ORIGINAL

Symptomatic adverse events of chemotherapy in breast cancer patients : Using CTCAE, PRO-CTCAE, and EORTC QLQ-C30

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Abstract : Background : The Common Terminology Criteria for Adverse Events (CTCAE) is used as a tool to evaluate the adverse events (AE) of chemotherapy in cancer patients. Since CTCAE by medical providers underestimates AE more than patient-reported outcomes (PRO), the National Cancer Institute developed PRO-CTCAE. The present study investigated differences between symptoms detected using CTCAE by medical providers and PRO-CTCAE by breast cancer patients. Methods : Patients received chemotherapy comprising epirubicin and cyclophosphamide pre- or postoperatively. AE were evaluated using 4 questionnaires : PRO-CTCAE, CTCAE, the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC-QLQ-30), and Hospital Anxiety and Depression Scale (HADS) after 1, 2, and 3 courses of chemotherapy. Results : Forty-two patients were registered. Regarding the recognition of psychological symptoms, such as fatigue, anxiety, and discouragement, and subjective symptoms, including heart palpitations and shortness of breath, PRO using PRO-CTCAE was significantly higher than medical provider-recognized outcomes using CTCAE. Concerning the recognition of regimen-specific symptoms, such as vomiting, nausea, and decreased appetite, medical provider-recognized outcomes were the same or higher than PRO. In QLQ-C30, the physical and role functions, fatigue and dyspnea significantly worsened after 2 and 3 courses of chemotherapy. J. Med. Invest. 71 : 82-91, February, 2024

Keywords **:** *Breast cancer, CTCAE, PRO-CTCAE, EORTC QLQ-C30, Chemotherapy*

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women (1). The number of cancer patients has recently been increasing, with more than 100,000 individuals being newly diagnosed in Japan in 2017 (2). However, the prognosis of breast cancer is slightly better than that of other cancers. The five-year survival rate of breast cancer was previously reported to be 92.3% in Japan (2). The current 5-year survival rates for early stage (I-II) or localized stage (III) breast cancer worldwide are 98.9 and 85.2%, respectively (3). Good survival rates may be attributed to advances in early detection methods, the prevalence of screening mammograms, and the efficacy of treatments, including surgery, radiation therapy, and chemotherapy. To select the most appropriate treatments, breast cancer has been categorized into 3 major subtypes : 1) estrogen or progesterone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative tumors (70%), 2) HER2-positive tumors (15-20%) and 3) tumors lacking all standard molecular markers (15%) (4).

Many different neoadjuvant and adjuvant chemotherapy regimens are currently available for the treatment of breast cancer. Chemotherapy regimens containing anthracycline and taxane (such as adriamycin/cyclophosphamide followed by taxane) achieve the greatest risk reduction for recurrence and remain the appropriate choice for high-risk patients. However, anthracycline-based chemotherapy followed by a taxane regimen is associated with an increased rate of adverse events (AE) (5).

The Common Terminology Criteria for Adverse Events (CTCAE) published by the National Cancer Institute (NCI) is commonly used in clinical trials and general practices worldwide as a tool to evaluate the AE of drug therapy (6). In Japan, standard practice involves an evaluation of AE using CTCAE translated by the Japan Clinical Oncology Group (JCOG) (the CTCAE-JCOG version) (7).

The United States Food and Drug Administration stated that patient-reported outcomes (PRO) are any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by medical staff (8). In comparisons with PRO, estimates using CTCAE by medical providers have been shown to slightly underestimate the incidence and severity of AE (9-15). Furthermore, Japanese nurses who specialize in the nursing care of cancer patients indicated that they may not accurately report the nursing needs and AE of patients (16). Therefore, the importance of PRO is recognized worldwide. The NCI research team developed the "Patient-Reported Outcome Common Terminology Criteria for Adverse Events" (PRO-CTCAE) (17).

Previous studies demonstrated the effectiveness and accuracy of the PRO questionnaire for the assessment of symptoms in patients receiving cancer treatments (12-16). Frequently used QOL questionnaires for cancer patients are the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC-QLQ C30) (18), Functional Assessment of Cancer Therapy (FACT) (19), and Medical Outcome Study Short Form-36 (MOS SF-36) (20). EORTC QLQ-C30 is a well-known

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and widely used representative self-administered questionnaire that investigates the quality of life (QOL) of cancer patients. Koller *et al* (21). reviewed the use of EORTC QLQ in 109 randomized controlled trials (RCT) on cancer patients, and showed that chemotherapy was the most frequently applied treatment (79%), followed by radiotherapy (16%) and targeted therapy (16%). RCT only included 2 surgery studies (1.8%).

The present study examined differences in estimates between CTCAE and PRO-CTCAE and the symptoms that medical doctors and nurses may easily detect and those only identified by self-administered questionnaires. We also investigated the role of PRO between PRO-CTCAE and EORTC QLQ-C30 for patients receiving chemotherapy.

