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ORIGINAL ARTICLE

Efficacy and safety of an amino acid jelly containing coenzyme Q10 and L-carnitine in controlling fatigue in breast cancer patients receiving chemotherapy: a multi-institutional, randomized, exploratory trial (JORTC-CAM01)

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Abstract
Purpose Cancer-related fatigue (CRF) is one of the most common symptoms reported by cancer patients. This randomized trial investigated the efficacy of the amino acid jelly Inner Power® (IP), a semi-solid, orally administrable dietary supplement containing coenzyme Q10 and L-carnitine, in controlling CRF in breast cancer patients in Japan.
Methods Breast cancer patients with CRF undergoing chemotherapy were randomly assigned to receive IP once daily or regular care for 21 days. The primary endpoint was the change in the worst level of fatigue during the past 24 h (Brief Fatigue Inventory [BFI] item 3 score) from day 1 (baseline) to day 22. Secondary endpoints were change in global fatigue score (GFS; the average of all BFI items), anxiety and depression assessed by the Hospital Anxiety and Depression Scale (HADS), quality of life assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC Breast Cancer-Specific QLQ (EORTC QLQ-BR23), and adverse events.
Results Fifty-nine patients were enrolled in the study, of whom 57 were included in the efficacy analysis. Median patient age was 50 years. Changes in the worst level of fatigue, GFS, and current feeling of fatigue were significantly different between the intervention and control groups, whereas the change in the average feeling of fatigue was not significantly different between groups. HADS, EORTC QLQ-C30, and EORTC QLQ-BR23 scores were not significantly different between the two groups. No severe adverse events were observed.
Conclusion IP may control moderate-severe CRF in breast cancer patients.

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Trial registration The registration number of this study in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) is UMIN000008646.

Keywords Cancer-related fatigue · Chemotherapy-induced fatigue · Supplement · Quality of life · Complementary and alternative medicine

Introduction

Cancer-related fatigue (CRF) is a persistent subjective sense of severe physical, psychological/cognitive tiredness or exhaustion related to cancer or its treatment and interferes with daily activities and functioning [1]. The incidence rate of CRF ranges from 28 to 91 % in breast cancer patients [2, 3]. Advanced disease appears to be associated with worsening in severity of CRF symptoms [4]. Fatigue is also one of the most common side effects reported by long-term breast cancer survivors [5]. The mechanisms underlying CRF development have not yet been elucidated; however, chemotherapy, molecularly targeted therapy, radiation therapy, surgery, and anemia have been suggested as potential contributory factors [6]. Breast cancer patients receiving adjuvant chemotherapy have been found to experience much more fatigue than controls [7]. On the other hand, Okuyama et al. reported that 56 % of 132 Japanese breast cancer patients receiving no active treatment after surgery-experienced fatigue [8]. These studies highlight the intricate involvement of diverse factors in the etiology of CRF, which complicates the establishment of effective treatment strategies.

Potential pharmacologic options for the treatment of CRF such as corticosteroids and psychostimulants have been investigated. However, there is limited evidence to support their use in the treatment of CRF [9, 10]. Randomized trials investigating the efficacy of methylphenidate, dexmethylphenidate, dextroamphetamine, and modafinil in the treatment of CRF have yielded inconsistent results [11–14]. Antidepressants, antidementia drugs, and multivitamins have shown a potential positive effect on fatigue in observational studies; however, this benefit has not been confirmed in randomized controlled trials. The use of complementary and alternative medicine (CAM) including supplements has gained popularity and has become an index for psychological pain or low quality of life (QOL) among early-stage breast cancer patients in the USA [15, 16]. The use of CAM for the management of CRF is also being explored; however, effective therapies have not been identified to date. Thus, the development and clinical verification of CAM treatments for CRF are needed [17]. Higashiguchi et al. found that Inner Power® (IP), an amino acid jelly formulated to improve metabolism, ameliorated pain severity, fatigue, breathing difficulties, insomnia, appetite loss, and constipation in patients with terminal-stage cancer [18]. IP contains multiple components including branched-chain amino acids, coenzyme Q10, and L-carnitine that have been suggested to improve fatigue [19]. Coenzyme Q10 and L-carnitine have been demonstrated to have a positive effect on fatigue in terminal cancer patients [20–22]. Branched-chain amino acids have been shown to reduce central fatigue [23]; therefore, we speculated that they would be effective in combating the exhaustive state associated with chemotherapy. Together, these findings provide strong rationale for investigating the combined use of coenzyme Q10, L-carnitine, and branched-chain amino acids in the treatment of CRF. Therefore, this study was designed to investigate the effect of IP on CRF and QOL in breast cancer patients. Anxiety and depression, which are strongly associated with fatigue, were also evaluated.

