section to help you get a good night sleep. • Try to get a good rest, napping for 30 minutes. • Incorporate the following supplemental foods to maintain the amount of food consumed. • Take protein in the form of ( ). • Add high-energy foods ( ). • Weigh and record your weight daily. • Include your preferred methods ( ).
15	References

Results

Demographic characteristics of participants

In the time frame from Jun, 2017 to March, 2019, eighteen patients were recruited and determined as eligible, and 15 patients consented (Registration number: UMIN 000026996; registered on June 30, 2017). On December 26 of 2017, the first participant was recruited. Table 3 shows details of the demographic characteristics. Participants ($n = 15$) were from 50 to 76 years old (Median: 68.00). At the time of recruitment, one male participant was 75, and he became 76 during the data collection period and his age was incorporated as 76 in the analysis.

All were Japanese and diagnosed with advanced stage lung cancer (Stage IV) or recurrence.

Females were 33.3% and 86.7% were married, and 73.3% ($n = 11$) were employed workers, 53.3% of the participants had associate degrees or higher. The mean length of time since diagnosis was 1490.27 days (median 864 days, range 154–4320 days), 39.9% ($n = 6$) were on molecular targeted therapy, 33.3% on chemotherapy, and 26.7% on immunotherapy. Despite the most advanced stage of lung cancer, 73.3% ($n = 11$) were not using pain medications (Table 3). Among the 15 participants with advanced NSCLC (Stage IV or recurrence) undergoing standard treatment, 14 (93.3%) completed the MDASI-J and QOL assessment form during the treatment periods, but one female (6.7%) participant completed these questionnaires at the follow-up time points (Wk1 and Wk2) while undergoing immunotherapy. The number of emergency department visits during the study period was zero for all participants at the baseline and at the three time points after the start of the intervention (Wk1, Wk2 and Wk10). We had the following missing data: at pretest (baseline) and posttests (Wk1, Wk2, and Wk10), Nausea (one response: 6.7%) in symptom severity (22 items), and no missing data in the daily life interference (6 items); in EORTC-QOL-C30 (30 items), one item (one response: 6.7%); at Wk1 ($n = 14$) one response (6.7%) of Vomiting and Weight loss of symptom severity and Work (including housework) in daily life interference (6 items), and one response (6.7%) for each of three items in EORTC-QLQ-C30 at Wk2 ($n = 13$) no missing data in the symptom severity, one response (7.7%) for each of the five items in daily life interference (6 items), two responses (15.4%) in Enjoyment of life, and one response (7.7%) in one item of EORTC-QOL-C30; at Wk10 ($n = 10$) no missing data in symptom severity and daily life interference, and one response (10.0%) in one item of EORTC-QOL-C30.

Table 3
Participant demographic characteristics and medical characteristics at baseline ($N = 15$).

Characteristics	*n*	%	Mean (SD)	Range	Median
Age (years)			67.00 (7.04)	50–76	68.00
Sex					
Female	5	33.3			
Male	10	66.7			
Marital status					
Married	13	86.7			
Single, divorced	2	13.3			
Employment status					
Employed	11	73.3			
Unemployed or retired	4	26.7			
Education (years)					
University, graduate school, or	5	33.3			
Junior college (> 12)	3	20.0			
Senior high school (≤ 12)	5	33.3			
Junior high school (≤ 9)	2	6.7			
Time since diagnosis (days)			1490.27 (1369.95)	154–4320	864
ECOG PS			0.86 (0.60)	0–1	1
0	2	13.3			
1	13	86.7			
Histological types of cancer					
Adenocarcinoma	15	100.0			
Cancer stage					
IIIB	0	0.0			
IV	9	60.0			
Recurrence	6	40.0			
Current treatment					
Chemotherapy	**5**	**33.3**			
CBDCA + nab-PTX	1				
PEM	1				
DOC	1				
DOC + RAM	2				
EGFR-TKI	**5**	**33.3**			
Gefitinib	1				
Erlotinib	1				
Afatinib	2				
Osimertinib	1				
ALK-inhibitor	**1**	**6.6**			
Alectinib	1				
Immune checkpoint inhibitor	**4**	**26.7**			
Nivolumab	2				
Pembrolizmab	1				
Atezolizumab	1				
No. of comorbidities					
0	2	13.3			
1 or more	13	86.7			
Current analgesics usage					
Yes	4	26.7			
No	11	73.3			

SD, Standard deviation; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CBDCA, Carboplatin; PTX, Paclitaxel; PEM, Pemetrexed; DOC, Docetaxel; RAM, Ramucirumab; ALK, Anaplastic lymphoma kinase; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

Feasibility

Participation and study completion

Fig. 1 is a flow diagram showing the retention rate of participants from the recruitment to study completion. The patients were adults (20–75 years old). Of the 18 who met the eligibility criteria, three withdrew consent before the intervention began. Finally, $n = 15$ were enrolled in the study with informed consent forms signed. In the Posttest at the Wk1 assessment, one patient was unable to continue the intervention, and at Wk2, one patient did not respond to the questionnaire, both due to progression of the disease.