METHODS

Study Design

A longitudinal descriptive study

Participants

Patients who were diagnosed with breast cancer and received chemotherapy consisting of a combination of epirubicin and cyclophosphamide (EC) or dose-dense EC preoperatively or postoperatively at Tokushima University Hospital between September 2019 and September 2021 were eligible.

EORTC-QLQ-30 and Hospital Anxiety and Depression Scale (HADS) questionnaires were administered before chemotherapy, after 1 course (immediately before the 2nd course), 2 courses (immediately before 3rd course), and 3 courses (immediately before the 4th course). PRO-CTCAE and CTCAE were administered after 1 course (immediately before the 2nd course), 2 courses (immediately before 3rd course), and 3 courses (immediately before the 4th course) on the same days (Figure 1-a).

Forty-five patients were enrolled in the present study. Three patients rejected the continuation of chemotherapy due to AE after 1 course. Three patients were excluded. The remaining 42 patients (93%) were considered for subsequent analyses (Figure 1-b).

Ethical considerations

The present study was approved by the Clinical Research Ethical Review Board of Tokushima University Hospital (approval no. 3530). Prior to the study, subjects were informed of all necessary information regarding the publication of the study data, both verbally and in writing. Participants were also provided with the following details : the privacy of the study subject will be protected, there will be no treatment-related disadvantage regardless of whether the patient participates in the study, the study subject will not be identifiable from study data, and the study subject may discontinue participating at any time. Patients who consented to these conditions were included in the study.

CTCAE v4.0 - JCOG (7)

Regarding NCI instructions for CTCAE, a score of 0 was defined as "no AE", 1 as "mild (asymptomatic or mild symptoms, clinical or diagnostic observations only)", 2 as "moderate (minimal, local, or non-invasive intervention indicated)", 3 as "severe (severe or medically significant, but not immediately life-threatening hospitalization)", 4 as "disabling (life-threatening consequences)", and 5 as "death related to AE". We defined a score higher than 1 as AE. In the present study, we used the CTCAE-JCOG version (version 4.0). Clinicians judged symptoms objectively in interviews with patients in the ambulatory medical examination, and they were documented in medical records.

The Japanese version of PRO-CTCAE

The original version of PRO-CTCAE comprises 124 self-administered items, reflecting 78 symptomatic AE. The Japanese version of PRO-CTCAE has been developed and linguistically validated (22). The reliability and validity of the Japanese version of PRO-CTCAE have also been verified (23). Reeve *et al* (24). identified 12 symptoms recommended for inclusion in clinical trials measuring PRO in a systematic review of evidence (fatigue, insomnia, pain, anorexia, dyspnea, cognitive impairment, anxiety, nausea, depression, sensory neuropathy, constipation, and diarrhea). Among these symptoms, 9 (fatigue, pain, anorexia,

Figure 1-a

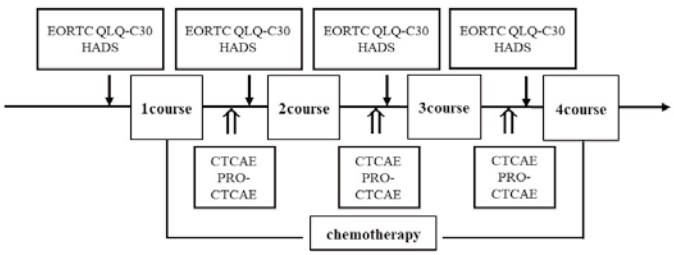

Figure 1-b

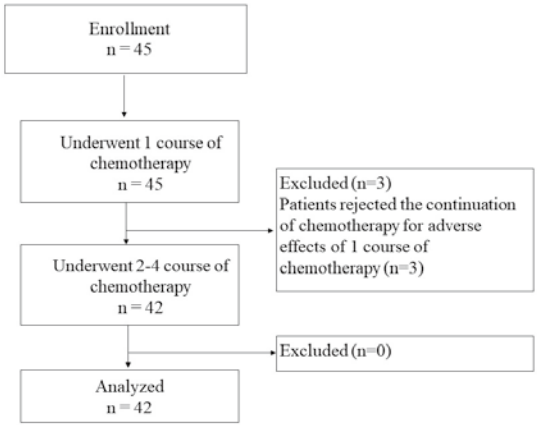

Figure 1-a. Time line of questionnaires.
EORTC-QLQ-30 and HADS were administered before chemotherapy, after 1 course (immediately before the 2nd course), 2 courses (immediately before 3rd course), and 3 courses (immediately before the 4th course). PRO-CTCAE and CTCAE were administered after 1 course (immediately before the 2nd course), 2 courses (immediately before 3rd course), and 3 courses (immediately before the 4th course) on the same day.
Figure 1-b. Flow diagram of the study population.
Recruitment took place between September 2019 and September 2021, with 45 patients being enrolled, 3 of whom were excluded due to adverse effects after 1 course of chemotherapy. The remaining 42 patients completed 4 courses of chemotherapy.

dyspnea, anxiety, nausea, sensory disturbance, constipation and diarrhea) were selected and 7 additional symptoms were included in this study (vomiting, mouth and throat pain, taste changes, heart palpitations, discouragement, urine color changes, and injection site abnormalities).