Methods

Study design and patients

This study was an open-label, multicenter, randomized controlled trial. Recruitment took place in Japan at six medical institutions with breast cancer specialists on staff. Female patients who met the following criteria were considered eligible for the study: histologically diagnosed breast cancer, age 20 to 80 years, Eastern Cooperative Oncology Group performance status of 0 to 1, able to complete the study questionnaires, currently receiving chemotherapy or planning to receive chemotherapy at the time of the trial, and fatigue score (Brief Fatigue Inventory [BFI] item 3) ≥4 in the previous course of chemotherapy. The exclusion criteria were as follows: currently receiving radiotherapy or interferon therapy, grade 3–4 nausea and/or anorexia (Common Terminology Criteria for Adverse Events v.4.0) in the previous course of chemotherapy, uncontrollable anemia, severe heart disease, mental disorder, monoamine oxidase inhibitor and/or central nervous system stimulant use, and regular steroid use. Informed consent was obtained from all individual participants included in the study.

Randomization

Randomization was performed at the central data center using a web-based registration system. Subjects were randomly allocated to the intervention or control group (1:1 ratio) using a stratified permuted-block randomization. Institution and age (under or over 60 years) were used as stratification factors to avoid biased assignment [8, 24].

Treatment

IP was provided by Otsuka Pharmaceutical Factory Incorporated (Tokushima, Japan). IP contains branched-chain amino

acids (2500 mg), coenzyme Q10 (30 mg), and L-carnitine (50 mg). The intervention group received oral IP (125 g) once daily for 21 days in addition to their regular care. A 21-day cycle is commonly used in standard breast cancer adjuvant chemotherapy regimens such as fluorouracil, epirubicin, and cyclophosphamide (FEC), docetaxel and cyclophosphamide (TC), doxorubicin and cyclophosphamide (AC), and epirubicin and cyclophosphamide (EC). According to Higashiguchi et al., IP becomes effective within 2 weeks (14 days) after initial administration [18]. Therefore, we concluded that IP efficacy would best be evaluated in the next chemotherapy course (21 days) to account for the therapeutic lag and to ensure the development of moderate-severe fatigue in patients receiving chemotherapy. Patients assigned to the control group received regular care consisting of recommendations for adequate exercise and relaxation. Neither group received medications for fatigue.

Endpoints

The primary endpoint was the change in the worst level of fatigue during the past 24 h (BFI item 3) from day 1 (baseline) to day 22. Secondary endpoints were change in global fatigue score (GFS; the average of all BFI items), anxiety, depression, QOL, and adverse events.

Fatigue We selected the BFI to assess fatigue, because it is a multidimensional and independent scale and widely used in cancer patients [25]. The BFI was developed for the rapid assessment of fatigue severity in both clinical practice and clinical trial settings. The Functional Assessment of Cancer Therapy-Fatigue (FACT-F) is also a widely used fatigue assessment tool. However, it is a unidimensional questionnaire that is part of the larger Functional Assessment of Chronic Illness Therapy Measurement System. In addition, the Japanese version of the FACT-F has not yet been validated. The validity and reliability of the English version of the BFI has been verified in cancer patients [26]. Okuyama et al. confirmed the validity of the Japanese version of the BFI [27]. The BFI consists of 9 items rated on an 11-point Likert scale (0 to 10). The GFS is obtained by averaging the scores of the 9 items and is categorized as follows: scores of 1–3, mild; scores of 4–6, moderate; and scores of 7–10, severe.

