

Physical Impairments, Sensory Disturbance and Functional Ability in Cancer Patient With and Without Chemotherapy-induced Peripheral Neuropathy Symptoms

Nida Rattanakrong

Chulabhorn Hospital

Noppawan Promma

Chulabhorn Hospital

Chanatsupang Saraboon

Chulabhorn Hospital

Pooriput Waongenngarm (✉ golffy_pw@hotmail.com)

HRH Princess Chulabhorn College of Medical Science <https://orcid.org/0000-0001-5653-3509>

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Abstract

Objective

The present study examined the objective and patient-reported measures of physical impairments, sensory disturbance and functional ability between cancer patients with and without chemotherapy-induced peripheral neuropathy (CIPN) symptoms.

Methods

41 cancer survivors exposed to neurotoxic chemotherapies were conveniently recruited and completed a single cross-sectional assessment of patient-reported outcomes (VAS for pain intensity and ABC scale) and objective assessments (SWM test, TUG test, 5xSTS test, Romberg test with eyes open and eyes closed, 6MWT, and FAB scale).

Results

Cancer patients who had undergone chemotherapy with CIPN symptoms did significantly worse in the SWM test, TUG test, 5xSTS test, Romberg test with eyes closed, 6MWT, FAB scale, and ABC scale ($p < 0.05$) when compared with cancer survivors without CIPN symptoms.

Conclusion

Cancer survivors with CIPN symptoms have lower physical performance, sensory perception, and functional ability, which may increase the risk of falling and disability. These findings further emphasize the need for effective rehabilitation and interventions to treat CIPN symptoms and related physical impairment and functional deficits.

Introduction

The chemotherapy-induced peripheral neuropathy (CIPN) is the most frequently disabling side effect of neurotoxic chemotherapy agents [1]. The previous systematic review and meta-analysis study showed that the prevalence rate of CIPN symptoms ranges from 19%-85%, which was highest in the first month after chemotherapy (68.1%), still persisted after three months (60.0%), and fell to half at six months or more (30.0%) [2]. Chemotherapy agents, especially taxane and platinum compounds, are associated with a high prevalence of CIPN symptoms, ranging from 71%-83% [3, 4]. Several studies have indicated many clinical risk factors associated with CIPN including the specific drug, dose, schedule, and therapy duration [5–7]. CIPN symptoms can precipitate the premature cessation of chemotherapy, which may increase the risks of morbidity and mortality [8, 9].

Falls are associated with the morbidity and mortality rate in patients with cancer [10, 11]. One previous systematic review suggested that patients with cancer are at higher risk of falls than the general population [12]. Moreover, cancer patients who receive neurotoxic chemotherapy are at greater risk of fall

than those who are not [13]. A previous study showed that patients with CIPN symptoms have a higher risk of falling of three times or more, [14] as evidenced by increased mean Time Up and Go (TUG) scores and decreased gait performance (gait speed and step length) [15]. Patients with persistent CIPN symptoms have been identified as experiencing greater functional limitations, greater disability, increased risk of falling and increased of health care utilization [16]. Moreover, many studies have reported that the functional ability of cancer survivors who receive neurotoxic chemotherapy agents decreases, such as a decrease in the 6 minute walk test (6MWT) distance [17], worse short physical performance battery scores [16], lower Fullerton Advanced Balance (FAB) scales and increased TUG times [18].

Cancer patients with CIPN symptoms usually present sensory impairments (reduction of sensation and perception of joint position) as early symptoms [19, 20]. The Semmes–Weinstein monofilaments (SWM) test is a screening tool for identifying sensory impairment (tactile dysfunction) and is commonly used to detect sensory impairment in a variety of patients, including patients with CIPN symptoms, diabetes and leprosy [21–23]. Although motor impairments such as lower limb muscle weakness, cramp, foot drop are uncommon in patients with CIPN, previous studies found that such individuals with CIPN symptoms with motor impairments are at increased risk of falls [24]. The five-time sit to stand (5xSTS) test is a valid and reliable measurement tool commonly used to assess lower-extremity strength and balance [25, 26]. Moreover, Winter-stone et al. indicated a high severity of CIPN symptoms associated with increased time to complete the 5xSTS test [16].