However, despite being at the most advanced stage of NSCLC, most participants (66.7%, $n = 10$) matriculated to the Posttest (Wk10). Consequently, the retention rate of participants in this study throughout the 10-week period was 66.7%. The most common CBS (problem solving) that met their preferences was deep breathing for relaxation, 86.7% ($n = 13$) for pain alleviation, and 80.0% ($n = 12$) for fatigue relief, with exercise using a pedometer (> 2000 steps/day of walking). There were no specific requests for adopting the strategies on their own. The range number of times of doing the exercises performed by the participants who chose CBS (relaxation: deep breathing) ($n = 13$) reported at the follow-up calls was 1–6 times/day. The timing of the CBS (deep breathing, multiple times/day) was prescribed for when the participants felt like doing the exercises and before going to bed. Similarly, the median number of steps reported by the participants who chose exercise therapy ($n = 12$) was 3183.5 (range: 500–20000) steps. Of these, 66.7% ($n = 8$) of the participants were consciously incorporating walking into their daily routine for the exercise therapy.

Change in symptom severity

Changes in symptom severity (median) before and after the brief CBS intervention over the study period are shown in (Figs. 2 and 3).

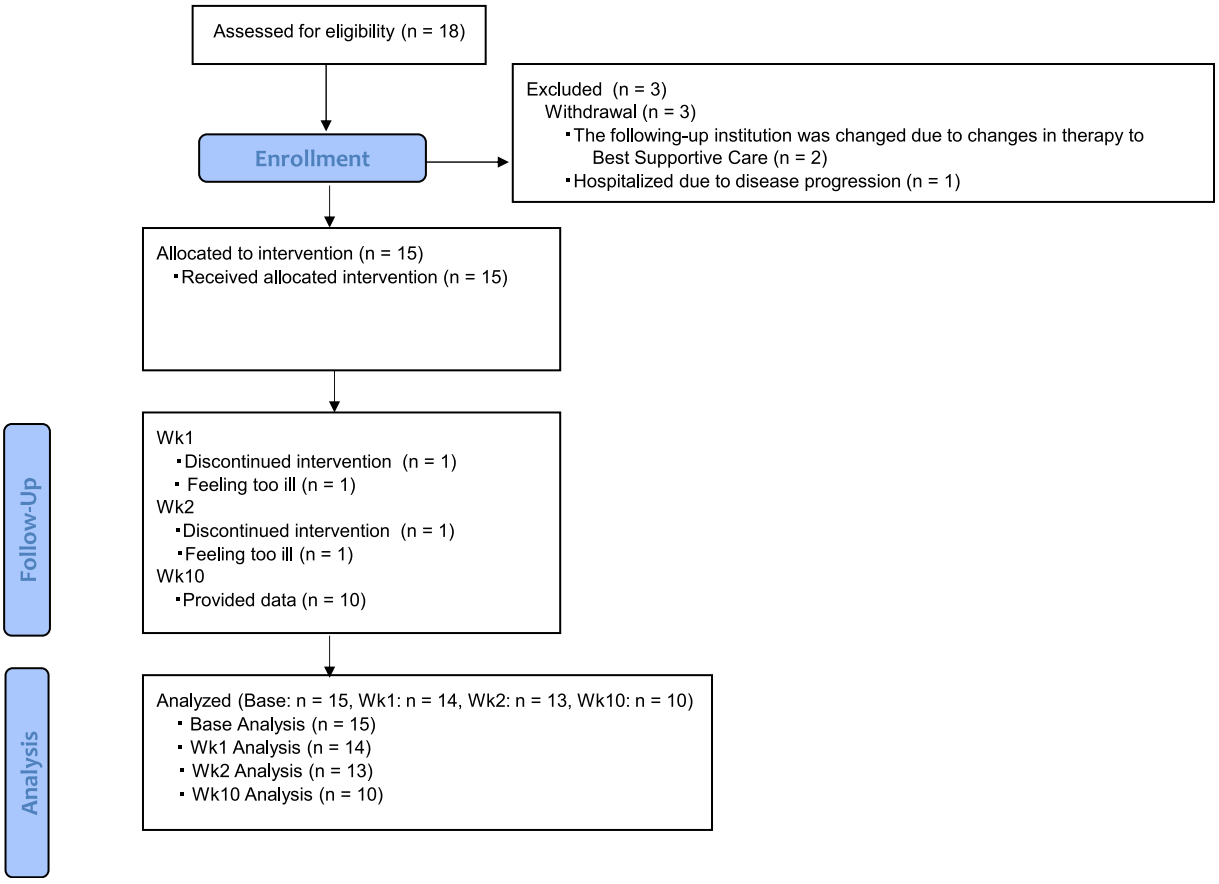

Fig. 1. Participant flow diagram

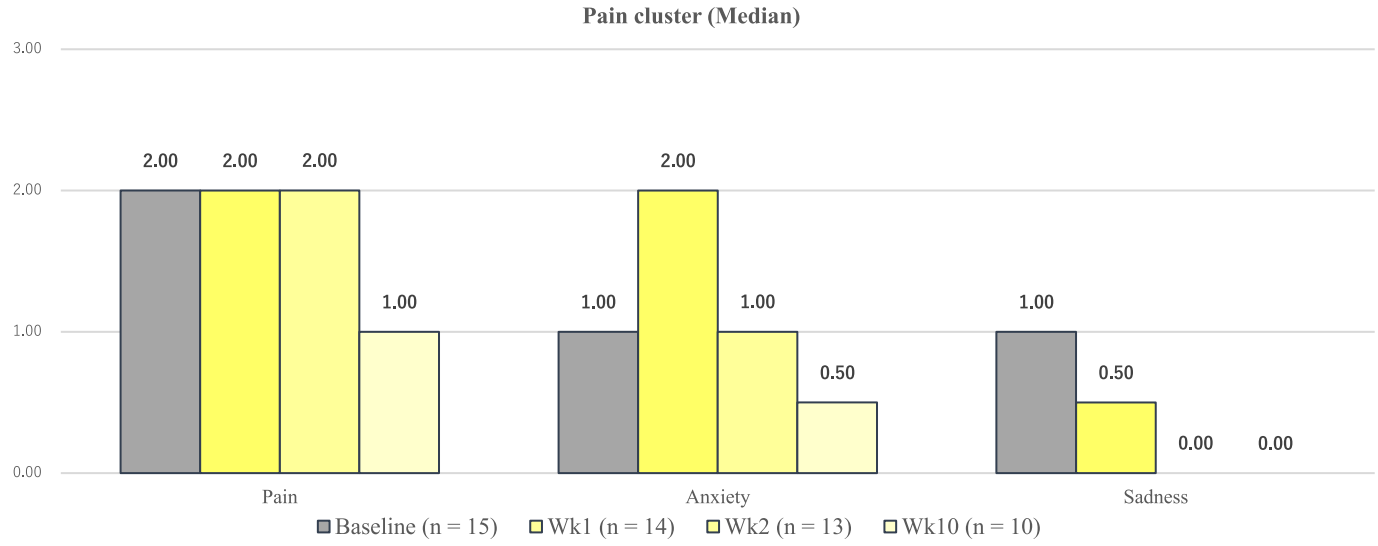

Fig. 2. Median symptom ratings pre (Baseline) - and post (at Wk1, Wk2 and Wk10)-treatment with a brief CBS intervention.

Change in daily life interference and quality of life

Medians scores for daily life interference (6 items) (at pre, Wk1, Wk2, Wk10) were as follows: Life in general (2.00, 2.00, 1.00, 1.00), Emotions (2.00, 1.50, 2.00, 1.00), Work (2.00, 1.50, 1.00, 1.00) interpersonal relationships (1.00, 1.00, 1.00, 0.00), Walking (3.00, 1.00, 2.00, 1.00), and enjoyment of life (2.00, 1.50, 2.00, 1.00) (Fig. 4). These show that daily life interferences in the majority of participants (n = 10, 66.7%) who continued to participate over the 10-week study period tended to be alleviated, particularly in walking, compared to baseline, although there were some fluctuations.

The median values of the standard scores (at pre, Wk1, Wk2, Wk10) in EORTC-QLQ-C30 (five functions and Global QOL) showed flat to upward tendencies compared to the baseline data. In Global QOL, the differences for each participant fluctuated and showed flat to upward