Anxiety and depression Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS), which consists of a 14-item questionnaire. The HADS has been validated and is widely use to assess anxiety and depression in cancer patients [28]. The construct validity of the Japanese version of the HADS was reported by Matsudaira et al. [29]. Seven items each assess anxiety and depression. Each item is scored from 0 to 3; thus, the final score for each subscale is between 0 and 21. An anxiety or depression subscale score ≥8 is indicative of clinically relevant symptoms.

QOL The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is used worldwide to evaluate the QOL of cancer patients. The validity of the Japanese version of the EORTC QLQ-C30 was confirmed by Kobayashi el al. [30]. This 30-item QOL measurement consists of nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QOL scale [31, 32]. The functional and symptom subscales are scored between 0 and 100. Higher functional subscale scores indicate better functioning, whereas lower symptom subscale scores indicate better physical condition. The EORTC Breast Cancer-Specific QLQ (EORTC QLQ-BR23) consists of two functional scales (body image and sexuality) and three symptom scales (arm symptoms, breast symptoms, and systemic therapy side effects). Validation of the EORTC QLQ-BR23 in breast cancer patients receiving treatment was reported in 1996 [33]. The reliability and validity of the Japanese version of the EORTC QLQ-BR23 was confirmed by Okamoto el al. [34].

Adverse events The frequency of adverse events and the incidence of grade 3 or higher adverse events were estimated and compared between groups.

Assessment and data collection

Fatigue, anxiety, depression, and QOL were assessed on days 1 and 22 using the BFI, EORTC QLQ-C30, EORTC QLQ-BR23, and HADS. Fatigue assessment (BFI) was also performed on days 8 and 15. A booklet of questionnaires was kept by the patients during treatment and collected at the time of chemotherapy on day 22.

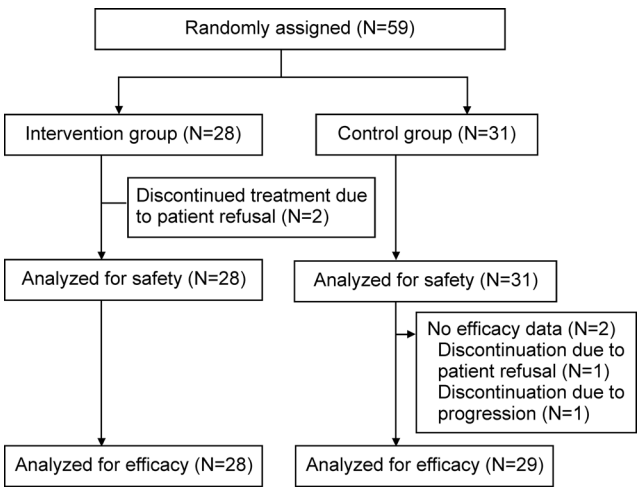

Fig. 1 Patient flow

Table 1 Baseline patient demographic and clinical characteristics

	Intervention group (N = 28)		Control group (N = 31)	
Characteristic	N	%	N	%
Age, years				
Median	49		52	
Range	29–70		22–70	
Performance status (ECOG)				
0	12	42.9	13	41.9
1	16	57.1	16	51.6
2	0	0.0	2	6.5
3	0	0.0	0	0.0
4	0	0.0	0	0.0
Recurrence status				
No recurrence	25	89.3	27	87.1
Recurrence	3	10.7	4	12.9
Metastasis status				
No metastasis	24	85.7	26	83.9
Metastasis	4	14.3	5	16.1
Menopausal status				
Pre	11	39.3	9	29.0
Post	14	50.0	15	48.4
Peri	3	10.7	5	16.1
Missing	0	0.0	2	6.5
Estrogen receptor status				
Positive	17	60.7	20	64.5
Negative	10	35.7	8	25.8
Boundary	1	3.6	2	6.5
Missing	0	0.0	1	3.2
Progesterone receptor status				
Positive	12	42.9	10	32.3
Negative	14	50.0	14	45.2
Boundary	2	7.1	6	19.4
Missing	0	0.0	1	3.2
HER2 status				
IHC 0	2	7.1	6	19.4
IHC 1+	16	57.1	18	58.1
IHC 2+/FISH non-amplified	2	7.1	4	12.9
IHC 2+/FISH amplified	1	3.6	0	0.0
IHC 3+	7	25.0	3	9.7
Ki-67 status				
≤15 %	5	17.9	5	16.1
>15 %	16	57.1	19	61.3
Missing	7	25. 0	7	22.6
T stage				
Tx	0	0.0	1	3.2
T1	7	25.0	10	32.3
T2	17	60.7	17	54.8
T3	4	14.3	2	6.5
T4	0	0.0	1	3.2
N stage				

