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Original Article

Relationship between chemotherapy-induced peripheral neuropathy and physical activity in cancer survivors: A prospective longitudinal study

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ABSTRACT

Objective: The purpose of this research is to evaluate the relationship between the degree of peripheral neuropathy associated with treatment and physical activity through the use of objective indicators such as wristband activity tracker and subjective evaluations obtained through interviews.
Methods: This study included 11 patients with gynecological cancer, gastrointestinal cancer, and malignant lymphoma. Participants were requested to wear a wristband activity meter at two time points: early and mid-treatment. Activity-meter step counts were compared with factors such as energy expenditure and Functional Assessment of Cancer Therapy-General during early and mid-treatment. Interviews were analyzed qualitatively and inductively.
Results: There was no difference in the number of steps taken by participants in the early and mid-treatment periods ($P = 0.050$), but they took more steps in the mid-treatment period than in the early period. Participants expended more energy during mid-treatment than early treatment, but these differences were not significant. We noted a correlation between the number of steps and energy expenditure in the mid-treatment period ($r = 0.883$). Comparisons between measures showed significant differences in "Impact" between early and mid-treatment on Distress and Impact Thermometer ($P = 0.034$). The impact of numbness on activity was assigned to three categories: loss of routine caused by numbness, coping with the numbness-related inconvenience using various resources, and acceptance of life with numbness with the support of others and self-strength.
Conclusions: The participants devised strategies to maintain activities despite experiencing chemotherapy-induced peripheral neurotoxicity. The use of activity meters may enhance patient motivation, which in our opinion, is beneficial for self-care education.

Introduction

Peripheral neuropathy occurs in as many as 68.1% of patients who have undergone chemotherapy for conditions including colorectal, breast, and gynecological cancers and multiple myeloma.[1] Persistent peripheral neuropathy was found in 41.9% of patients even after 2 years of treatment,[2] while chemotherapy-induced peripheral neurotoxicity (CIPN) was confirmed in 41% of patients 5 years after chemotherapy,[3] and these patients are currently living with peripheral neuropathy. Chemotherapy-induced neuropathy is a serious clinical problem caused by a substantial number of cytotoxic drugs, including taxanes, platinums, vinca alkaloids, epothilones, eribulin, and bortezomib; these drugs cause different pathologic insults to neurons.[4] Although the mechanism of development and symptoms differ depending on the drug, the incidence generally increases in a dose-dependent manner.[2] In patients with CIPN, recovery is in general partial with residual deficits in most patients.[5] In addition, once it occurs, it may last for months to years,[3,4] and it may be necessary to continue self-care for a long time even after the treatment ends.

The most common clinical presentation of CIPN is a predominant sensory axonal neuropathy with occasional motor and autonomic involvement. Predominantly sensory fibers are affected, but some

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cytostatic agents cause a sensory-motor pattern.[5] Patients with CIPN are prone to falls and impaired balance function and muscle strength.[6,7] Consequently, the patient may avoid going out or be unable to continue work, leading to a decline in quality of life (QOL) and causing spiritual pain.[7–9]

Exercise therapy is one of the self-care methods for peripheral neuropathy. The 2020 American Society of Clinical Oncology (ASCO) CIPN Guidelines,[4] ESCO2020,[5] meta-analysis[10,11] suggests the benefits of exercise therapy for the prevention and treatment of CIPN. Current data from an RCT also suggest that exercise is a feasible, safe, and promising supportive measure for patients with cancer who experience CIPN.[4] It was found that a four-week physiotherapy home program significantly reduced the frequency of pain in the upper extremities.[12] A meta-analysis suggests improvement of CIPN symptoms with exercise therapy.[13] However, the evidence has not been established and research on CIPN and the required activities needs to be promoted.

Research using wearable devices for patients with CIPN has been conducted for early diagnosis screening,[14,15] assessing the relationship between activity and sleep quality during and after treatment for one year,[16] and measuring balance abnormalities.[14,17] However, many of these studies used relatively short-term measurements, typically lasting from a few days to one week.[16,17] Since drugs like oxaliplatin and paclitaxel show significant changes in CIPN around 2–3 days after administration,[4] measuring long-term physical activity to elucidate changes during the course of treatment is of great significance.

The purpose of this research is to evaluate the relationship between the degree of peripheral neuropathy associated with treatment and physical activity through the use of objective indicators such as wristband activity tracker and subjective evaluations obtained through interviews. Further, based on our findings, we aimed to provide suggestions for self-care education to maintain safety and QOL.

Methods

Participants

Patients in the outpatient chemotherapy rooms of three Japanese hospitals who met the criteria mentioned below were invited to participate in the study; those who provided consent were included in the study. The three hospitals were one prefectural central cancer hospital, one regional cancer hospital, and one prefectural cancer hospital. Two are large hospitals with 600 beds or more and one is a medium-sized hospital with 300 beds or less.