In the present study, 12 symptoms of similar severity were analyzed, and PRO-CTCAE was scored for each symptom (0 -4). (0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe). Symptoms with scores higher than 1 in PRO-CTCAE were considered to be AE. We compared the severities of 12 symptoms between CTCAE and PRO-CTCAE over time (Figure 2). We also showed the frequency, severity, and interference with daily activities of several symptoms in PRO-CTCAE over time (Supplementary Figure 1).

EORTC-QLQ-30 (18)

EORTC QLQ-C30 consists of a global health/QOL scale score, 5 functional (physical, role, emotional, social, and cognitive) scale scores, and 9 symptom (fatigue, nausea and vomiting, pain, dyspnea, insomnia, anorexia, constipation, diarrhea, and financial difficulties) scale scores. Scale and single item scores (1~100) were used in evaluations, with higher scores indicating better function and lower scores reflecting less severe symptoms. The symptom scales in EORTC-QLQ 30 were adapted to PRO-CTCAE questionnaire items, and seven items (fatigue, dyspnea, nausea, vomiting, anxiety, diarrhea, and constipation) were analyzed.

HADS

HADS is a scale that was developed in the United Kingdom for the purpose of measuring anxiety and depression in patients receiving general ambulatory treatments and medical examination (25). It comprises 14 items : 7 (question odd number) on anxiety and 7 (question even number) on depression, with scores reflecting the condition of the patient in the previous week. Each item consists of 4 levels of 1 ~ 4 points, and the highest score is 42 points. Reliability and validity were examined in studies on patients receiving chemotherapy (26). The Japanese version of HADS was used in the present study (27).

The scores for the 7 items on anxiety and the 7 items on depression were summed, with 0~7 points being classified as "no anxiety or depression", 8~10 points as a suspected diagnosis, and more than 11 points as a definite diagnosis (25).

Statistical analysis

Comparisons of PRO-CTCAE and CTCAE in each course of chemotherapy were performed using Fisher's exact test. Changes in EORTC QLQ-C30 and HADS scores over time were evaluated using Friedman's analysis followed by Scheffé's post hoc test (multiple comparison). Statistical analyses were conducted using Excel statistics version 3.21 (BellCurve, Inc.), with $P < .05$ indicating a significant difference.

Figure 2-a

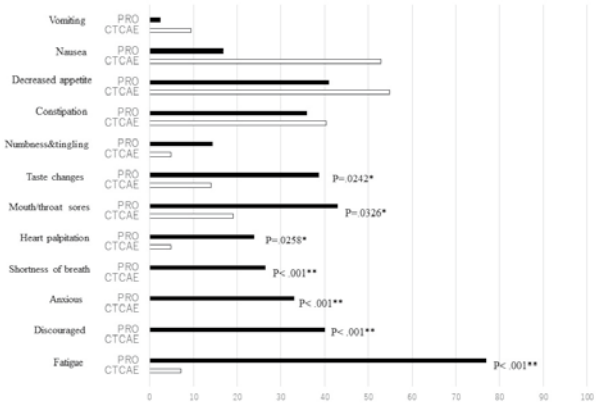

Figure 2-b

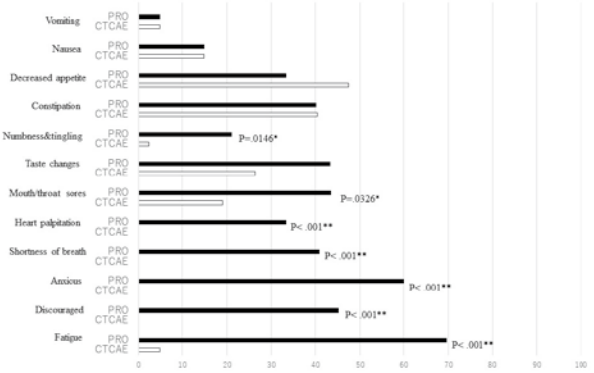

Figure 2-c

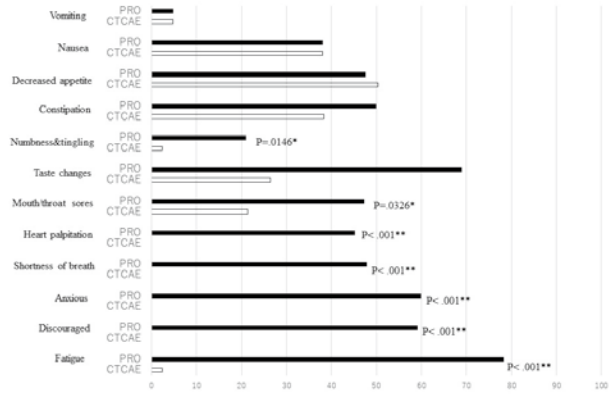

Figure 2. Comparison of estimates between PRO-CTCAE and CTCAE
(a) After 1 course of chemotherapy, (b) after 2 courses of chemotherapy, and (c) after 3 courses of chemotherapy. Comparisons of PRO-CTCAE and CTCAE at each course of chemotherapy were performed using Fisher's exact test.