Table 1 (continued)

Characteristic	Intervention group (N = 28)		Control group (N = 31)	
	N	%	N	%
Nx	0	0.0	1	3.2
N0	11	39.3	11	35.5
N1	17	60.7	17	54.8
N2	0	0.0	1	3.2
N3	0	0.0	1	3.2
Chemotherapy regimen				
FEC	9	32.1	9	29.0
AC	7	25.0	8	25.8
EC	1	3.6	1	3.2
TC	4	14.3	4	12.9
DTX	4	14.3	2	6.5
PTX	1	3.6	2	6.5
Others	2	7.1	5	16.1
Chemotherapy cycles at the time of study				
Median	3		3	
Range	2–12		2–9	

Sample size

A significantly greater mean change in the worst level of fatigue during the past 24 h (BFI item 3 score) in the intervention group versus the control group was used to verify IP efficacy. The minimal clinically important difference in the assessment of CRF has not yet been defined. In a US clinical trial to verify the effect of modafinil on fatigue symptoms, the difference in the mean change scores between the intervention and control groups was 0.75 [14]. In a study to assess the effect of blood transfusion (conceived as a clinically effective measure) on CRF, the difference in the mean change scores between the intervention and control groups was 1.5 [35]. Based on these studies, we estimated the mean (standard deviation [SD]) difference between groups to be 1.0 (2.0) (with a clinical effect size of 0.5). Assuming a 10 % attrition rate, 5 % one-sided type I error rate, and 80 % power, we calculated that a sample size of 110 patients was required to detect a difference between the two groups.

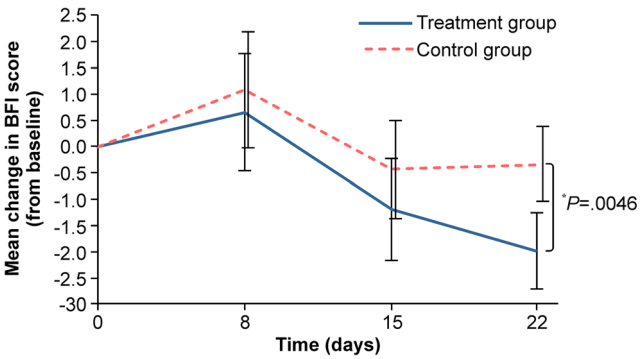

Fig. 2 Mean change in the worst level of fatigue during the past 24 h (BFI Item 3). A negative change score indicates improvement. *Error bars* represent 90 % confidence intervals. *BFI* Brief Fatigue Inventory

Statistical analysis

For the analysis of primary and secondary endpoints, point estimates and 90 % confidence intervals (95 % for secondary endpoints) were calculated for the mean values in the intervention and control groups. The differences between the mean values of the two groups were also determined. One-sided t tests were used to compare mean values. A P value <0.05 was

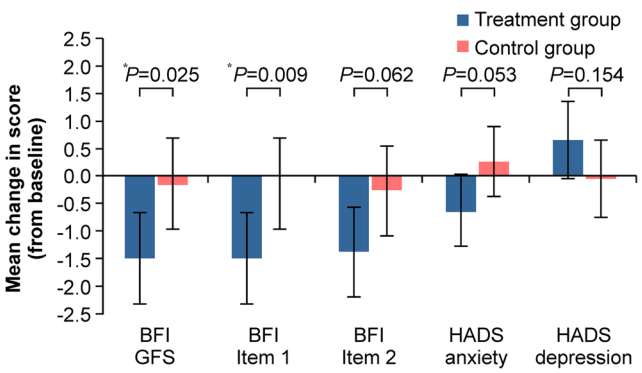

Fig. 3 Mean change in BFI GFS, BFI Items 1 and 2 scores, and HADS score during the past 24 h. The mean change score was calculated by subtracting the mean day 1 (baseline) score from the day 22 score. A negative change score indicates improvement. *Error bars* represent 95 % confidence intervals. *BFI* Brief Fatigue Inventory, *GFS* global fatigue score, *HADS* Hospital Anxiety and Depression Scale

considered significant. All analyses were done using SAS version 9.2 and JMP PRO version 11 (SAS Institute Inc.).