Eligibility Criteria: A patient with breast cancer, gynecological cancer, gastrointestinal cancer, or malignant lymphoma, with an Eastern Cooperative Oncology Group Performance Status score of 0–2, who is scheduled to receive at least six outpatient regimens containing platinum, taxane, and vinca alkaloids. A total of 30 patients met these criteria. Patients who did not develop peripheral neuropathy were included. There was no age specification.

Exclusion criteria: Patients who had difficulty wearing wristband-type activity meters, using various measuring scales, and being interviewed, whether for physical or mental reasons. Physical reasons included severe adverse events associated with chemotherapy, such as nausea and general malaise, which make it difficult to participate in research, or physical problems, such as edema, which preclude the use of wristband-type activity of instrumentation. Mental reasons included conditions such as anxiety and depression and cognitive decline such as delirium and brain metastases that make it difficult to participate in the study.

Discontinuation criteria: When it becomes difficult to continue the study due to withdrawal of consent or discontinuation of treatment.

The survey period was from March 2021 to April 2022.

Measures

Measurement with a wristband activity measuring device

Day-time activity was measured by wearing a wristband device for 14 days, from the day of the second treatment in the early treatment period, and from the day of the fifth–sixth treatment in the middle of the treatment period. Measurements during the treatment period needed to be taken at least 2 months subsequent to the early treatment period. For the 2-week-interval treatment regimen, the day of the sixth treatment was used, and for the three- to four-week-interval regimen, the day of the fifth treatment was used. The activity meter was collected on the next outpatient day, and the data were transferred. From the activity meter, data on steps per minute and energy expenditure (EE) were collected. Participants were asked to wear the activity meter when they woke up in the morning, and not to remove it except when bathing, and to charge or turn off the power before going to bed in the evening. Normally, the clock was visible, and when the participant tapped it, the number of steps accumulated from 0:00, the power on/off screen, etc., became visible.

Furthermore, the effectiveness and safety of measurements obtained through this device have been verified.[18]

Questionnaires

Participants were instructed to fill in the preliminary questionnaire on the second treatment day. On the third (early-treatment periods) and sixth treatments (mid-treatment periods), they were asked to fill the Distress and Impact Thermometer (DIT),[19] Comprehensive Assessment Scale for Chemotherapy-induced Peripheral Neuropathy in Survivors of Cancer (CAS-CIPN),[20] Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-NTX) subscale,[21] Japanese version of the Falls Efficiency Scale – International (FES-I),[22,23] the General Self-Efficiency Scale (GSES),[24] and the Functional Assessment of Cancer Therapy-General (FACT-G).[25] If self-reporting was difficult, the investigator conducted an interview. In addition, the nurse inquired about stumbling or falling incidents during the third and sixth treatments. Information on the severity of numbness, assessed using Common Terminology Criteria for Adverse Events (CTCAE) for peripheral motor neuropathy and peripheral sensory neuropathy, was collected from the medical records.

DIT[19] is a validated self-administered questionnaire for screening adjustment disorders and depression in cancer patients. Points are assigned on a scale of 0–10 points; the higher the number of points, the greater the discomfort or disturbance. The cut-off value for distinguishing between adjustment disorders or depression and cases where psychiatric diagnosis is not possible, is a score of four or more for pain and three or more for disturbances, with a sensitivity of 0.82 and a specificity of 0.82.

CAS-CIPN[20] is a measure developed by Kanda et al.,[6] and its reliability and validity have been verified. It consists of 15 items and the following 4 sub-scales: 'Threatened interference in daily life by negative feelings', 'Impaired hand fine motor skills', 'Confidence in choice of treatment/management', and 'Dysesthesia of the palms and soles'. A 0–4 Likert scale, where 0 is the lowest score and 60 is the highest score, is used. The higher the score, the stronger the effect of peripheral neuropathy and its symptoms on life and feelings.

FACT/GOG-NTX[21] is an additional subscale of FACT-G, an 11-question survey of the neurotoxicity of taxane-based chemotherapy drugs. Its reliability and validity have been demonstrated with Cronbach's α 0.84–0.90. Each item is scored from 0 to 4 points to provide a total score out of 44, with higher scores indicating more severe neuropathic symptoms.

The Japanese version of the FES-I[22,23] scale measures how much care is taken on a regular basis to avoid falling, and its reliability and validity have been verified. The patient selected one of the four responses from

'Do not worry at all (1 point)' to 'Be very careful (4 points)' for the 16 items on the scale. The lowest score was 16 points, and the highest score was 64 points; the higher the score, the lower the self-efficacy for falls.

The GSES[24] is a scale that measures the strength of general self-efficacy of individuals in the various activities of their daily living. The reliability and validity have been verified. For each of the 16 items on the scale, the participants respond with a 'Yes' (1 point) if the item is true or a 'No' (0 point) if the item is untrue. The lowest score is 0, whereas the highest is 16. The higher the score, the higher the self-efficacy.