RESULTS

Participants

Forty-two patients were analyzed in the present study. They completed the Japanese versions of PRO-CTCAE, EORTC QLQ-C30, and HADS, and underwent a medical examination by a doctor and nurse using CTCAE. The demographic and clinical characteristics of patients are shown in Table 1. The mean age of patients was 56.1 (38-76) years and all patients were female. There were 8 patients (19%) in stage I, 24 (57%) in stage II, and 8 (19%) in stage III. Two-thirds of patients received preoperative chemotherapy (67%) and the EC regimen (69%). The performance status of all patients was 0 or 1.

Comparisons of CTCAE and PRO-CTCAE estimates for chemotherapy over time

We showed the degree of "frequency" of 7 symptoms in PRO-CTCAE after 1, 2, and 3 courses of chemotherapy (Supplementary Figure 1-a). We showed the degree of "severity" of 12 symptoms in PRO-CTCAE over time (Supplementary Figure 1-b). We showed the degree of "interference with daily activities" by 8 symptoms in PRO-CTCAE over time (Supplementary Figure 1-c).

Comparisons between CTCAE and PRO-CTCAE after 1 (Fig. 2-a), 2 (Fig. 2-b), and 3 courses of chemotherapy (Fig. 2-c) are shown in Figure 2. The recognition of "fatigue" using PRO-CTCAE was high over time (70-80%). The recognition of "anxiety" and "discouragement" using PRO-CTCAE increased over time (from 30 to 60%). However, CTCAE did not recognize "fatigue", "anxiety", or "discouragement". Regarding the recognition of "fatigue", "anxiety", and "discouragement", PRO using PRO-CTCAE was significantly higher than doctor- and nurse-recognized outcomes using CTCAE during chemotherapy ($p < .001$).

The recognition of "heart palpitations" and "shortness of breath" using PRO-CTCAE increased over time (from 20 to 40%). However, CTCAE did not recognize "heart palpitations" or "shortness of breath". Regarding the recognition of "heart palpitations" and "shortness of breath", PRO using PRO-CTCAE was significantly higher than doctor- and nurse-recognized outcomes using CTCAE during chemotherapy ($p < .001$).

Concerning the recognition of "vomiting", "nausea", "decreased appetite", and "constipation", doctor- and nurse-recognized outcomes using CTCAE were similar or higher than PRO using PRO-CTCAE.

Regarding the recognition of "numbness and tingling", "taste changes", and "mouth/throat sores", PRO using PRO-CTCAE was higher than doctor- and nurse-recognized outcomes using CTCAE.

Chemotherapy affects QOL (EORTC-QLQ-30)

Changes in QOL over time are shown in Figure 3 and Table 2. In the 5 functional (physical, role, emotional, social, and

Table 1. Demographic and clinical characteristics of patients

		mean	SD
age		56.1 (38-76)	10
		case number	percentage
sex	female	42	100
stage			
	I	8	19.1
	II	24	57.1
	III	9	21.4
	unknown	1	2.4
timing of chemotherapy			
	preoperative	28	66.7
	postoperative	14	33.3
type of regimen			
	EC	29	69
	dose-dense EC	13	31
ECOG PS			
	0	20	47.6
	1	22	52.4

SD ; standard deviation, EC ; epirubicin/cyclophosphamide, ECOG ; Eastern Cooperative Oncology Group, PS ; performance status

Table 2. Time-dependent changes in EORTC-QLQ-30 in breast cancer patients receiving chemotherapy

Scales	before chemotherapy (mean ± SD)	after 1 course (mean ± SD)	P	after 2 courses (mean ± SD)	P	after 3 courses (mean ± SD)	P
EORTC QLQ-C30							
Global health status · QOL	72.62 ± 22.34	64.29 ± 23.95		65.87 ± 19.72		61.71 ± 22.99	**0.01**
Physical functioning	97.14 ± 4.69	92.38 ± 9.38		91.59 ± 9.2	**0.007**	89.84 ± 11.43	**<0.001**
Role functioning	95.24 ± 12.9	86.51 ± 18.12		83.33 ± 21.15	**0.012**	79.76 ± 23.44	**0.001**
Emotional functioning	78.77 ± 16.69	81.94 ± 15.28		85.71 ± 12.25		84.52 ± 11.58	
Cognitive functioning	90.48 ± 13.34	91.67 ± 12.35		88.49 ± 14.01		88.1 ± 12.9	
Social functioning	83.33 ± 18.77	83.33 ± 18.03		80.16 ± 18.12		80.56 ± 21.75	
Fatigue	16.67 ± 16.69	23.81 ± 16.93		30.42 ± 19.18	**<0.001**	31.48 ± 17.85	**<0.001**
Nausea and vomiting	1.59 ± 6.17	4.37 ± 9.78		3.17 ± 6.62		5.56 ± 8.76	**0.025**
Pain	13.1 ± 16.27	13.49 ± 17.36		15.87 ± 15.6		13.89 ± 15.58	
Dyspnea	2.38 ± 8.69	11.9 ± 16.17	**0.01**	10.32 ± 15.6	**0.048**	13.49 ± 16.56	**<0.001**
Insomnia	13.49 ± 20.9	17.46 ± 21.13		15.87 ± 21.13		19.84 ± 22.16	
Appetite loss	4.76 ± 11.81	13.49 ± 18.12		11.9 ± 16.17		19.05 ± 19.68	**<0.001**
Constipation	8.73 ± 16.56	16.67 ± 24.69		18.25 ± 27.74		19.84 ± 24.48	**0.015**
Diarrhea	10.32 ± 15.6	13.49 ± 16.56		13.49 ± 16.56		9.52 ± 16.93	