Ethical considerations

This study conformed to the ethical standards of the Declaration of Helsinki and Japanese Ethical Guidelines for Clinical Research [36, 37]. The study protocol was reviewed and approved by the ethics review committee of the not-for-profit organization TACTICS and ethics review committees of the participating institutions. Written informed consent was obtained prior to participation in the study. The registration number of this study in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) is UMIN000008646.

Results

Patient flow and baseline characteristics

Between October 2012 and March 2014, 59 patients were enrolled in the study. Two patients who refused to complete the questionnaires were excluded and thus, 57 patients were included in the efficacy analysis (intervention $n = 28$; control $n = 29$; Fig. 1). Patient baseline characteristics are summarized in Table 1. Baseline characteristics were well balanced between the intervention and control arms. The average baseline values for fatigue, anxiety, depression, and QOL were not significantly different between the two arms.

Efficacy

Fatigue

Change in the worst level of fatigue during the past 24 h (BFI item 3) The mean change in the worst level of fatigue during the past 24 h (BFI item 3) was significantly greater in the intervention group than in the control group ($P = 0.005$; Fig. 2). The mean (SD) change in the BFI item 3 score from baseline to day 22 was −0.34 (2.47) and −2.00 (2.14) in the control and intervention groups, respectively. This finding indicates a significant improvement in fatigue in the intervention group.

Change in GFS The mean change in GFS was significantly greater in the intervention group than in the control group ($P = 0.025$; Fig. 3). The mean (SD) change in GFS was −0.15 (2.18) in the control group and −1.50 (2.21) in the intervention group.

Change in the current feeling of fatigue (BFI item 1) The mean change in the current feeling of fatigue (BFI item 1) was significantly different between the intervention and control groups ($P = 0.009$; Fig. 3). The mean (SD) change in the BFI item 1 score was −0.03 (2.24) and −1.50 (1.82) in the