FACT-G[25] measures cancer-specific health-related QOL, and Cronbach's α for the entire scale was 0.89. Its subscales comprised of 27 items grouped into four factors: physical, functional, emotional, and social/-family well-being. It is scored on a four-point Likert scale, with higher scores indicating better QOL. There is a Japanese version, and its reliability and validity have been confirmed.[26]

Semi-structured interview survey

Awareness of physical and physiological changes, impact on activity, how activity was maintained during treatment, ingenuity, emotional changes, and factors concerning what cannot be done were included in the interview. The interview was conducted on the sixth or seventh treatments. The single interview was estimated to take about 30 minutes and was recorded with the consent of the participant. In addition, information on the participant's treatment information, age, CTCAE, and other general background information was obtained from interviews and medical records.

Data analysis

Activity meter and questionnaire survey

The activity meter data from 8 to 12 hours after waking up was used to calculate the mean (range) of steps in the early and mid-treatment periods, and the mean (range) of EE in the early and mid-treatment periods. The Wilcoxon signed-rank test was performed to compare the data obtained from the questionnaire on each scale using the third treatment day as the early treatment period and the sixth treatment day as the mid-treatment period. Furthermore, participants' mid-treatment stumbling or falling incidents and CTCAE (peripheral motor neuropathy, peripheral sensory neuropathy) were compared using the χ^2 test (Fisher-Freeman-Halton exact test).

All P-values were two-sided, and $P < 0.05$ were considered statistically significant. All analyses were performed using the IBM SPSS Statistics ver. software package.

Semi-structured interview survey

A qualitative inductive analysis was conducted on the relationship between the degree of numbness and activities (effects on daily life, effects on activities, ingenuity, and feelings).[27,28] The context describing the relationship between the degree of numbness and activity was extracted as a recording unit, summarized into a short sentence, and made into a code. Codes were integrated and categorized according to the similarity of the semantic content. Categories were combined relating to the similarity of the semantic content, and the theme was then developed.

Trustworthiness

The researchers referred to the verbatim records many times throughout all the steps of the analysis, and to ensure the trustworthiness of the analysis, the researchers held repeated discussions.

Ethical considerations

This study was conducted with the approval of the Ethical Review Board for Medical Research Involving Human Participants. All patients provided written informed consent prior to enrollment in the study. The purpose and objectives of the study were explained to the study participants using a written explanation, and their informed consent was obtained after confirming their voluntary participation and the protection of the confidentiality of their personal information. Interviews were discontinued or postponed based on nurses' judgment of the participants' physical and mental capacity to answer during the interview depending on their conditions.

Results

Participant overview

Study briefings were given to 29 patients, and consent was obtained from 14 (Fig. 1 and Table 1). However, one patient discontinued treatment, and one patient was unable to wear the activity meter in the second round due to increased mental anxiety regarding the treatment. Finally, after excluding one patient who wore the meter for less than one week, 11 patients were included in the analysis. However, for qualitative data analysis, the interviews of 12 participants were analyzed. The summary is shown in Table 1. At the end of the survey, for the CTCAE: Peripheral motor neuropathy, five patients had Grade 2, and for CTCAE: Peripheral sensory neuropathy, six had Grade 2, and eight responded that they had numbness. Five patients had tripped and two had fallen over the course of the study.

The comparison of trips and falls with CTCAE (motion and sensation) in the early treatment period showed no significant differences, nor was there a significant difference for either trips or falls in the mid-treatment period.

Activity meters and scales

The median early- and mid-treatment step counts for participants were 1759.63 (range 722.21–6931.29) and 2483.25 (range 1023.96–5937.99), respectively. The median EE of early-treatment periods for participants was 785.41 (range 339.39–6931.29), while the median mid-treatment EE was 941.98 (range 567.68–1372.65) (Fig. 2, Table 2). The mid-treatment phase showed a higher count when

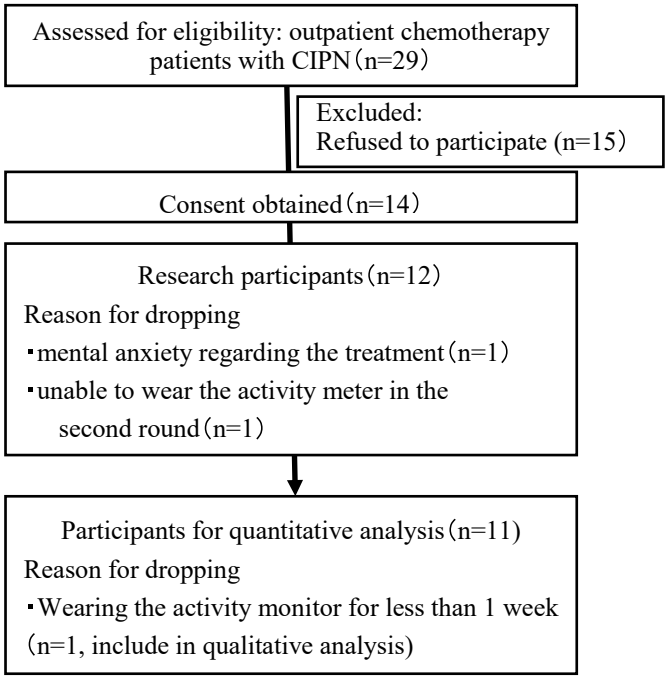

Fig. 1. Flow diagram of the participants selection.

