The Evaluation of Fatigue in Patients with Malignant Lymphoma Receiving Chemotherapy in Japan

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Abstract

Background: Fatigue is the most common symptom in cancer patients, resulting from a variety of factors. About 80% of cancer patients undergoing chemotherapy are believed to experience fatigue.

Objective: Levels of fatigue in patients with malignant lymphoma who received chemotherapy were evaluated.

Interventions/Methods: Participants were malignant lymphoma patients who received CHOP (R-CHOP) treatment or THP-COP (R-THP-COP) treatment. A fatigue questionnaire was given to evaluate patients’ levels of fatigue and weakness at the baseline and on the 4th, 8th and 12th days after chemotherapy.

Results: After treatment, the level of fatigue based on the Cancer Fatigue Scale (CFS) was the highest on the 8th day. The difference in the levels between the 8th day and the first day was significant (p<0.001).

Conclusions: The results suggest that the most marked physical fatigue was experienced on day 8 during each treatment period.

Implications for Nursing/Interpretation: It is important to focus more attention through nursing intervention research on circumstances involving patients’ feelings of fatigue during malignant lymphoma chemotherapy.

Introduction

Fatigue is the most common symptom in cancer patients, resulting from a variety of factors.¹⁻⁴ About 80% of cancer patients undergoing chemotherapy are believed to experience fatigue.⁵⁻⁶ Since the 1980s, surveys on fatigue have been conducted in several countries. Surveys have also been conducted on specific diseases or therapies, including the occurrence of adverse reactions in patients with malignant lymphoma who received Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (CHOP) therapy. Sitzia et al. reported that tiredness affected over 90% of non-Hodgkin’s lymphoma patients after cycle 1 and the trend for incidence was to decrease as treatment progressed; only 70% of the sample reported tiredness after cycle 6.⁷ In recent years, intervention studies have been performed mainly on patients with breast cancer; several reports suggested that exercises, such as walking, in particular, were effective in alleviating fatigue.⁸ However, there has been little research on fatigue in Japan, and the actual level of fatigue experienced by Japanese patients with specific diseases and receiving specific therapies remain to be elucidated. Fatigue is a subjective symptom and varies across patients worldwide. It has been considered that factors such as cultural backgrounds and differences in physical characteristics and perception may affect the development of cancer-related fatigue. Hirai et al. reported that fatigue in Japanese cancer patients was “a sensation characterized by unpleasant sensations perceived physically, a decline in physical function and a loss of physical control” and this was same as western
individuals. However, Hirai et al. also reported that Japanese cancer patients did not express “I’m fed up,” which is an expression of a scale developed in the West. 

Levkovich et al. reported that “The coping strategies with the fatigue were varied, and the one that stood out as being used frequently by the participants was the instrumental coping, a reorganization enabling them to function with the fatigue, to carry out most vital actions and withdraw from less indispensable or urgent ones.” Energy conservation therapy and exercise therapy are the main methods of dealing with fatigue in Europe and the United States, while aromatherapy and reflexology are the most common interventions in Japan. In that regard, the study results on fatigue in other countries cannot be applied to Japanese patients. Hence, this study aimed to longitudinally elucidate the degree of fatigue in patients with malignant lymphoma who received CHOP therapy or rituximab plus CHOP (R-CHOP) therapy and its modification depending on the course of treatment.

**Methods**

**Study design**

The study design was a questionnaire-based survey.

**Subjects**

The present study included hematological cancer patients aged ≥18, who met the conditions described below and gave informed consent to participate in the trial. They were admitted to Hospital A or B to receive R-CHOP (Fig. 1a), CHOP (Fig. 1b), Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone (R-THP-COP) (Fig. 1c), or THP-COP (Fig. 1d) therapy or its alternative treatment. Hospital A and B are general hospitals of the National Hospital Organization, including their related facilities.

The inclusion criteria were as follows:

1. Patients with a confirmed diagnosis of malignant lymphoma
2. Patients without cognitive decline resulting from brain metastases or electrolyte abnormality
3. Patients who were able to complete the Cancer Fatigue Scale (CFS) questionnaire
4. Patients who could be surveyed using the CFS questionnaire at 4 survey points in total: on days 0 (baseline), 4, 8, and 12
5. Patients who could be surveyed after the second course of the 6- or 8-course treatment regimen

**Measurement scales**

(1) **CFS (Table 1)**

CFS is a scale for measuring cancer-related fatigue, developed by Okuyama et al. in 2000. Its reliability and validity have been well-established. The scale comprises 15 items and the following 3 subscales: physical, affective, and cognitive. Cronbach’s alpha coefficients for the physical, affective, cognitive, and total fatigue scales are 0.89, 0.79, 0.79, and 0.88, respectively. Each item is rated on a scale from 1 to 5, where the total score obtained by the calculation formula of each factor is assessed. The subscale scores are calculated using formulas designed by the instrument author. The minimum score is 0, and maximum score is 60. Since the number of the items is few, the questionnaire can be completed in less than two minutes. The higher the CFS score, the clinical fatigue; a score of 19 or higher is categorized as clinical fatigue. 