To date, there has only been a few studies investigating the physical impairments and functional limitations in cancer patients with and without CIPN symptoms. Therefore, the purpose of this study was to investigate the objective and patient-reported measures of physical impairments, sensory disturbance and functional limitation between cancer patients with and without CIPN symptom. The hypothesis of this study was that there are differences in physical impairments and functional limitations between cancer patients with and without CIPN symptoms. Such information would provide oncology teams information for use in screening patients for referral to rehabilitation teams.

Materials And Methods

Participants

Forty-one cancer patients who received a complete course of chemotherapy treatment were conveniently recruited. Participants were recruited from Chulabhorn hospital in Bangkok, Thailand. Individuals were included if they were 20–70 years of age, had an ECOG score ≤ 2 , had completely received chemotherapy treatment within 30 days, and were able to read and understand the Thai language. Exclusion criteria were bone metastasis, brain metastasis, bleeding precaution, nerve compression syndrome, current or past history of underlying diseases that affect neurological deficits (i.e., diabetes mellitus, HIV, alcoholism, SLE, GBS, inherited disorder, or vitamin deficiency). Additionally, our classification of patients with or without CIPN symptoms was based on CTCAE version 5.0 score, which was obtained during the screening procedure. All subjects were provided information about the study and signed an informed

consent form prior to their participation. The study was approved by the Human Research Ethics Committee of Chulabhorn Research Institute (028/2560).

Measures and procedures

Demographics and cancer status

All outcomes used for this analysis were obtained from baseline data collected before patients were allocated to the CIPN or non-CIPN groups. Participants were asked to report age, gender, type of cancer, cumulative dose of chemotherapy drugs, and pain score using the 100-mm visual analogue scale (VAS). The CTCAE sensory version 5.0 was used to assess the severity of CIPN [27]. The CTCAE grade is a 5-point Likert scale; a grade of 2 is associated with impairment of activities associated with normal daily living. Therefore, in this study, the CTCAE score was used to classify patients with CIPN symptoms (≥ 2 score) and without CIPN symptoms (<2 score).

Semmes-Weinstein monofilaments (SWM) test

The sensory assessment was tested using Semmes-Weinstein monofilaments (SWM) (Monofilament, Berlin Pharmaceutical Industry, Bangkok, Thailand). The SWMs are used to determine light touch sensation in various populations [21–23]. In this study, the SWM testing was performed with monofilament 5.07 (10g) applied to the surface of the skin in an up-down fashion on both feet of the subject. The assessment was conducted in a quiet setting and subjects were instructed to close their eyes during the test. First, the monofilament was applied to the subject's forearm and they were asked about the feeling and location of the test to ensure the subject's understanding. All subjects were tested at four points in both feet three times including the plantar surface of the hallux, and the first, third, and fifth metatarsal heads in each foot. The monofilament was applied to the skin for approximately 1.5 seconds in each area. Subjects were asked to name the exact location where a monofilament was detected. If subjects perceived the test location correctly 2 out of 3 times, the subject's sensory score was noted as intact.

Timed Up and Go (TUG) test

The Timed Up and Go (TUG) test was used to determine functional mobility and the ability to maintain balance while walking. The TUG was measured using a standard chair (seat height 43 cm) and the subject's usual walking aid. The subject was asked to get up from the chair, walk 3 meters to a line of colored tape on the floor, turn around and return to the chair, and sit back down. The stop watch was started when the subject's buttocks lifted from the seat, and the timing was completed when the buttocks retouched the chair.

Five-time sit to stand (5xSTS) test

The five-time sit to stand (5xSTS) test was used to measure functional ability and lower limb muscle strength. Participants were asked to stand up from a standard chair (seat height: 43 cm) as quickly as

possible for five times without any hand support. The time to finish 5xSTS was recorded as an outcome measure.