Table 1
Participants overview.

Index			$n = 11$	%
Gender	Male		5	45.5
	Female		6	54.5
Age (year)	Range		42–73	
	Mean		57.7	
	Standard deviation		9.2	
Diagnosis	Gastrointestinal cancer		5	45.5
	Gynecological cancer		5	45.5
	Malignant lymphoma		1	9.1
Disease stage	I		4	36.4
	II		2	18.2
	III		1	9.1
	IV		4	36.4
Drugs used	XELOX		4	36.4
	TC		4	36.4
	Bv + FOLFOXIRI		1	9.1
	DC		1	9.1
	R-CHOP HD-MTX,IT		1	9.1
Metastasis/recurrence	No		5	45.5
	Yes		6	54.5
Complications	No		7	63.6
	Yes		4	36.4
Living together	No		1	9.1
	Yes		10	90.9
	With elementary school child/children		1	9.1
	With junior high school child/children		4	36.4
Academic background	Junior high/high school		6	54.5
	Vocational school		2	18.2
	Junior college/university		3	27.3
Treatment purpose	Healing		6	54.5
	Progression control		5	45.5
PS	Early treatment	0	4	36.4
		1	6	54.5
		2	1	9.1
	Mid-treatment	0	4	36.4
		1	6	54.5
		2	1	9.1
CTCAE: Peripheral motor neuropathy	Early treatment	0	2	18.2
		1	6	54.5
		2	3	27.3
	Mid-treatment	0	3	27.3
		1	3	27.3
		2	5	45.5
CTCAE: Peripheral sensory neuropathy	Early treatment	0	2	18.2
		1	5	45.5
		2	4	36.4
	Mid-treatment	0	3	27.3
		1	2	18.2
		2	6	54.5
Employment	Early treatment	Full time	3	27.3
		Leave of absence	6	54.5
		Housewife	1	9.1
		Unemployed	1	9.1
	Mid-treatment	Full time	4	36.4
		Leave of absence	4	36.4
		Housewife	1	9.1
		Unemployed	2	18.2
Daily life	Early treatment	Sitting	4	36.4
		Standing	5	45.5
		Walking	2	18.2
	Mid-treatment	Sitting	5	45.5
		Standing	4	36.4
		Walking	2	18.2
Leisure activities	Early treatment	No	4	36.4
		Yes	7	63.6
	Mid-treatment	No	4	36.4
		Yes	7	63.6
DIT: Distress	Early treatment	0–3	8	72.7
		over 4	3	27.3
	Mid-treatment	0–3	9	81.8
		over 4	2	18.2
DIT: Impact	Early treatment	0–2	10	90.9
		over 3	1	9.1
	Mid-treatment	0–2	10	90.9
		over 3	1	9.1

(*continued on next page*)

Table 1 (*continued*)

Index			$n = 11$	%
Tripping/stumbling		No	6	54.5
		Yes	5	45.5
Falling		No	9	81.8
		Yes	2	18.2
Numbness	Early treatment	No	1	9.1
		Yes	10	90.9
	Mid-treatment	No	3	27.3
		Yes	8	72.7

PS, performance status; CTCAE, Common Terminology Criteria for Adverse Events; DIT, Distress and Impact Thermometer.

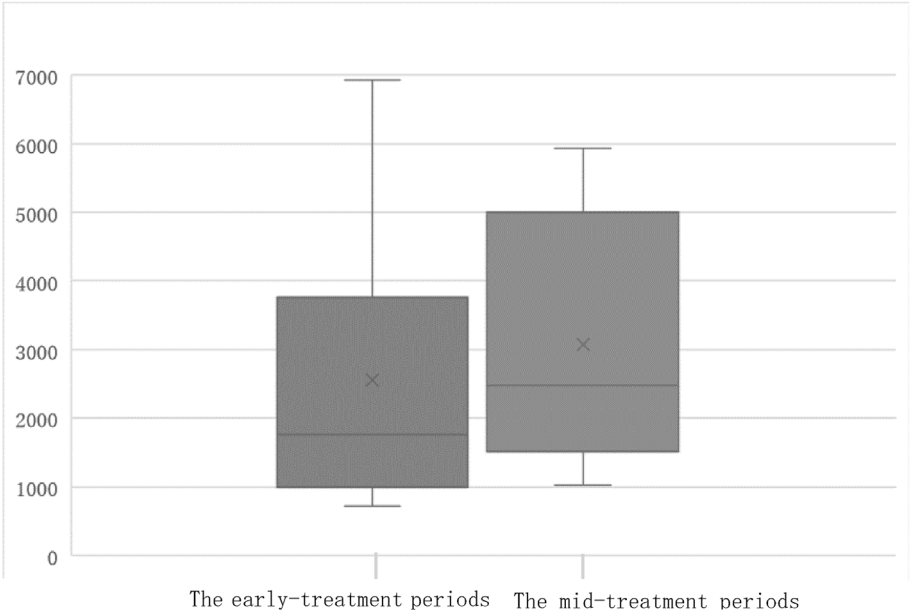

Fig. 2. Box plot of the number of steps in the early and mid-treatment periods.

compared with the step count of the early-treatment periods, although it was not statistically significant ($P = 0.050$). Similarly, the mid-treatment EE was higher than the EE of the early-treatment periods, but no statistically significant difference was observed ($P = 0.182$) (Fig. 3).