SD ; standard deviation, P ; Statistical analyses were performed using the Friedman test and Scheffé's test (post-hoc), EORTC QLQ ; European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire

Figure 3-a

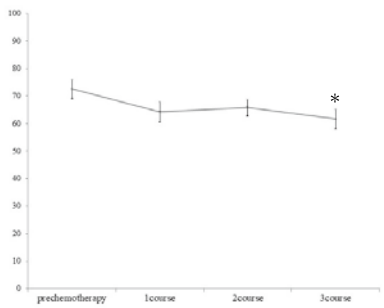

Figure 3-b

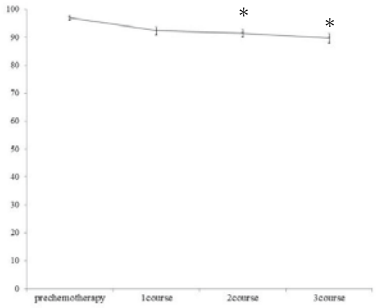

Figure 3-c

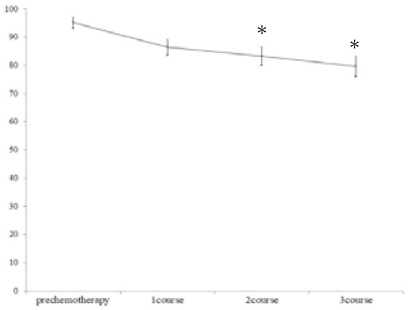

Figure 3-d

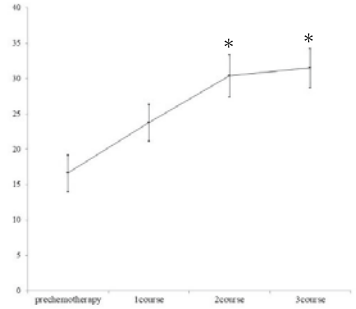

Figure 3-e

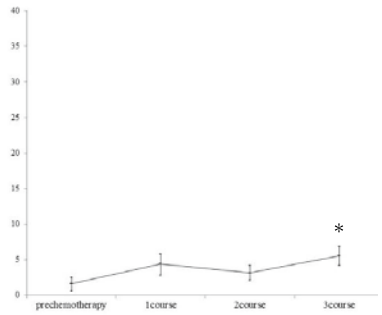

Figure 3-f

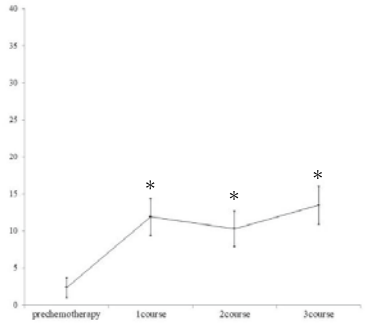

Figure 3-g

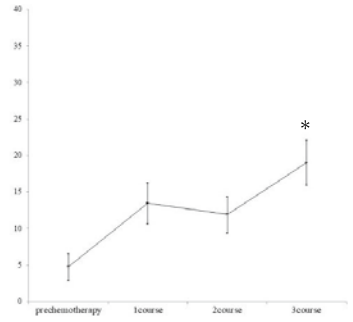

Figure 3-h

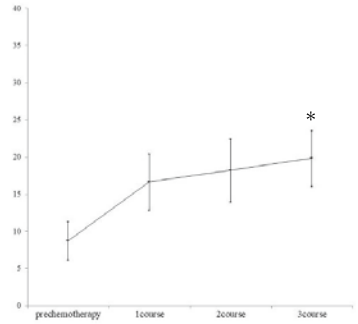

Figure 3. Time-dependent changes in EORTC-QLQ-30 in breast cancer patients receiving chemotherapy.
Statistical analyses were performed using the Friedman test and Scheffé's test (post-hoc).
3-a : The global health status (GHS) (Friedman : P < .001). GHS scores were significantly lower after 3 (P = .010) courses of chemotherapy than before chemotherapy.
3-b : Physical function (Friedman : P < .001). Physical function scores were significantly lower after 2 (P = .007) and 3 (P < .001) courses of chemotherapy than before chemotherapy.
3-c : Role function (Friedman : P < .001). Role function scores were significantly lower after 2 (P = .012) and 3 (P < .001) courses of chemotherapy than before chemotherapy.
3-d : Fatigue (Friedman : P < .001). Fatigue scores were significantly higher after 2 (P < .001) and 3 (P < .001) courses of chemotherapy than before chemotherapy.
3-e : Nausea/vomiting (Friedman : P < .001). Nausea/vomiting scores were significantly higher after 3 (P = .025) courses of chemotherapy than before chemotherapy.
3-f : Dyspnea (Friedman : P < .001). Dyspnea scores were significantly higher after 1 (P =. 010), 2 (P = .048), and 3 (P = .015) courses of chemotherapy than before chemotherapy.
3-g : Appetite loss (Friedman : P < .001). Appetite loss scores were significantly higher after 3 (P < .001) courses of chemotherapy than before chemotherapy.
3-h : Constipation (Friedman : P < .001). Constipation scores were significantly higher after 3 (P < .015) courses of chemotherapy than before chemotherapy.

cognitive) scale scores, physical and role function scale scores were significantly lower after 2 and 3 courses of chemotherapy than before chemotherapy (Fig. 3-b and 3-c). The general health status score was significantly lower after 3 courses of chemotherapy than before chemotherapy (Fig. 3-a).

In the 9 symptom (fatigue, nausea and vomiting, pain, dyspnea, insomnia, anorexia, constipation, diarrhea, and financial difficulties) scale scores, the fatigue score was significantly higher after 2 and 3 courses of chemotherapy than before chemotherapy (Fig. 3-d), and the dyspnea score was significantly higher during than before chemotherapy (Fig. 3-f). Nausea/vomiting, appetite loss, and constipation scores were higher after 3 courses of chemotherapy than before chemotherapy (Fig. 3-e, 3-g, and 3-h).

Chemotherapy affects HADS

Changes in anxiety and depression over time are shown in Figure 4. The anxiety score was lower during than before chemotherapy and was significantly lower after 2 and 3 courses of chemotherapy (Fig. 4-a). No significant differences were observed in the depression score during chemotherapy (Fig. 4-b).