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**Fig. 1a** R-CHOP therapy

|          | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 |
|----------|-------|-------|-------|-------|-------|-------|
| Rituximab | 375 mg/m² | ↓     |       |       |       |       |
| Cyclophosphamide | 750mg/m² | ↓     |       |       |       |       |
| Doxorubicin | 50 mg/m² | ↓     |       |       |       |       |
| Vincristine | 1.4 mg/m² (max: 2.0 mg) | ↓     |       |       |       |       |
| Prednisolone | 100 mg/body | ↓     | ↓     | ↓     | ↓     | ↓     |

**Fig. 1b** CHOP therapy

|          | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 |
|----------|-------|-------|-------|-------|-------|
| Cyclophosphamide | 750 mg/m² | ↓     |       |       |       |
| Doxorubicin | 50 mg/m² | ↓     |       |       |       |
| Vincristine | 1.4 mg/m² (max: 2.0 mg) | ↓     |       |       |       |
| Prednisolone | 100 mg/body | ↓     | ↓     | ↓     | ↓     |
Performance Status (PS)

PS is an indicator of systemic conditions, developed by the Eastern Cooperative Oncology Group (ECOG). Systemic conditions are categorized into 5 grades from 0 to 4, using the grades as an objective indicator. Because these criteria are indicators of systemic conditions, in the case where physical activity is limited due to local symptoms, a clinical judgment should be made.

Procedure

(1) The patients were given a study overview, including the objectives of this study and methods, and ethical considerations, after we obtained permission from their primary doctors.

(2) Patients who agreed to participate in the CFS questionnaire survey were asked to provide written informed consent.

(3) The CFS questionnaires were distributed to the patients in the morning on the days the measurement was performed (days 0 (baseline), 4, 8, and 12).

- Day 0 (includes day 1 before therapy): Baseline
- Day 4: During the oral administration period of Prednisolone (PSL)
- Day 8: After the oral period of PSL
- Day 12: Prior to the next treatment

(4) The completed CFS questionnaires were collected at 15:00 on the days of the questionnaire survey.

(5) Background data (age, PS etc.) were collected from patients’ care records at the baseline.

Study period

October 2004 ~ September 2007

Ethical consideration

1) This study was approved by the Ethics Review Boards of National Hospital Organization of hospitals A and B.

2) Patients willingly participated in this study and were allowed to withdraw their participation at any point during the study even after they had consented to participate. Furthermore, written/verbal explanations were given to the patients who were withdrawn from the survey to avoid the development of any adverse effects; patients who completed the survey were assessed. In this study, completed questionnaires were collected by medical staff (doctors or nurses, not include researcher).
Data analysis

We analyzed data obtained from 59 subjects who completed all 4 longitudinal surveys. The analysis was performed as follows:

1) General background analysis (1) Descriptive statistics regarding the characteristics of the surveyed population were calculated.

2) Analysis of CFS scores

(1) Calculation of CFS score: The CFS score was calculated using the calculation formula for each subscale.12

Physical fatigue score = (Q1 + Q2 + Q3 + Q6 + Q9 + Q12 + Q15) - 7,

Affective fatigue score = 20 - (Q5 + Q8 + Q11 + Q14),

Cognitive fatigue score = (Q4 + Q7 + Q10 + Q13) - 4,

and Total fatigue score = the sum of each subscale score.

(2) The mean value and standard deviation of the total fatigue scores, physical fatigue scores, affective fatigue scores, and cognitive fatigue scores for each survey point were obtained.

(3) The mean values of CFS scores (total fatigue score, physical fatigue score, cognitive fatigue score, and affective fatigue score) obtained at each survey point were compared using the Friedman’s Test.

(4) In the case significant difference was found in Friedman’s test, Bonferroni’s multiple comparison test was further performed to confirm the significances in differences among each survey point.

Statistical package for social sciences (SPSS) 11.0J for Windows (SPSS Inc.) was used for these analyses. P-values of <0.05 were considered significant.