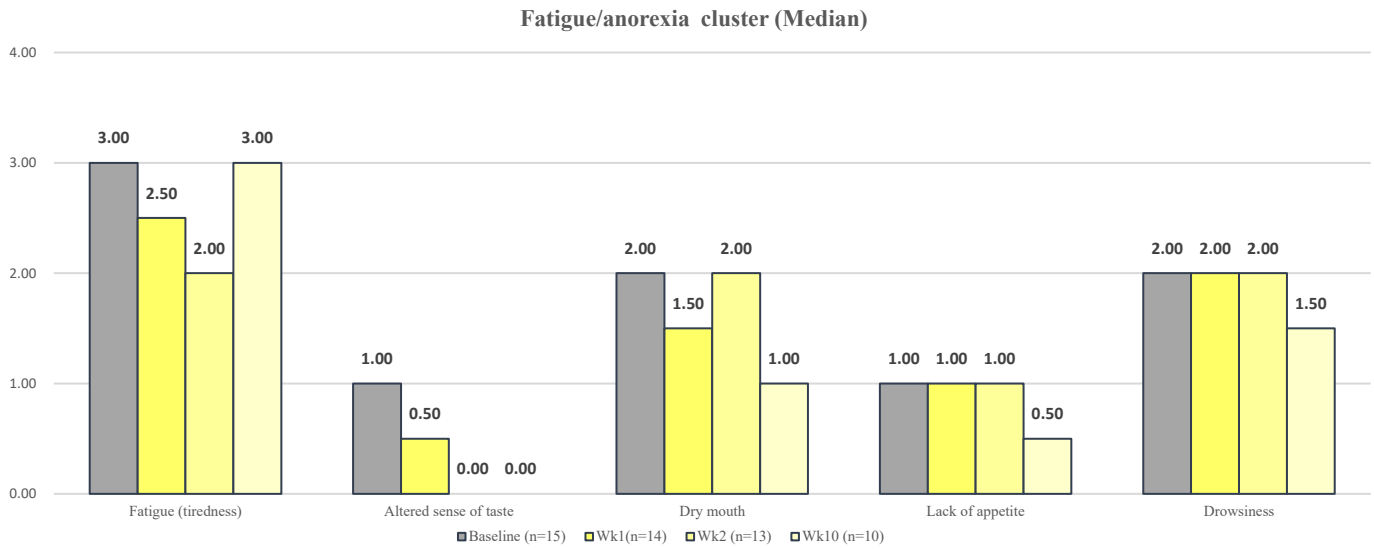

Fig. 3. Median symptom ratings pre (Baseline)- and post (at Wk1, Wk2 and Wk10)- treatment with a brief CBS intervention. CBS, cognitive-behavioral strategy.

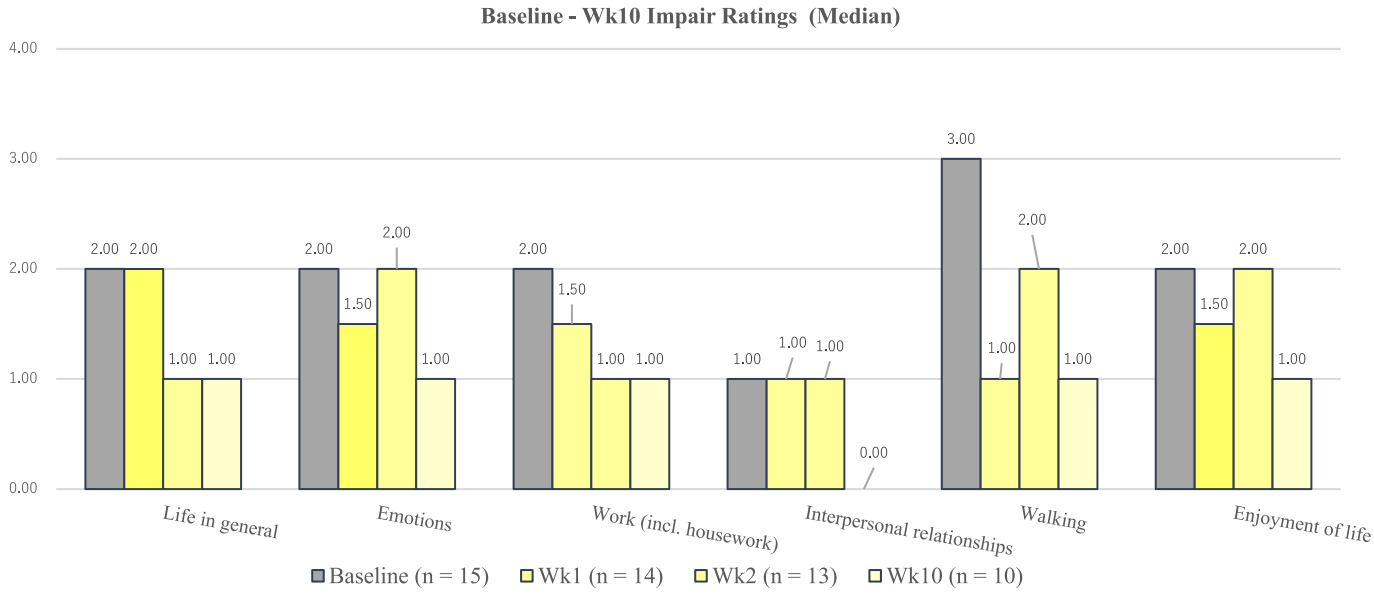

Fig. 4. Median Impair ratings pre (Baseline)- and post (at Wk1, Wk2 and Wk10)- treatment with a brief CBS intervention. CBS, cognitive-behavioral strategy.

tendencies. There were also changes in the scores of five functions: Social Functioning (+25.0), Role functioning (+8.3), Emotional functioning (+8.3), Physical functioning (+6.7), and Cognitive functioning (+0) in ascending order from the baseline. There was a consistent trend toward improvement in the global quality of life and emotional functioning (Fig. 5).