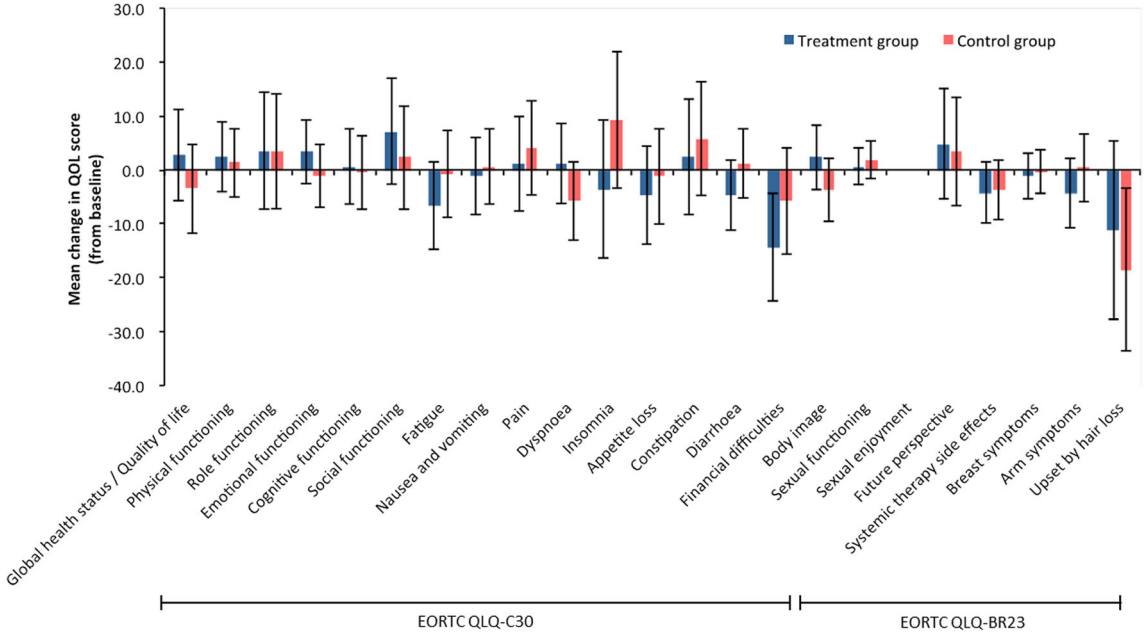

Fig. 4 Mean change in EORTC QLQ-C30 and EORTC QLQ-BR23 Scores. The mean change score was calculated by subtracting the mean day 1 (baseline) score from the day 22 score. A positive change score indicates improvement except for symptoms. *Error bars* represent 95 % confidence intervals. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-BR23, European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire; *QOL* quality of life

Table 2 Adverse events

Adverse event	Intervention group (N = 28)			Control group (N = 31)		
	All(%)	Grade 3(%)	Grade 4(%)	All(%)	Grade 3(%)	Grade 4(%)
Hematologic						
Leucopenia	39.3	3.6	7.1	41.9	16.1	6.5
Neutropenia	42.9	10.7	14.3	35.5	9.7	16.1
Anemia	25.0	3.6	0.0	32.3	0.0	0.0
Thrombocytopenia	7.1	0.0	0.0	3.2	0.0	0.0
Non-hematologic						
Febrile neutropenia	0.0	0.0	0.0	3.2	3.2	0.0
Fever	3.6	0.0	0.0	6.5	0.0	0.0
Nausea	64.3	0.0	0.0	51.6	0.0	0.0
Vomiting	28.6	0.0	0.0	12.9	0.0	0.0
Arthralgia	21.4	3.6	0.0	22.6	0.0	0.0
Myalgia	25.0	0.0	0.0	19.4	0.0	0.0
Fatigue	85.7	0.0	0.0	87.1	0.0	0.0
Watering eyes	14.3	0.0	0.0	3.2	0.0	0.0
Gastritis	10.7	0.0	0.0	0.0	0.0	0.0
Edema limbs	14.3	0.0	0.0	12.9	0.0	0.0
Alopecia	92.9	0.0	0.0	83.9	0.0	0.0
Phlebitis	10.7	0.0	0.0	0.0	0.0	0.0
Diarrhea	14.3	0.0	0.0	3.2	0.0	0.0
Constipation	17.9	0.0	0.0	3.2	0.0	0.0
Peripheral sensory neuropathy	10.7	0.0	0.0	3.2	0.0	0.0
Mucositis oral	17.9	0.0	0.0	3.2	3.2	0.0
Lip infection	0.0	0.0	0.0	3.2	3.2	0.0
Dysgeusia	7.1	0.0	0.0	0.0	0.0	0.0
Anorexia	3.6	0.0	0.0	0.0	0.0	0.0
Palpitations	3.6	0.0	0.0	0.0	0.0	0.0

intervention and control groups, respectively. The difference in mean change scores between groups was −1.4.

Change in the average feeling of fatigue within 24 h (BFI item 2) The mean change in the average feeling of fatigue within 24 h (BFI item 2) was not significantly different between groups (P = 0.062; Fig. 3). The mean (SD) change in the BFI item 2 score was −0.29 (2.32) and −1.39 (2.01) in the intervention and control groups, respectively. The difference in mean change scores between groups was −1.11.

Anxiety and depression The mean change in the HADS anxiety scores was not significantly different between the intervention and control groups (P = 0.053; Fig. 3). The mean (SD) change in HADS anxiety score was 0.25 (1.48) in the control group and −0.64 (1.87) in the intervention group. The difference in mean change scores between groups was −0.89. The mean change in the HADS depression score was also not significantly different between the control and intervention groups (−0.07 [1.61] vs. 0.64 [2.06]; P = 0.154; Fig. 3).

QOL The mean change in global health/QOL scores (EORTC QLQ-C30 items 29 and 30) from day 1 (baseline) to day 22 was not significantly different between the intervention and control groups (P = 0.303; Fig. 4). The mean (SD) global health status/QOL score was −3.4 (20.4) and 2.7 (24.0) in the intervention and control groups, respectively. The remaining EORTC QLQ-C30 and EORTC QLQ-BR23 scores were also not significantly different between the two groups (Fig. 4).