Results

Characteristics of the samples (Table 2)

Of the 64 subjects who were given an explanation of the survey procedure, 60 provided consent to participate. Of the 60 patients, 59 were able to complete the questionnaire survey at all 4 survey points (return rate: 98.3%); all the completed questionnaires obtained from the 59 patients were effective (analysis rate: 100%) and hence were regarded as valid responses. The response of 1 patient was considered invalid because he had been discharged from the hospital before completing the survey on day 12 and failed to provide all 4 measurements.

The general backgrounds of the subjects are shown in Table 2. Of the 59 subjects diagnosed with malignant lymphoma, 31 were male (52.5%) and 28 were female (47.5%); hence, there was no sex-related bias. Their age ranged from 40 to 85 years (66.4 ± 10.63 years). In terms of therapy, 23 (39.0%) patients each received R-CHOP and R-THP-COP therapy; the highest number of patients received these therapies, followed by the number of those who received THP-COP therapy, Rituximab, Cyclophosphamide, Vincristine and Prednisolone (R-CVP) therapy, and CHOP therapy. Regarding the number of courses, patients in the early stage of treatment, who were receiving the second or third course, comprised the highest number, accounting for approximately 70% of the study population. With reference to PS, 86.4% of the patients had Grade 0-1, indicating that most of the patients had a good systemic condition.

Cronbach’s alpha Coefficient

Cronbach’s alpha coefficients for the Cancer Fatigue Scales for the sample of patients in this study were distributed over a range of 0.70-0.86 on day 0 (baseline), 0.80-0.89 on day 4, 0.83-0.94 on day 8 and 0.81-0.86 on day 12, respectively.

Changes in CFS scores

Mean CFS scores and mean CFS subscale scores are shown in Table 3, and changes in the CFS scores during treatment are shown in Table 4 and Fig 2. Total CFS

### Table 2  Characteristics of Sample (n=59)

|               | n  | %   |
|---------------|----|-----|
| Sex           |    |     |
| male          | 31 | 52.5|
| female        | 28 | 47.5|
| Age           |    |     |
| Mean          | 66.4|  |
| Standard deviation | ± 10.63| |
| Range         | 40-85|  |
| Cancer site   |    |     |
| lymphoma      | 59 | 100.0|
| Hospital unit |    |     |
| inpatient     | 59 | 100.0|
| Chemotherapy regimen | |    |
| CHOP          | 2  | 3.4 |
| R-CHOP        | 23 | 39.0|
| THP-COP       | 7  | 11.9|
| R-THP-COP     | 23 | 39.0|
| R-CVP         | 4  | 6.8 |
| Chemotherapy cycle | |    |
| 2             | 25 | 42.4|
| 3             | 17 | 28.8|
| 4             | 6  | 10.2|
| 5             | 3  | 5.1 |
| 6             | 6  | 10.2|
| 7             | 1  | 1.7 |
| 8             | 1  | 1.7 |
| Performance Status | |    |
| 0             | 36 | 61.0|
| 1             | 15 | 25.4|
| 2             | 7  | 11.9|
| 3             | 1  | 1.7 |

Abbreviations: CHOP, Cyclophosphamide Doxorubicin Vincristine Prednisolone; R-CHOP, Rituximab Cyclophosphamide Doxorubicin Vincristine Prednisolone; R-CVP, Rituximab Cyclophosphamide Vincristine Prednisolone; R-THP-COP, Rituximab Cyclophosphamide Pirarubicin Vincristine Prednisolone; THP-COP, Cyclophosphamide Pirarubicin Vincristine Prednisolone.
scores were distributed over a range of 0-40 on day 0 (baseline), 0-34 on day 4, 0-56 on day 8, and 0-51 on day 12; the highest score was observed on day 8. CFS physical fatigue scores were distributed over a range of 0-23 on day 0 (baseline), 0-16 on day 4, 0-28 on day 8, and 0-27 on day 12; the highest score was observed on day 8.

The Friedman’s test revealed significant difference among survey points in CFS total score ($F(2.75, 159.50) = 5.93, p=0.001$) and CFS physical score ($F(3,174) = 6.77, p=0.000$). There were no significant differences in the other subscales.

At treatment process (Table 4 and Fig 2), there was a significant difference in the physical fatigue score between day 0 (baseline) and day 8 ($p=0.000$). In addition, there was a significant difference in the physical fatigues score between day 4 and day 8 ($p=0.020$).

As shown in Table 4, there was almost no change in the affective fatigue score or cognitive fatigue score over the course of therapy. There was no significant difference in the CFS affective fatigue and cognitive fatigue scores between each survey point.