Discussion

This study provided a nurse-initiated, brief CBS intervention for patients with advanced NSCLC undergoing standard treatment for the first time in Asia (Japan). This intervention aimed to alleviate symptom severity of pain included in two symptom clusters (Pain and Fatigue/anorexia) experienced by this population. It appears that the results showed acceptability and some initial efficacy for symptom severity over the 10-week intervention period.

Kwekkeboom[7] conducted a patient-controlled cognitive behavioral feasibility study to evaluate the first efficacy of the intervention in controlling symptoms -pain, fatigue, and sleep disturbance in patients with advanced cancer in the treatment phase [30 patients (83%) were treated with chemotherapy, 8 (27%) were patients with lung cancer and 15 (50%) were patients with GYN], and reported good tolerability with a retention rate of 90% ($n = 27$) in their 2-week study period. In the present study of 15 patients with advanced NSCLC (33.3% chemotherapy, 39.9% molecular targeted therapy, 26.7% immunotherapy), the retention rate at week 2 was 86.7% ($n = 13$), showing a similarly good tolerability. In this study with a 10-week follow-up, the retention rate at week 10 was 66.7% ($n = 10$). Although it is difficult to make simple comparisons, the acceptability of the nurse-initiated brief CBS intervention in this study, where all participants were patients with advanced NSCLC at the most advanced stage (Stage IV) (100%), may be interpreted as good because we obtained a retention rate which is almost equivalent to that of Kwekkeboom.[7]

For the recruitment method, the eligibility criteria are not clear because only a limited number of studies have focused on symptom clusters.[7] In the feasibility study for patients with cancer ($n = 30$, 27%

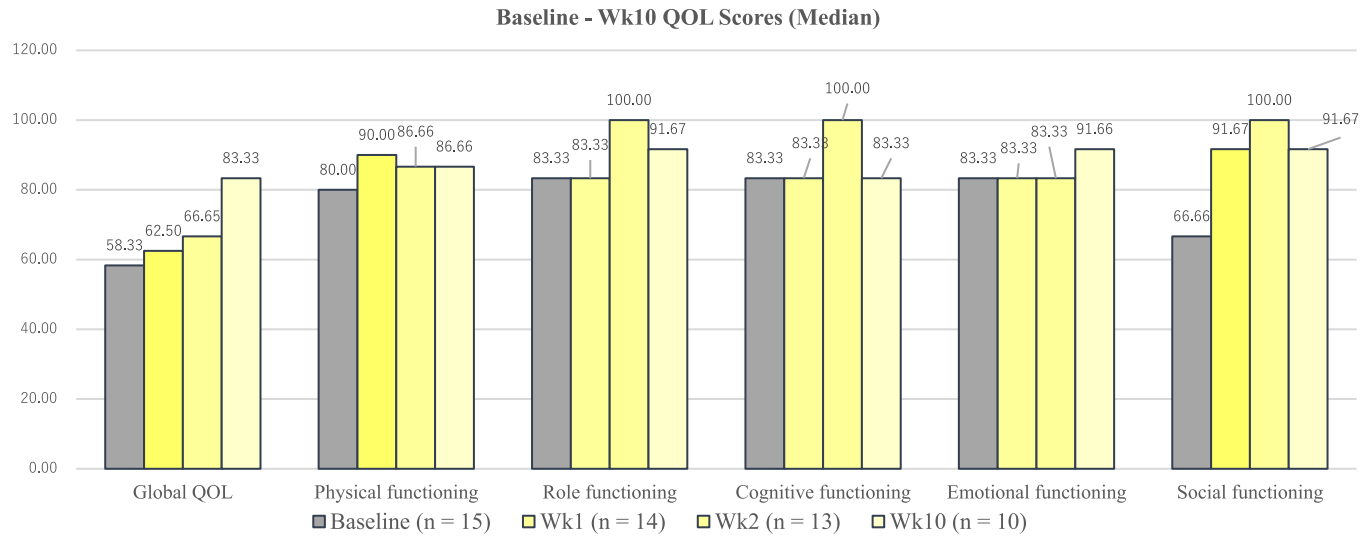

Fig. 5. Median EORTC QLQ C-30 five functions and global QOL ratings pre (Baseline)- and post (at Wk1, Wk2 and Wk10)- treatment with a brief CBS intervention. CBS, cognitive-behavioral strategy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QOL, quality of life.