DISCUSSION

AE associated with chemotherapy are prevalent among a large percentage of patients receiving treatment. AE in CTCAE are characterized as 1) laboratory-based events, such as anemia, 2) observable and measurable events, including hypertension, and 3) symptomatic events, such as pain and fatigue (28). Previous studies showed that reports of symptomatic toxicities directly from patients using PRO measures improved the accuracy of identifying and characterizing the symptomatic AE of chemotherapy (9-15). NCI reported that the combination of CTCAE and PRO-CTCAE may refine our understanding of the prevalence and trajectory of lower-grade AE that may lead to the elective discontinuation of therapy and diminished QOL (29). Although the use of PRO-CTCAE provided more precise and reliable data on symptomatic AE than CTCAE (9,10,12,23), limited information is currently available on differences in detectable AE between CTCAE and PRO-CTCAE. The present study identified symptoms that were easily recognized by medical providers and those that were only detected by patients undergoing chemotherapy.

The results obtained herein demonstrated that the symptoms of "fatigue", "anxiety", and "discouragement" were easily detected using PRO-CTCAE, but not CTCAE. The present results on PRO-CTCAE showed that the recognition rate of "fatigue" was very high (70-80%) from the early to late period of chemotherapy. Laugsand *et al*. compared differences in symptoms detected by medical providers and PRO symptoms in 1933 patients with various cancers, and reported that providers under- and overestimated symptoms in approximately 10 and 1% of patients, respectively. The highest rates of underestimation by providers were for anorexia (19%) and fatigue (13%) (30). In previous studies, fatigue was reported in between 80 and 99% of cancer patients treated with chemotherapy, radiotherapy, or both (31-33). More than 50% of patients reported that fatigue lasted longer than nausea, depression, and pain (34). These findings are consistent with the present results on PRO-CTCAE. Medical providers using CACTE underestimated fatigue symptoms more than PRO. Although patients treated with chemotherapy developed "fatigue", "anxiety", and "discouragement" at a high frequency during chemotherapy, they were not recognized by medical staff and, thus, were not treated. Fatigue is multidimensional, may be described in terms of perceived energy, mental capacity, and the psychological status, and impairs daily activities and QOL (35, 36). In the present study, impairments in physical and role functions were associated with the appearance of fatigue symptoms after 2 and 3 courses of chemotherapy. Vogelzang *et al*. demonstrated that 45% of patients with fatigue did not discuss fatigue more often with medical providers because they did not consider it possible to treat (37). The use of not only CTCAE, but also PRO-CTCAE and discussing fatigue with patients and medical providers will promote the early detection and treatment of fatigue.