All surveyed patients who received R-CHOP (CHOP) and R-THP-COP (THP-COP) therapies received the oral administration of PSL on day 4 in compliance with the treatment regimens. PSL treatment ended before day 8.

**Discussion**

In this study, a questionnaire survey was longitudinally performed involving 59 patients with malignant lymphoma receiving chemotherapy, at 4 survey points: days 0 (baseline), 4, 8, and 12.

We performed this analysis in patients with a single disease, i.e., malignant lymphoma, and, moreover, assessed the effects on patients receiving different types of treatments such as CHOP therapy and THP-COP therapy and their modifications. This survey was performed under controlled conditions such that an assessment could be performed using a larger sample size of 59 sub-

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**Table 3** Changes in CFS Scores ($n=59$)

| CFS item          | Treatment process |
|-------------------|-------------------|
|                   | day 0 | day 4 | day 8 | day 12 |
|                   | Mean  | SD    | Mean  | SD    | Mean  | SD    | Mean  | SD    |
| CFS Total scores  | 13.9  | 7.2   | 15.9  | 7.9   | 18.3  | 9.8   | 16.2  | 8.9   |
| Subscale          |       |       |       |       |       |       |       |       |
| Physical          | 3.6   | 4.0   | 4.6   | 4.3   | 6.7   | 6.3   | 7.4   | 5.5   |
| Affective         | 7.8   | 3.4   | 8.4   | 3.4   | 8.4   | 3.8   | 7.7   | 3.5   |
| Cognitive         | 2.4   | 2.5   | 2.9   | 3.1   | 3.3   | 2.9   | 3.1   | 3.0   |

Abbreviation: CFS, Cancer Fatigue Scale.

**Table 4** Comparison of the Scores Between Treatments

| CFS items          | Treatment process (p-value) |
|--------------------|-----------------------------|
|                    | days 0-4 | days 0-8 | days 0-12 | days 4-8 | days 4-12 | days 8-12 |
| Total Score        | 0.030    | 0.000    | 0.227     | 0.190    | 1.000     | 0.538     |
| Subscale           |          |          |           |          |           |           |
| Physical           | 0.511    | 0.000    | 0.142     | 0.020    | 0.733     | 0.821     |
| Affective          | 0.520    | 0.514    | 0.501     | 0.461    | 0.454     | 0.485     |
| Cognitive          | 0.289    | 0.329    | 0.345     | 0.317    | 0.304     | 0.338     |

Bonfferoni’s multiple comparison test. Abbreviation: CFS, Cancer Fatigue Scale.

$^a:p < 0.01$ $^b:p < 0.05$

CFS total score shows significant differences among therapeutic process (day 0 and day 8, $p<0.01$). In CFS subscale(physical) score, significant differences are observed among therapeutic process (day 4 and day 8, $p<0.05$; day 0 and day 8, $p<0.01$).
jcts compared with the sample sizes used in previous studies, which were performed in patients with a limited disease receiving limited therapies. Furthermore, we performed this longitudinal survey at 4 survey points: day 0 (baseline), day 4, day 8, and day 12. We used sophisticated research methods. The following are important results obtained in this study:

1. Changes in the CFS score over the course of treatment

One of the findings of our study was that physical fatigue was the highest on day 8 during the course of treatment: there was a significant difference between the physical fatigue scores on day 0 (baseline) and day 8 ($p=0.000$). Moreover, there was a significant difference ($p=0.020$) between the scores on day 4 and day 8. Difference in CFS total score was also significant between day 0 (baseline) and day 8. This result suggested that the most marked physical fatigue was experienced on day 8 during each treatment period. In addition, there was no change in the affective fatigue or cognitive fatigue scores over the course of treatment. These results confirmed that changes in fatigue experienced during the course of treatment were physical.

Clinical fatigue as an adverse reaction is experienced by patients receiving chemotherapy. Concerning the drugs used in CHOP (R-CHOP) and THP-COP (R-THP-COP) therapies, which were used in this study, fatigue is reported to be developed at a frequency of 5% or more in patients receiving rituximab (Rituxan®)14, and pirarubicin hydrochloride (Pinorubin®)15, 0.1–5% in those receiving doxorubicin hydrochloride (Adriacin®)16; and frequency unknown in those receiving cyclophosphamide (Endoxan®)17, and vincristine sulfate (Oncovin®).18

The factors influencing the development of fatigue should be assessed considering that fatigue might develop as an adverse reaction to chemotherapy drugs.