LC) by Kwekkeboom[7] described above, based on the idea that ideal eligibility criteria have not yet been determined for symptom conditions at the baseline, cancer patients with at least two of the three symptoms that are considered to form a cluster at the baseline were included, and recruitment and retention statistics (Wk2) were evaluated as good at 73% and 90%. In a pilot randomized controlled trial (RCT) of a similar CBI study of patients with advanced cancer (n = 86: 23% LC),[28] the recruitment and retention statistics were 37.7% and 90.7%, respectively. The present study for advanced cancer patients included patients with pain or fatigue symptoms, which are considered to form two (Pain, Fatigue/anorexia) symptom clusters, and only 3 of 18 (16.7%) eligible patients did not participate in the study. In short, the recruitment and retention (Wk10) statistics were 83.4% and 66.7%, respectively, suggesting that the eligibility criteria for this study were reasonable. Therefore, we may evaluate the retention statistics as good.

However, the prognosis of the participants of the present study was limited with the 5-year survival rates for patients with advanced lung cancer at 5% (U.S.)[3] and 6.7% (Japan).[2] Further, more than half had been diagnosed more than 2 years before the participation, with 864 days (median) from the diagnosis. Considering these conditions, the impact of the disease progression on retention rates was unavoidable to some degree even after participation began, though the performance status (PS) (0–1) was good at the start of participation. For a larger study, one important intervention may be early recruitment by attending physicians or nurses who determine that the patients have met eligible conditions for treatment.

In this study we introduced interventions based on CBS to manage symptoms for pain, fatigue/tiredness, and anorexia in the symptom cluster to patients with advanced NSCLC in the treatment phase. This CBS intervention helped patients alleviate pain and fatigue symptoms through self-selected multiple options (five options for each). Next, the research nurse explained how to conduct the therapy and use tools. When providing follow-up calls, the research nurse paid careful attention to verify specific details for each of the participants because they were outpatients with advanced lung cancer. Most participants (80%–87%) chose two alleviation strategies: relaxation (deep breathing) for pain and exercise therapy (at least 2000 steps with pedometer) for fatigue/tiredness. The patient's preferences were consistent with those reported in a previous study[7] and with alternative therapies (relaxation therapy).[43] Corbin et al.[43] also reported that 344 (33%) patients with advanced-stage cancer who had been in hospice or undergoing palliative care underwent one of the Complementary and Alternative Medicine (CAM) Therapies, with an average of 2 CAM therapies per patient (such as relaxation therapy). All participants (100%) in the present study were in the most advanced stage of lung cancer (IV). However, they were not experiencing great symptom distress and enjoyed a good performance status, largely with PS (0–1). The participants in the present study (NSCLC patients in advanced stages) reported good pain control at baseline, 73.3% were employed, and without taking pain medication. Introducing two CBS interventions may be appropriate. Simple pedometer use and relaxation may be preferred and effective within this population.

In general, CAM use in patients with advanced cancer was reported to be more frequent among females and patients with higher educational backgrounds.[43] In the present study, 53.3% (> 12) of participants have completed junior college, university, or graduate school and 33.3% completed high school (years of education ≤12), consistent with the educational aspect in the report described above. The male to female ratio was 2:1 (at pretest, 66.7%:33.3%) (baseline: n = 15) compared to 2.3:1 (at posttest, Wk10: n = 10), indicating good retention. This suggests that CBS interventions such as deep breathing is generally simple for patients with advanced lung cancer to accept, as it was chosen by 86.7% of participants for the method of relaxation.

For the impact of the initial efficacy of the CBS interventions on the severity of symptoms in the symptom clusters, the participants in the present study showed tendencies to maintain a mild pain severity (median) from pretest 2.00 to posttests 2.00 (at Wk1, Wk2), and decrease at the posttest (Wk10). In a previous study[6] that used the MDASI-J[38] (at one time point), which is similar to the present study, symptom severities (mean ± SD) of patients with advanced NSCLC were as follows: pain (2.22 ± 2.62), sadness (1.95 ± 2.63), and anxiety (2.45 ± 2.66) in three symptoms in the pain symptom cluster. Further, the fatigue/tiredness severity (median) decreased from pretest 3.00 to posttests 2.50, 2.00 (at Wk1, Wk2) and maintained a mild pain level till the 10th week. In the previous study,[6] fatigue/tiredness (3.77 ± 3.02), altered sense of taste (1.77 ± 2.60), dry mouth (2.30 ± 2.59), lack of appetite (3.05 ± 2.91), and drowsiness (3.12 ± 2.62) among five symptoms in the fatigue/anorexia cluster. Although it is difficult to make comparisons, symptom severities in the symptom clusters show low likelihood of increases in tendencies while there are fluctuations after the baseline, suggesting the possibility of self-management. For the average number of symptoms experienced, this decreased from 14 (pretest) to 12 (at posttest, Wk10), suggesting some initial efficacy of the intervention.