Romberg test

The body's sense of positioning (proprioception) was measured by using the Romberg test, which is a part of the standard neurological assessment. A positive result of the Romberg test indicates the presence of a neurological disease. Participants were instructed to remain still with both feet together and cross their arms for a period of 30s. The researcher asked the participants to perform the test twice (open eyes and closed eyes). The test was initiated when the participants assumed the correct position and stopped when they moved their feet, lost the positioning of their upper limbs, or opened their eyes. The duration for which the subjects could maintain balance was defined as the balance time (in seconds).

6-minute walk test (6MWT)

The 6-minute walk test (6MWT) was performed according to international guidelines. Participants were instructed to walk at their own pace while attempting to cover the greatest distance possible. Standardized encouragement was provided every minute by telling the patients either "You are doing well" or "Keep up the good work" and informing them of the remaining time. The tests were supervised by qualified staff that walked behind the participant. Participants were permitted to stop (if required) during the test but were also instructed to resume walking once able. The 6MWT was registered in meters and patients were allowed to use their walking aids during the tests.

Fullerton advanced balance scale (FAB)

The Fullerton advanced balance scale (FAB) was used to test the functional balance state of individuals. The FAB scale is a balance scale with a 5-point ordinal scale (0–4) for each item and a maximum score of 40 points (higher values indicate better performance). The FAB scale consists of 10 items: balancing with the feet together and eyes closed, forward reach, turn 360 degrees, stepping up, onto and over a 6-inch bench, tandem walk, standing on one leg, standing on foam with eyes closed, two-footed jump, walking with head turns, and postural reaction.

Activities-Specific Balance Confidence scale (ABC scale)

The Activities-Specific Balance Confidence scale (ABC scale) is used to measure the balance confidence of a patient during performing various activities. The ABC scale is a 16-item self-report questionnaire, which is rated on a scale ranging from 0-100 (0 denotes no confidence and 100 denotes complete confidence).

Statistical analysis

Participants' characteristics, type of cancer, cumulative dose of chemotherapy drugs, and pain score, and number of CIPN and non-CIPN cases were described by means or proportions. The independent t test for continuous data and the chi-square test for non-continuous data were used to determine baseline group differences. The Shapiro-Wilk test was performed to check the distribution of data, the results indicated

non-normal distribution. Therefore, the physical impairment and functional ability data between CIPN and non-CIPN groups were analyzed by the Mann-Whitney U test. All statistical analyses were conducted using SPSS statistical software, version 23.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was accepted for values of $p < 0.05$.

Results

A total of 41 cancer patients participated in the study. Table 1 presents the characteristics of the participants. The sample population comprised mainly middle-aged females. Their average BMI was in the normal range. The majority of participants (56%) had breast cancer. Of the participants 46% received 6 cycles of chemotherapy drugs (3 weeks between cycles). According to the CTCAE sensory score, 13 participants were classified as belonging to CIPN group and 28 participants to the non-CIPN group. There were no significant differences in any of the characteristics of the participants between two groups, except for CTCAE sensory, CTCAE motor, and pain score using VAS. All of the patients in this study were able to walk without assistance or mobility aids.

Table 1
Demographic data in the CIPN group and non-CIPN group. (n=41)