Adverse events

Table 2 highlights the adverse events that occurred in the study. The most common grade 3 or higher adverse events were leucopenia and neutropenia in both groups. Other grade

3 adverse events were anemia and arthralgia in one patient each in the intervention group and febrile neutropenia, oral mucositis, and lip infection in one patient each in the control group. The mean hemoglobin values at baseline and day 22 were not significantly different between the intervention and control groups (12.01 [1.30] g/dL vs. 11.82 [1.27] g/dL; $P = 0.56$; 11.63 [1.48] g/dL vs. 11.56 [1.23] g/dL; $P = 0.85$).

Discussion

This study investigated the efficacy of IP in controlling CRF in breast cancer patients undergoing chemotherapy. The primary efficacy endpoint was met, as the mean change in the worst level of fatigue was significantly greater in the intervention group than in the control group. Other mean changes in the BFI scores except for item 2 were also significantly greater in the intervention group than in the control group. In open-label studies, many variables can potentially confound the interpretation of the results. Therefore, although IP had a positive effect on peak symptoms, it did not improve average symptoms, including anxiety and depression. QOL and frequency of severe adverse events were also not different between the two groups.

The cause of CRF in cancer patients is usually complex. Anxiety and depression are thought to be strongly associated with CRF. Therefore, we assumed that changes in anxiety and depression would accompany the improvement in CRF. However, no significant changes in anxiety or depression were observed. In our previous study, oral nutritional support with IP seemed to have a positive effect on QOL and survival in terminally ill cancer patients [38]. Cancer patients receiving chemotherapy experience physical exhaustion similar to terminally ill patients. Therefore, our results imply that IP may improve CRF caused by physical factors.

Branched-chain amino acids, coenzyme Q10, and L-carnitine, which are contained within IP, been suggested to improve fatigue [19–23] and have been clinically investigated as potential agents for managing CRF in Europe and the USA. However, phase III, randomized, double-blind, placebo-controlled studies have demonstrated a lack of improvement in CRF in cancer patients receiving coenzyme Q10 (100 mg three times daily) and L-carnitine (1 g twice daily) supplements [39, 40]. Considering that lower doses of coenzyme Q10 (30 mg) and L-carnitine (50 mg) were used in our study than in these previous studies, the combination of IP components including branched-chain amino acids most likely contributed to the improvement in CRF observed in our study.

Our study has limitations. Non-severe non-hematologic adverse events seemed to occur more frequently in the intervention group than in the control group. However, this may have resulted from a biased evaluation of information as the occurrence of non-severe hematologic adverse events, which were determined objectively based on the laboratory data, including hemoglobin values, seemed not to differ between the two groups. We provided the patients with paper questionnaires. Therefore, "parking lot compliance," in which patients complete the questionnaires retrospectively just prior to the site visit, was a concern [41]. The change trend in BFI item 3 score from baseline to day 22 was similar between groups, indicating the minimal effect of this bias in the study. In both groups, the change in the BFI item 3 score was worse than baseline on day 8, better than baseline on day 15, and similar to or better than baseline on day 22. Although this might indicate a placebo effect, the similar score change trends between groups suggests this effect was negligible. We used a no-intervention control arm when a placebo control arm should have been used. Regulatory issues led to the loss of study funding; therefore, we were unable to cover the financial costs of placebo manufacturing.

Our planned sample size was 110 patients. However, the study was terminated early because of funding issues, limiting the sample size to 59 patients. The small sample size is reflected in the wide confidence intervals. Despite the study limitations, our findings provide meaningful evidence of the efficacy of IP in controlling CRF. Further research is needed to confirm our findings.

Conflict of interest This was a joint study conducted by The University of Tokyo and Otsuka Pharmaceutical Factory Incorporated. Financial resources and Inner Power® were provided by Otsuka Pharmaceutical Factory Incorporated. The funding source had no influence on the study outcomes, and the authors were free to interpret the data according to a strict scientific rationale. The authors have no other conflicts of interest to disclose. The authors have full control of all primary data and agree to allow the journal to review their data if requested.

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