Figure 4-a

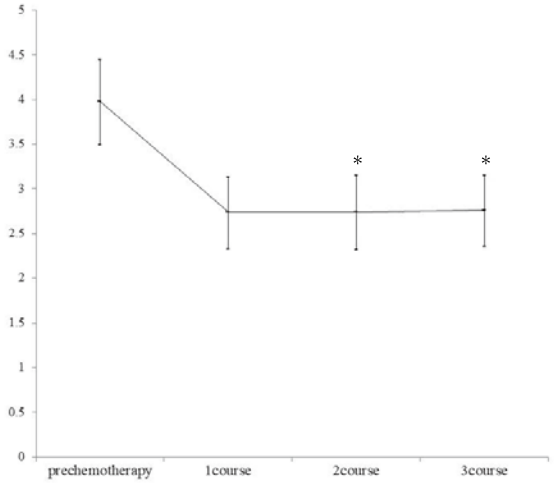

Figure 4-b

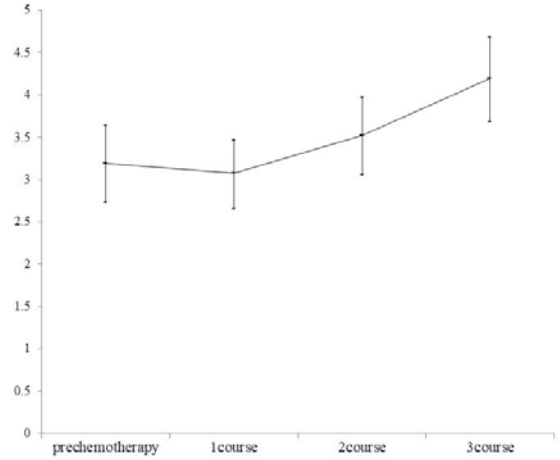

Figure 4. Time-dependent changes in HADS in breast cancer patients receiving chemotherapy.
Statistical analyses were performed using the Friedman test and Scheffé's test (post-hoc).
4-a : Anxiety (Friedman : $P < .001$). Anxiety scores were significantly lower after 2 ($P = .014$) and 3 ($P = .014$) courses of chemotherapy than before chemotherapy.
4-b : Depression. No significant time-dependent changes were observed.

Although "heart palpitations" and "shortness of breath" were not detected by doctors and nurses using CTCAE, the recognition of these symptoms by patients using PRO-CTCAE was significantly higher (20-40%). "Heart palpitations" and "shortness of breath" have not yet been compared between CTCAE and PRO-CTCAE. The symptoms of "heart palpitations" and "shortness of breath" are included in physical AE, but are subjective. Since difficulties are associated with recognizing physical and subjective AE by medical providers using CTCAE, the assessment of AE by patients themselves using PRO-CTCAE is necessary.

The recognition of "vomiting", "nausea", "decreased appetite", and "constipation" by doctors and nurses using CTCAE was the same or higher than PRO using PRO-CTCAE. Anthracyclines are the most effective cytotoxic drugs for the treatment of breast cancer (38, 39). They induce nausea (54%), vomiting (70%), and decreased appetite (34%) at G1 and G2 of AE. Furthermore, the addition of taxanes causes severe symptoms (40). In the present study, patients were treated with 2-4 courses of anthracyclines (epirubicin) and cyclophosphamide with/without taxanes. Vomiting, nausea, and decreased appetite are regimen-specific AE. Medical providers may detect regimen-specific AE using CTCAE at a high rate. This rate of detection was higher than or the same as that of PRO-CTCAE. Basch *et al*. compared 11 symptomatic AE reported by clinicians and 400 lung and genitourinary cancer patients, and reported that agreement was higher for AE that were directly observable, such as vomiting and diarrhea, than for more subjective AE, including fatigue and dyspnea (12). Psychological symptoms, such as "fatigue", "anxiety", and "discouragement", were easily detected using PRO-CTCAE. Medical providers detected regimen-specific AE using CTCAE at a high rate. CTCAE and PRO-CTCAE provide different and complementary information for a more detailed understanding of the tolerability of AE and the more accurate identification of AE that need to be monitored and managed.

PRO-CTCAE and EORTC-QLQ C30 are well-known and widely used PRO questionnaires for cancer patients. They were developed for different reasons. PRO-CTCAE is an instrument for monitoring symptomatic toxicities during cancer treatment (22-24), whereas QLQC30 covers multidimensional aspects of health-related QOL (18). In the present study, physical and role functioning scale scores in EORTC QLQ-C30 were significantly impaired after 2 courses of chemotherapy. Dyspnea and fatigue appeared after an early (1 or 2) course of chemotherapy and nausea and vomiting, appetite loss, and constipation after a late course of chemotherapy. In PRO-CTCAE, fatigue appeared after an early course of chemotherapy and frequency was constant (70-80%). Furthermore, vomiting (5%), decreased appetite (40-50%), and constipation (40-50%) were almost constant. Nausea increased (from 15 to 40%) with the number of courses of chemotherapy. The present study revealed no relationships between symptoms (fatigue, vomiting, decreased appetite, and constipation) in EORTC QLQ-C30 and PRO-CTCAE according to the number of chemotherapy courses. Taarnhoj *et al*. examined the relationships of 6 items (pain, nausea, vomiting, constipation, diarrhea, and fatigue) between EORTC QLQ-C30 and PRO-CTCAE in patients with various cancers, and revealed good reliability and consistency between the two PRO questionnaires, except for nausea and vomiting (41). PRO-CTCAE items on frequency more strongly correlated with QLQ-C30 items than PRO-CTCAE items on severity. The discordance between Taarnhoj's findings and the present results may be due to which aspect is used, namely, frequency, severity, and interference with daily activities. Dueck *et al*. also reported a strong correlation between analogous items in two PRO questionnaires (42). They suggested minimizing patient burdens by shortening the questionnaires.