Characteristics	CIPN group (n=13)	Non-CIPN group (n=28)	P- value
Age (years; mean (SD))	57.62 (10.9)	52.07 (10.3)	0.123
Gender (N (%))	1 (7.7)	2 (7.1)	0.950
Male	12 (92.3)	26 (92.9)	
Female			
Body mass index (kg/m ² ; mean (SD))	25.45 (4.0)	23.21 (3.5)	0.074
Type of cancer (N (%))	6 (46.2)	17 (60.7)	0.543
Breast cancer	6 (46.2)	8 (28.6)	
Gynecologic cancer	1 (7.6)	3 (10.7)	
Lung cancer			
Cumulative dose of chemotherapy drugs (mg/m ² ; mean (SD))	1446.64 (314.4)	1463.31 (290.0)	0.872
Duration of receiving chemotherapy drugs (N (%))	1 (7.7)	5 (17.8)	0.719
12 weekly	5 (38.5)	10 (35.7)	
4 cycles	7 (53.8)	12 (42.9)	
6 cycles	0	1 (3.6)	
9 cycles			
CTCAE Sensory (N (%))	0	5 (17.9)	0.000*
Score 0	0	23 (82.1)	
Score 1	11 (84.6)	0	
Score 2	2 (15.4)	0	
Score 3			
CTCAE Motor (N (%))	1 (7.7)	10 (35.7)	0.004*
Score 0	7 (53.8)	18 (64.3)	
Score 1	3 (23.0)	0	
Score 2	2 (15.4)	0	
Score 3			
Pain score using VAS (mean (SD))	0.26 (0.88)	2.02 (2.65)	0.036*

* p<0.05

Physical impairment and functional performance

Table 2 summarizes the results of the monofilaments test, Timed Up and Go test, 5-time sit to stand test, Romberg test, 6-minute walk test, Fullerton advanced balance scale, and Activities-Specific Balance Confidence Scale in the CIPN and non-CIPN groups.

The Mann-Whitney U test revealed there was a significant difference in the SWM test, TUG test, 5xSTS test, Romberg test with eyes closed, 6MWT, FAB scale, and ABC scale between CIPN and non-CIPN groups ($p<0.05$). No significant difference was found in the Romberg test with eyes open.

Table 2

Mean (SD) of monofilaments test, Timed Up and Go test, 5-time sit to stand test, Romberg test, 6-minute walk test, Fullerton advanced balance scale, and Activities-Specific Balance Confidence Scale in the CIPN and non-CIPN groups

Variables	CIPN group (n=13)	Non-CIPN group (n=28)	P-value
Semmes-Weinstein monofilaments test	3.92 (3.0)	7.29 (1.6)	0.000*
Timed Up and Go test	12.72 (4.9)	7.99 (1.8)	0.001*
5-time sit to stand test	16.71 (6.9)	12.03 (3.1)	0.015*
Romberg test	28.37 (5.9)	30.00 (0.0)	0.142
Eyes open	25.92 (9.4)	30.00 (0.0)	0.009*
Eyes closed			
6-minute walk test	295.54 (93.5)	400.29 (57.5)	0.000*
Fullerton advanced balance scale	26.23 (10.1)	36.93 (3.1)	0.000*
Activities-Specific Balance Confidence Scale	66.27 (17.9)	92.25 (10.3)	0.000*

* p<0.05

Discussion

The present study demonstrated the physical impairments, sensory disturbance and functional ability between cancer patients with and without CIPN symptoms. The Mann-Whitney U test was used to evaluate the differences in the SWM test, TUG test, 5xSTS test, Romberg test, 6MWT, FAB scale, and ABC scale between CIPN and non-CIPN groups. The findings of this study showed that cancer patients with CIPN symptoms had significantly more physical impairment, sensory disturbance, and functional limitation, which may partly lead to a fall in patients with CIPN symptoms.

Our results indicated the monofilaments score in the CIPN group was significantly lower than those in the non-CIPN group. SWM test is the most common tool used to evaluate the sensory disturbance in patients with diabetes mellitus and determine changes in light touch sensation in patients with CIPN symptoms [21, 22, 28, 29]. The results of the present study are in line with the findings of previous studies showing that cancer survivors with CIPN symptoms have significantly lower monofilaments scores when compared with cancer survivors without CIPN symptoms [21]. Possible causes of sensory change are the accumulation of neurotoxic chemotherapy drugs in the dorsal root ganglia (DRG) and its ability to pass through the blood-nerve barriers, which leads to sensory neuron damage and alterations of sensory perception regarding touch, pinpricks, and vibrations [30]. Moreover, the CIPN group were significantly weaker in their lower extremities using the 5xSTS test, which was used to assess lower limb muscle strength [31]. Our results are consistent with Winter-Stone et al (2017) study, showing women with CIPN symptoms performed significantly worse on the 5xSTS test when compared with women without CIPN symptoms [16]. To our knowledge, taxane-based chemotherapy agents may induce sensory and motor neuropathy according to which nerve fibers are affected [4]. Lower-extremity motor neuron impairment can cause muscle weakness and is associated with reducing lower-extremity physical function [32]. The findings of this study lend further support to the notion that cancer patients with CIPN symptoms may be at increased risk of falling and disability.