A comparison of the number of steps and EE of the participants in the early treatment period showed a correlation ($r = 0.781$). A correlation was also observed between the number of steps in the mid-treatment period and EE in the mid-treatment period ($r = 0.883$).

Comparison of treatment for each scale for the early and mid-treatment periods showed no significant differences for the peripheral neuropathy scale, GSES, or the QOL scale. However, with the Distress and Impact Thermometer, the distress levels in the early-treatment phase tended to be higher than in the mid-treatment phase, although the difference was not statistically significant ($P = 0.059$). The impact in the early-treatment phase was significantly higher than in the mid-treatment phase ($P = 0.034$) (Table 3).

Participant awareness

Participants' perceptions of the relationship between the degree of CIPN and activities were based on three themes: Safety considerations, balance between activity and rest, and their acceptance of life changes due to numbness.

Table 4 shows the participants' history of trips and falls, the degree of numbness, the degree of pain and hindrance, the number of steps, EE, and a list of categories. There was no correlation between the status of their history of trips or falls and safety considerations for the swaying caused by numbness. Even among participants with CTCAE grade 2 or higher or high DIT, there were some who spoke of the category of 'even numbness does not interfere with activity.' Participants with reduced steps and EE did not necessarily respond that they were aware of decreased exercise due to numbness or that they would rest comfortably when the numbness was strong.

Table 2
Comparison of number of steps and EE between the early- and the mid-treatment periods.

	Early-treatment periods		Mid-treatment periods		*P*	Z	*r*
	Median ± IQR	Range	Median ± IQR	Range			
Steps	1759.63 ± 2765.73	722.21–6931.29	2483.25 ± 3496.23	1023.96–5937.99	0.050	1.956	0.59
EE	785.41 ± 502.88	339.39–6931.29	941.98 ± 509.95	567.68–1374-65	0.182	1.334	0.40

Wilcoxon signed-rank test. EE, energy expenditure; IQR, interquartile range.
*$P < 0.05$.

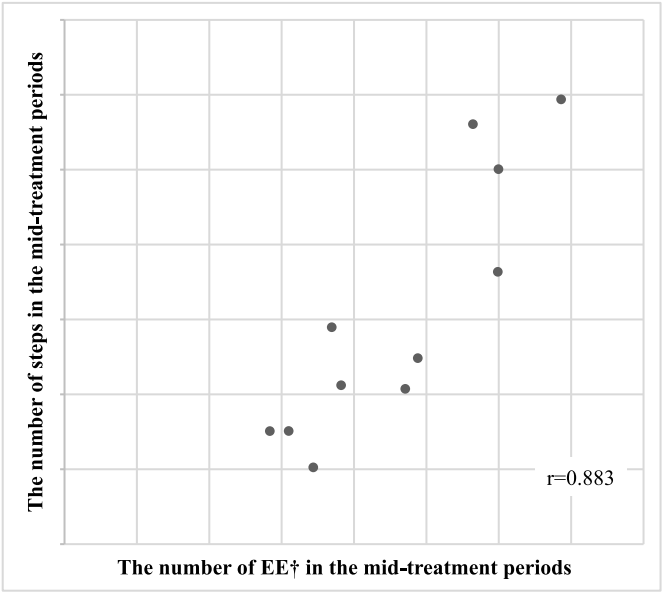

Fig. 3. Correlation diagram between the number of steps in the mid-treatment periods and the number of EE in the mid-treatment periods. Note: † Divide the EE value by two to get an estimate of METs, which indicates the intensity of exercise. EE, energy expenditure.

Consideration for safety of sway caused by numbness

This theme was extracted from the categories of difficulty in driving due to numbness, unexpected falls due to numbness, ingenuity to prevent falling due to numbness in the legs, and cooperation from family members to prevent falling.

The participants reported the danger of driving cars and bicycles owing to numbness in their hands and feet.

> *I used to commute by bicycle before I started the treatment, but after I started the treatment, I decided to commute by car because I thought it might be dangerous to ride a bicycle. Even if I had numbness, I could not hold the steering wheel of a bicycle in the cold of winter. I couldn't even grip the steering wheel without gloves. I tried to take measures against the cold as much as possible, or to commute by car considering the feeling. (P11, male)*

Some participants also stumbled on stairs and flat floors. Participants had devised ways not to fall, such as trying not to wear slippers and using handrails and canes.