The anxiety score was lower during than before chemotherapy. Anxiety symptoms may disappear as a patient adjusts to chemotherapy ; therefore, anxiety is high before chemotherapy due to uncertainty about whether treatment will be successful, but decreases as chemotherapy progresses through one, two, and three courses (43).

LIMITATIONS

This study has several limitations. 1) It was a single-center analysis of a small sample of patients (n = 42). However, the patient population was almost homologous, namely, advanced breast cancer, with a similar regimen of chemotherapy, including EC with/without taxanes, and a longitudinal descriptive analysis was performed. 2) PRO-CTCAE has five aspects (presence, amount, frequency, severity, and interference with daily activities). In the present study, symptoms with scores higher than 1 for the severity aspect were considered to be AE, and the other aspects were ruled out. 3) We herein compared assessments by patients and medical providers and not those by subgroups of nurses and physicians.

CONCLUSIONS

Psychological symptoms, such as "fatigue", "anxiety", and "discouragement", were easily detected using PRO-CTCAE. Medical providers detected regimen-specific AE using CTCAE at a high rate. In EORTC QLQ C-30, the physical and role functions, dyspnea and fatigue worsened with each course of chemotherapy. These three assessment methods complement each other and contribute to reducing AE and maintaining QOL in patients.

CONFLICTS OF INTEREST

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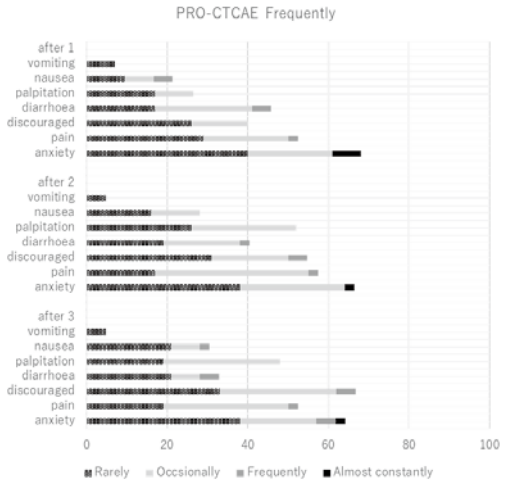
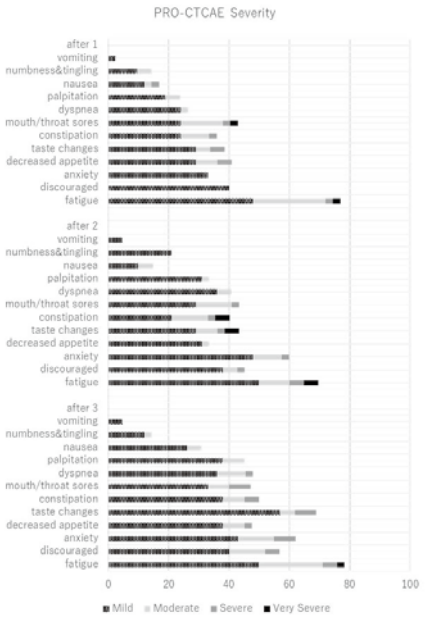
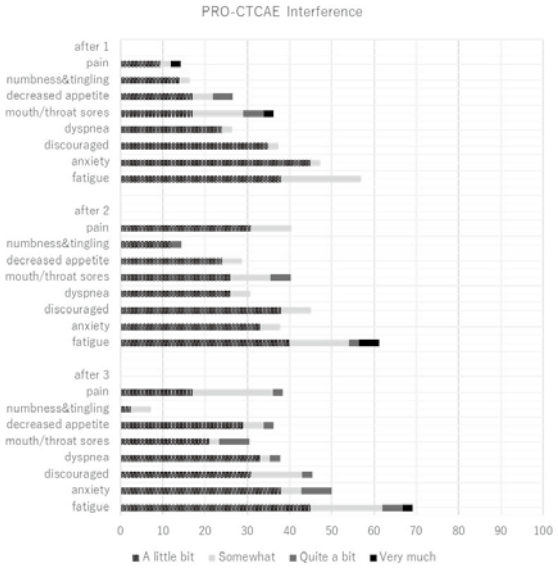
Appendices A.1



Appendices A.2



Appendices A.3



Appendices Figure.
A.1 The degree of "frequency" of PRO-CTCAE in 7 symptoms after 1, 2, and 3 courses of chemotherapy
B.2 The degree of "severity" in 12 symptoms in PRO-CTCAE after 1, 2, and 3 courses of chemotherapy
C.3 The degree of "interference with daily activities" in 8 symptoms in PRO-CTCAE after 1, 2, and 3 courses of chemotherapy