The regimens of CHOP (R-CHOP) and THP-COP (R-THP-COP) therapies, which were administered in this study, include the oral administration of PSL (Prednisolone®), an adrenal cortex hormone, for 5 days from the start of treatment. PSL causes increased excitability, which is a neuropsychiatric symptom, as an adverse reaction. This influence of prednisolone could be partially responsible for the absence of an increase in fatigue on day 4 of the survey.20

According to a report by Okuyama et al., the higher the CFS score, the clinical fatigue; a score of 19 or higher is categorized as clinical fatigue.13 The mean values of CFS scores for patients in our study with malignant lymphoma receiving chemotherapy ranged between 13.9 and 18.3 at any stage of therapy, thereby indicating no reasonable possibility of the development of clinical fatigue. Nonetheless, in our study, the total CFS scores ranged between 0 and 56 on day 8. One possible interpretation for this result is that the level of fatigue varies across patients, and hence, an increase in the fatigue level cannot be ruled out in patients receiving R-CHOP (CHOP) or R-THP-COP (THP-COP) therapy. Degner et al. reported that the incidence of fatigue in lung cancer patients at the time of cancer diagnosis was 40%.1 The incidence was 83% in cancer patients who were in the final stages. Smets et al. reported that the incidence of fatigue in cancer patients after radiotherapy was 46%.6 A report by Love et al. indicated that the incidence of fatigue in patients with breast cancer and those with malignant lymphoma receiving chemotherapy was 80% or higher.2 Patients receiving chemotherapy often have a relatively good performance status (PS, 0–1), which allows them to independently perform activities of daily living (ADL). Hence, despite a high incidence of fatigue, the fatigue level in these patients is probably underestimated compared with that in patients with a poor performance status.

2. Nursing intervention for alleviating fatigue

We observed a significantly higher physical fatigue level on day 8 in the patients receiving chemotherapy. Studies on fatigue in cancer patients performed in other countries often involve the interventions of exercise and different programs, such as coaching, counseling, and relaxation. In 2009, Courneya et al. enrolled patients in an Aerobic exercise training (AET) program, and compared the FACT-An and Fatigue subscale scores between exercise and usual care (control) groups. The results revealed that there was a significant difference in the scores between the two groups.21 In 2012, Cheville et al. enrolled patients in the Rapid, Easy, Strength Training (REST) exercise program and compared FACT-F scores between the exercise and control groups.

They found that there was a significant difference in scores between the two groups.22 Schwartz et al. performed interventions with exercise and the oral administration of methylphenidate, and reported that although the fatigue level decreased only with exercise, there was a greater reduction of the fatigue level when patients underwent exercise combined with the oral administration of methylphenidate, in 2002.23 Regarding studies on interventions used in Japan to reduce fatigue, in 2002, Kohara et al. assessed the effect of a foot bath by providing cancer patients with aromatherapy using CFS. They observed a significant decrease in general, physical, and cognitive fatigue.24

Although the mean total CFS scores obtained in this study did not indicate the presence of clinical fatigue, there was an increase in the fatigue level on day 8 after chemotherapy. This time period coincides with the period of marked bone marrow depression (7–14 days after treatment). In this context, patients should be provided with nursing care to manage the changes in the fatigue level, which might affect the physical activities of patients, caused by the treatment.

Many reports suggest that exercise is effective for alleviating fatigue.25 However, in Japan, a few studies have assessed the effects of interventions such as foot baths and aromatherapies on fatigue level; interventions with exercises have not yet been explored, and there is a need to establish an intervention strategy for Japanese cancer patients. In Japan, studies focusing on the level of fatigue, as well as those on the development of scales for
measuring the fatigue level, have not yet been performed.

While providing daily nursing care, patients are often overheard saying that they feel tired and want to take a short rest. Patients are sometimes asked to lie on beds without performing any form of activity. In Japan, nurses are less aware of the effects of fatigue on patients, and they consider that allowing the patients to rest is adequate to manage fatigue.

Winningham stated that, “developing a balance between activity and rest accelerates a patient’s recovery and an unbalance between them accelerates fatigue or malaise,” indicating that a patient’s efforts to take a walk are effective for alleviating fatigue.26

Patients should also be made aware of methods to manage fatigue on their own. Hence, they should be provided with specific information to identify cancer-related fatigue (inability to overcome fatigue even after taking some rest, tire easily, inability to focus their attention, feeling too tired to independently perform daily activities, etc.), and patients experiencing cancer-related fatigue should be provided with instructions on managing activity-related energy (what type of activities should be performed with the activity-related energy).

Thus, intervention measures should be developed to alleviate fatigue in cancer patients, such as bedside exercise, which can be performed even during the marked bone marrow depression period.

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