> *(I don't think I would stumble), but I was worried so I didn't go upstairs. If I stumble, I'll be in trouble, so I try to finish things on the first floor as much as possible …. But after all, it's scary when going down the stairs. So I rushed to have a handrail installed. I wear these thick socks instead of slippers. Slippers are dangerous, aren't they? (P6, female)*

They also asked their family members to take the lead when walking their dogs.

Balance between activity and rest

This theme was extracted from the categories of awareness of decreased exercise due to numbness, difficulty with work due to numbness, how to avoid worsening of numbness due to cold while working, using information from health care providers to help you cope, devices for continuing exercise as much as possible, resting without overdoing when numbness is strong, and even numbness does not interfere with activity.

The participants noticed a decline in their ability to walk and other physical activities, and found it difficult to drive or use a keyboard, which hindered their work. The participants took measures against the cold, such as wearing triple gloves, and referring to the numbness pamphlet that they received from the medical staff at the beginning of the treatment.

In addition, the participants continued exercises such as taking a walk even for a short distance.

> *(Even before the treatment) I didn't do much exercise, but I went for a walk when I was off. (Numbness appears) I walk slowly and take care to walk from my heels. You can't walk without being conscious of it. I really understand that my physical strength is declining, so I have the feeling that I have to improve my physical strength even a little while on foot. I devise ways to walk. (P3, female)*

The participants ensured a balance between activities and rest by taking a rest when exercising was difficult.

The participants were aware of their numbness, but some said that this was not a major hindrance to their activities.

> *The numbness has gone away over time, and now I don't have to be nervous to move around so much at home. When I was in the hospital, I had to hold on to (the handrails) because the hallways were long, but after I was discharged from the hospital, I surprisingly felt that I was able to (walk even without the handrails). I don't care about it at all now. … Even though I said it was numb, I didn't really feel like I was going to fall or that I actually fell, so I didn't have to be all that nervous. (P4, female)*

Acceptance of a life that has changed due to numbness

This theme was formed from the following categories: alleviation of anxiety by knowing when numbness is due to occur, as a result of the progress in treatment even if activity is reduced; change in feelings to normal even if numbness affects activity; feeling relieved by the support of family, friends, and close friends in the workplace; feeling relieved even if numbness occurs due to the trust in the medical personnel; and

Table 3
Differences between the early and mid-treatment periods for each scale.

	Early-treatment periods		Mid-treatment periods		*P*	Z	*r*
	Median ± IQR	Range	Median ± IQR	Range			
DIT							
Distress thermometer	1 ± 5	0–5	1 ± 2	0–5	0.059	−1.890	0.57
Impact thermometer	1 ± 2	0–4	0 ± 1	0–3	0.034[a]	−2.121	0.64
CAS-CIPN	10 ± 6	4–38	12 ± 10	1–42	0.688	−0.401	0.12
FACT/GOG-NTX	3 ± 4	0–19	4 ± 6	1–25	0.443	0.767	0.23
FES-I	21 ± 23	16–55	20 ± 16	16–46	0.180	1.341	0.04
GSES	10 ± 4	2–15	10 ± 3	3–16	0.796	−0.259	0.08
FACT-G	86 ± 12	69–104	90 ± 22	57–107	0.953	0.059	0.02

Wilcoxon signed-rank test. DIT, Distress and Impact Thermometer; CAS-CIPN, Comprehensive Assessment Scale for Chemotherapy-induced Peripheral Neuropathy; FACT/GOG-NTX, Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group – Neurotoxicity; FES-I, Falls Efficiency Scale – International; GSES, General Self-Efficiency Scale; FACT-G, Functional Assessment of Cancer Therapy-General; IQR, interquartile range.

[a] $P < 0.05$.

Table 4
Relationship between the degree of numbness and activities.

		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
Items	Presence of stumbling and falling: Yes			✓	✓	✓			✓			✓	
	CTCAE (motor or sensory) at the end: two or more			✓	✓		✓	✓	✓			✓	
	DIT: Distress four or higher or impact three or higher			✓					✓				✓
	Numbness at the end: Yes		✓	✓	✓	✓	✓	✓	✓			✓	
	Decrease in total number of steps: Early stage > middle stage	✓				✓							N/A
Themes	Categories												
Consideration for safety of sway caused by numbness	Difficulty in driving due to numbness								✓		✓	✓[a]	✓
	Unexpected falls due to numbness			✓		✓	✓		✓				
	Ingenuity to prevent falling due to numbness in the legs	✓		✓	✓		✓[a]		✓				
	Cooperation from family members to prevent falling	✓					✓		✓				
Balance between activity and rest	Awareness of decreased exercise due to numbness	✓			✓	✓		✓				✓	
	Difficulty with work due to numbness			✓								✓	✓
	How to avoid worsening of numbness due to cold while working			✓				✓	✓	✓	✓	✓	
	Using information from health care providers to help you cope				✓						✓		✓
	Devices for continuing exercise as much as possible			✓[a]			✓		✓				
	Resting without overdoing when numbness is strong				✓				✓			✓	✓
	Even numbness does not interfere with activity		✓		✓[a]	✓	✓	✓		✓	✓		✓
Acceptance of a life that has changed due to numbness	Alleviation of anxiety by knowing when numbness is due to occur, as a result of the progress in treatment even if activity is reduced				✓			✓					
	Change in feelings to normal even if numbness affects activity		✓		✓				✓[a]		✓		
	Feeling relieved by the support of family, friends, and close friends in the workplace		✓	✓	✓		✓		✓	✓	✓		
	Feeling relieved even if numbness occurs due to the trust in the medical personnel	✓		✓	✓		✓	✓[a]		✓		✓	
	Feeling relieved when medical personnel understand numbness that other people do not understand			✓					✓			✓[a]	