In a previous study of patients with advanced NSCLC (n = 60, median age 64.0, PS 0-1: 80%, Stage IV: 72%, no pain medications 62%) by the authors of the present study, the severity of pain and fatigue were mild, averaging 2.22 and 3.77, respectively, using the MDASI-J[38] and the

NSCLC symptom modules but a pain symptom cluster was formed. This had the greatest impact on QOL (Emotional function) ($\beta = -0.49$, $P < 0.001$, adjusted $R^2 = 0.24$), followed by QOL (Physical function) ($\beta = -0.43$, $P < 0.001$, adjusted $R^2 = 0.18$) and Fatigue/anorexia cluster was formed. Next, the cluster had the strongest impact on QOL (Role function) ($\beta = -0.45$, $P < 0.001$, adjusted $R^2 = 0.23$), followed by QOL (Cognitive function) ($\beta = -0.45$, $P < 0.001$, adjusted $R^2 = 0.19$).[6] Similarly, it is possible that the QOL of the present sample may have been affected to some extent. It was suggested that the participants in the present study may maintain and improve QOL (Emotional Functioning, Global QOL), and that this tendency will continue to Wk10 although they were in the most advanced stage (Stage IV). The results in the previous study that investigated 60 patients with advanced NSCLC undergoing standard treatments[6] reported that the mean (SD) scores of Emotional, Physical, and Global QOL in the EORTC-QLQ-C30 were 80.28 (16.45), 67.66 (22.99), and 49.58 (24.52), respectively. The participants in the present study showed the tendency of decreased daily life interference (Emotions, Walking, Enjoyment of life) and improvement in QOL (Physical, Emotional, Global) although there were some fluctuations. For QOL, we are planning to report about LC-13 at another opportunity, and the present study focuses on the EORTC-QLQ-C30. However, these results suggest that the efficacy of CBS intervention that focused on pain and fatigue/tiredness would be promising.

Patients with lung cancer are reported as a population that requires attention and monitoring due to the impact of symptoms on QOL.[44,45] Also, Mcgrath[46] reported in a qualitative descriptive study that "paying attention" was meaningful to evaluate positive aspects for patients receiving follow-up calls, suggesting that "Receptivity" may play an essential role in the attitudes of patients who receive telephone follow-up support. Further, as Pistrang et al.[47] showed the working relationship between support providers and recipients (patients) affects the success of follow-up calls. As many as 10 (66.7%) participants in the present study were able to complete the follow-up calls over 10 weeks. This may be due to a positive effect of the relationship with the research nurse. A possible reason for this positive effect on the efficacy of the intervention may be that the follow-up calls provided by the research nurse, who paid attention to individual participants,[46] became meaningful and were positively evaluated by the participants.[48] Next, this positive evaluation may have influenced the mutual working relationship. The monitoring with the symptom assessment chart may have encouraged the participants to be aware of their symptoms and to do self-reporting.[49]

For patients with advanced lung cancer, pain may indicate "disease progression", causing anxiety-provoking psychological effects when patients perceive a life-threatening meaning.[50] For this reason, alleviating symptoms in patient-centered care has been increasingly important during the life-prolonging period.[51] Fatigue is also a symptom experienced by 80% of patients with advanced NSCLC, which interferes with daily life and reduces QOL.[6] Therefore, the intervention in the present study could be evaluated to be useful considering the high retention rate (66.7%) and the high selection rate of contents of CBS intervention and exercise therapy. It is also suggested that the nurse-initiated brief CBS interventions that incorporated the CBS of the interventions targeting these two symptom clusters and follow-up calls may be useful for NSCLC patients with unavoidable disease progression in the treatment phase. The benefit may be due to the following two elements: developing the patient's potential to engage in selfcare for pain alleviation, and providing care that leads to stable QOL. However, the present feasibility study was the first to be conducted in clinical settings in Japan. There is no specific sample size recommended to evaluate feasibility.[52] Therefore, it makes sense to adopt a sample size ($n = 15$) based on the achievable number derived from previous studies.[6,7] Next, we need to examine the efficacy of the nurse-initiated brief CBS intervention program with a high degree of accuracy with a larger study design. For this purpose, it may be important to incorporate a Pilot RCT to estimate the sample size. The missing values in the present study with participants with advanced NSCLC ranged between 6.7 and 10% in both the MDASI-J and EORTTC-QOL-C30, and we may not be able to avoid MNAR. For these unavoidable missing values, making every effort to prevent the occurrence of missing values is always recommended.[53] For the future, it will be necessary to consider an imputation method for missing values for each item.