CTCAE, Common Terminology Criteria for Adverse Events.
[a] Examples of participant narratives.

feeling relieved when medical personnel understand numbness that other people do not understand.

As treatment progressed, participants were able to know when anticancer drugs were administered, when numbness was strong, and when it reduced, so they did not feel depressed.

The participants adjusted their perspectives by thinking that this was normal, even if numbness was present.

> *I'm getting used to the feeling that this is normal for me. So I was a little more careful in dangerous areas such as when I feel lightheadedness. There are things like the paper can't turn over, and I don't know how many banknotes I have taken out. Maybe this is who I am in myself. When I started to accept that this is normal, I didn't care so much about it. (P8, female)*.

The participants felt supported by their close friends. The participants felt a sense of security even when they felt numbness by trusting medical professionals.

> *The doctor told me a very good thing beforehand, 'If it's really difficult, there are options to reduce the dose or stop the medicine, so don't worry'. I think that is the fine play of the doctor. Doctor counseling should be commended. When I see the doctor's face, I feel like my illness will get better. It's true. There is a great sense of security. (P7, male)*

The participants felt relieved that the medical professionals understood the symptoms of numbness, which were difficult for friends and family to understand.

> *Even if I tell my (partner) or other people about it, they won't understand (about numbness) ….Actually, it is difficult to tell a third party about the inconvenience caused by numbness. It's hard to express in words how and where I'm having trouble.…However, the nurses here take this kind of feeling with nuance, so it's worth saying. That makes it much easier for me mentally. The nurses here are great. (P11, male)*

Discussion

Discussion of this study

Objective analysis of CIPN and volume of activity

At the end of the survey, approximately half of the participants had CTCAE grade 2, and 70% of the participants reported having numbness. However, they were able to continue leisure activities, and social activities, including regular work, were maintained. Although participants' step count between the early- and mid-treatment phases showed no significant difference, the number of steps and EE increased in the mid-treatment phase compared to the early-treatment phase. These results contradict initial predictions that CIPN would restrict activity and reduce the amount of activity. The reason for this is thought to be that the patients were able to get used to CIPN and cope with it, and were able to maintain motivation by wearing the activity meter.[29] There was a correlation between step count and EE in both the early- and mid-treatment phases. The step count and EE of the early-treatment phase showed significant variability, reflecting the individual's baseline physical activity and motivation. However, step count variability and EE decreased in the mid-treatment phase. This might indicate that wearing the activity tracker motivated participants with initially low awareness of their activity. However, despite numbness, the overlapping side effects of treatment may have hindered participants who were previously active from maintaining the same activity levels.

In Distress and Impact Thermometer Scales comparison, the impact of the early-treatment phase was higher than the mid-treatment phase, and a significant difference was observed ($P = 0.034$). Although the actual level of visible activity did not increase, participants engaged in activities within their abilities. Numbness did not significantly affect their daily life. This might be related to the increased step count in the mid-treatment phase compared to the early-treatment phase, even though the difference was not statistically significant. Engaging in physical activity from the early stages of treatment may contribute to the alleviation of CIPN,[30] and the use of activity trackers in this study might have played a role in mitigating numbness.

Becoming familiar with and coping with CIPN

The number of participants who answered that they had numbness decreased from 10 to 8 by the mid-treatment treatment. In the interview survey, the category of anxiety reduction by knowing the time of the numbness in which the treatment progresses even if activity decreased, and the change in feelings to normal, even if the activity was affected by the numbness occurred. In addition, many participants stated that the category of numbness did not affect their activities significantly, suggesting that they had become accustomed to CIPN.

Participants also took measures to prevent falling due to the numbness in their feet, to keep exercising as much as possible, and to avoid exacerbation of the numbness due to being cold. This is consistent with previous research showing that patients actively seek ways to manage their CIPN symptoms.[31,32] Patients adapt by getting used to it.

The participants felt relieved to receive support from family, friends, close colleagues, and medical professionals. Previous studies have pointed to challenges in symptom management, with clinicians 'ignoring' CIPN and focusing on pharmacological approaches to managing pain, without providing practical advice.[31,33] The category 'Feeling relieved when medical personnel understand numbness that other people do not understand' is considered to be a characteristic of this study. Trust in health care providers is key for patients to accept the changes in their lives due to CIPN. This can lead to openness between patients and clinicians in symptom reporting, information provision, and CIPN management.[32]

Patients accepting CIPN and employing their own strategies to alleviate and manage it have been shown in previous studies to re-establish a satisfactory level of well-being.[34] Although regular walking has been perceived by patients as reducing CIPN symptoms, there is a lack of information regarding a walking regime that works for neurotoxicity impairments, as noted in previous studies.[35] Thus, it is important to consider investigating the relationship.

Effects with wearing an activity meter

The consent rate for this study was 48.3%, and it is possible that patients who were interested in, and motivated to participate in the study were selected. In addition, having participants wear activity meter for a total of 4 weeks at an interval of two weeks may have had an effect on maintaining the participants' interest and motivation in their activities. The activity meter used this time showed the number of steps and displayed this to the participants in real time. It is not known how often the participants checked the number of steps, but at least due to the timing of charging at night, and turning off the power, it is likely that they observed the number of steps for the day at those times. Therefore, it is considered that the activity meter led the participants to self-monitor the number of steps taken per day, and maintained their interest in and motivation regarding the activities.

In other words, it was shown that self-monitoring of the number of steps per day may prevent decreased activity without exercise therapy, or instruction in the activity program. We believe this is an epoch-making discovery. The reason is that many exercise therapies and activity programs combine aerobic, strength, balance training, and yoga, and they require experts' guidance.[10,11,36,37] Outpatient chemotherapy rooms operate with a limited amount of time and personnel, and do not necessarily have rehabilitation staff. The results of this study have important implications because of the urgency in establishing intervention methods to maintain activity levels, without experts in exercise therapy. In addition, we measured both the number of steps and EE in

this study, and there was a correlation between the two. As such, it is evident that measuring the number of steps alone could assess physical activity levels. Pedometers are inexpensive and simple, and can also be measured with a smartphone. Therefore, this can also be applied in Low-income countries where a survey of the volume of activity using a pedometer is required. CIPN has been noted to have an impact on QOL and social life such as household chores, sleep, social activities, hobbies, sports, and work.[38,39] Maintaining an active level can be expected to have the effect of alleviating the impact of CIPN on social life, and future research is required.

Implications for nursing practice and research

It was shown that self-monitoring of the number of steps per day may prevent decreased activity without exercise therapy, or instruction in the activity program. The simple method of a pedometer is expected to facilitate self-monitoring by patients and to prevent activity from decreasing in the presence of CIPN. Intervention studies using pedometers are required in the future to help patients with CIPN maintain their level of activity.

Limitations

This study is limited in its generalizability because it had a limited number of participants. Additionally, it is unclear how treatments to alleviate CIPN affected study results. It is necessary to collect data from a variety of facilities and treatment modalities in order to develop more effective interventions used by an activity meter in the future. In addition, it is necessary to clarify not only the effects of maintaining and increasing activity on the strength of CIPN, but also the effects on patients' social lives.

Conclusions

This study was a prospective study to determine the effect of CIPN on the degree and amount of activity during treatment in patients using drugs that cause CIPN. At the end of the survey, approximately half of the participants had CTCAE grade 2, and 70% of the participants reported having numbness. Five had tripped and two had fallen over the course of the study. There was no significant difference between CTCAE and slips or falls. There was no significance in the comparison of the number of steps in the early treatment period and in the mid-treatment period of the participants, but this increased in the mid-treatment period. Even though there was no significant difference, the comparison of EE between the early- and mid-treatment periods showed an increase in the mid-treatment period. Further, there was a correlation between the number of steps of the participants and EE. The distress and impact on the thermometer scale comparison between the early- and mid-treatment periods showed a significant difference in impact ($P = 0.034$). Participants' perceptions of the relationship between the degree of CIPN and activities were based on three themes: Safety considerations, balance between activity and rest, and acceptance of the life changes due to numbness. The results contradict early predictions that CIPN would restrict activity and reduce the amount of activity. We think that the reason for this was that the patients became accustomed to and coped with CIPN and maintained their motivation by wearing the activity meter. The simple method of a pedometer is expected to facilitate self-monitoring by patients and to prevent activity from decreasing in the presence of CIPN.

Ethics statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Gunma University (IRB No. HS2020-220), the Ethics Committee of Medical Corporation Hidaka-kai Hidaka Hospital (IRB No. 337), the Ethics Committee of Iwate Prefectural University (IRB No. 297) and the Ethics Committee of Iwate Prefectural Central Hospital (IRB No. R3-Jinsoku-29). All participants provided written informed consent.

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CRediT authorship contribution statement

Ayumi Kyota: Conceptualization, Methodology, Software, Investigation, Data curation, Formal analysis, Writing – original draft, Visualization. **Taeko Kinjo**: Validation, Investigation, Data curation, Formal analysis, Writing – original draft, Visualization. **Kiyoko Kanda**: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Mai Hosokawa**: Validation, Investigation, Methodology, Writing – review & editing. **Daisuke Higuchi**: Methodology, Validation, Formal analysis, Resources, 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 that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, Ayumi Kyota, upon reasonable request.

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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