The participants with advanced NSCLC (homogeneous, Stage IIIB or IV, recurrent) undergoing treatments in Japanese clinical practice were able to continue the intervention with two selected components: a brief CBS component (deep breathing 1–6 times/day under tension or before bed/day) and exercise therapy (approximately 3200 steps/day) without feeling it a burden, suggesting this combination as suitable to the patients and also showing the beginning efficacy of the intervention. The findings of this study suggest the potential for nursing interventions that are highly sensitive to these patients and that we can expect the effectiveness of the interventions in the future. Therefore, it would be essential to move this study forward by a subsequent RCT to test the effectiveness of the nurse-initiated intervention which is expected to be highly effective with the two selected components: the brief CBS and exercise therapy, and with follow-up calls.

Implications of practice

The nurse-initiated brief CBS intervention program is a strategy that is simple and easy to continue if follow-up calls are incorporated, specifically at the time when outpatient face-to-face contact is limited. The findings of the present study suggest that patients with advanced NSCLC undergoing standard treatments do have self-management skills to continue the brief CBS and exercise therapy for 10 weeks although they experience multiple symptoms in the symptom cluster. It is also suggested that nurses may be able to help patients identify the brief CBS (problem solving strategies) strategies to improve the effectiveness of their self-management, and encourage them to continue the CBS. To improve the effectiveness, it is necessary to provide nursing interventions that use the booklet as a guide for patients to understand their symptoms, enabling patients to apply the interventions accurately in a consistent manner. The challenge for nurses may be acquiring skills to adjust to the limited prognosis of patients with advanced NSCLC, who experience multiple concurrent symptoms, causing daily life interference and reduced QOL, and to consider their diverse needs to utilize their potential. Improving these skills may make it possible to aim at overcoming the challenges to the implementation timing of the nurse-initiated brief CBS intervention. Lastly, incorporating follow-up calls into the next RCT may also increase the efficacy of the intervention.

Limitations

This study has the following limitations. First, because of the limited sample size, the comparison of pre-post test data of the participants with access to standard care was limited by the statistical methods and lacked sufficient support as evidence. Second, the progression of the disease in patients with advanced lung cancer makes it difficult for participants to return the questionnaire. It is important to overcome this shortcoming through measures against missing data and dropouts. Third, there was a limitation in manpower to recruit participants, and we were unable to confirm the ages of potential participants. For this reason, in the next study we need to improve recruitment procedures so that we can see if the potential participants meet the inclusion criteria. Fourth, there is no sufficient evaluation scheme to ensure the fidelity of the intervention. If we create an objective evaluation scheme that consistently ensures the fidelity at each point in time, it would be possible to evaluate the effectiveness of the intervention. Fifth, there are cases, we cannot confirm the accuracy of the number of steps on a pedometer reported by participants as a real number, and there may be influence of the instruction to use integer notation introduced in the booklet on the numbers reported. We need to improve the instructions, such as to use the actual numbers. Lastly, if we start with patients early in the treatment process and expand

the intervention scheme that incorporates advanced practices in Japanese clinical practice, RCT effectiveness evaluation studies with improved intervention content may yield beneficial effects on symptom management in patients with advanced NSCLC undergoing standard treatments.

Conclusions

The findings of the study suggest that the nurse-initiated brief CBS intervention program for patients with advanced NSCLC undergoing standard treatments is clinically practical and effective for Japanese patients with advanced stage lung cancer. As the next step, it would be beneficial to conduct a subsequent RCT study on targeted interventions (up to two proposed strategies) that aim to alleviate symptoms of two symptom clusters (Pain and Fatigue/anorexia clusters) in order to verify the effectiveness of the nurse-initiated brief CBS intervention.

Ethics statement

The study was approved by the Institutional Review Board of the Asahikawa Medical University (IRB No. 16185). All participants provided written informed consent.

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CRediT authorship contribution statement

Tamami Hamada: Conceptualization, Methodology, Investigation, Data Curation, Project administration, Writing – original, Funding acquisition. **Hiroko Ishikawa**: Investigation. **Margaret Quinn Rosenzweig**: Writing – review & Editing, Supervision. **Naoki Nishimura**: Resources, Writing – review & Editing. **Jun Sakakibara-Konishi**: Resources, Writing – review & Editing. **Toshihiro Itoh**: Software, Writing – review & Editing. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability statement

The data are not publicly available due to restrictions their containing information that could compromise the privacy of research participants.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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