This study found that the CIPN group had significantly less functional capacity, as assessed by 6MWT, when compared to the non-CIPN group. These results are similar to those of McCrary et al (2019), which showed that increased CIPN symptom severity was significantly associated with decreased 6MWT distance in cancer patients [17]. However, the 6MWT distance of patients with CIPN symptoms in this study was greater than our study (416.4 m and 295.5 m). One possible explanation for this finding is that the difference in the gender proportions between the two studies. McCrary et al's (2019) study was near equal between male (40%) and female (60%) subjects but in our study most participants were female (92.3%). The literature suggests that gender might be associated with 6MWT distance [17]. Unsurprisingly, males have greater muscle strength and are taller than females, and are associated with a longer stride. This is one possible reason resulting in the greater 6MWT distance in males when compared with females.

The results of this study indicate that cancer patients with CIPN symptoms have significantly less balance ability and postural control according to the TUG test, Romberg test with eyes closed, and FAB scale. Our results are similar to a previous study that determines balance and postural control in cancer patients [18]. Wampler et al (2007) study showed that breast cancer patients had worse balance and postural control based on TUG time and FAB score when compared with healthy women's control (TUG: 6.69 ± 0.994 and 5.85 ± 0.86 ; $p < 0.008$, and FAB: 33.90 ± 3.46 and 36.48 ± 2.13 ; $p < 0.02$) [18]. The postural control components, which include the interaction between the musculoskeletal and sensorimotor integration systems, are associated with the ability to control balance [33]. A previous study suggested that FAB and TUG were related to many components of postural control including the musculoskeletal, muscle synergies, sensory system, sensory organization, postural orientation, reactive balance system, and proactive balance system [34]. Moreover, Einarsson et al. found that patients who had neurotoxic

side effects from chemotherapy agents might have reduced sensorimotor adaptation and poor balance performance [35]. In addition, cancer patients with CIPN symptoms who had positive Romberg signs with the eyes closed, an indication of problems in sensory ataxia, were found to be significantly associated with an increased risk of falling [36]. To our knowledge, chemotherapy agents can have toxic effects on the sensory and motor fibers, leading to sensory ataxia and balance problems [14, 16]. Therefore, sensory ataxia or low balance ability may contribute to the risk of falls among cancer patients.

In addition, we found that the balance confidence score using the ABC scale in the CIPN group was significantly less than the non-CIPN group. Previous studies suggested that patients with CIPN symptoms might experience reduced sensation and proprioception in their lower extremities and this leads to an increased risk of fall [14, 16]. Moreover, a recent study suggested that patients who have a high risk of falls might develop a fear of falling which restricts their mobility [37]. The results of Huang et al's (2016) study found that the individual's self-reported balance confidence using the ABC scale was strongly associated with TUG. Balance confidence is a strong predictor of perceived mobility limitations during daily activities in older cancer survivors [38]. Thus, thorough screening or monitoring of the balance confidence of patients who received neurotoxic chemotherapy and have CIPN symptoms may facilitate effective strategies for fall prevention.

A strength of the present study is the use of several objective measurements for assessing physical impairments, sensory disturbance, and functional abilities. However, there are a number of methodological limitations that are noteworthy. First, the sample size was relatively small (n=41), increasing the likelihood of a type II error. Future studies with a larger sample size are required to confirm the present study findings. Second, cancer patients in this study had normal BMI and were recruited by convenience sampling, which limits the external validity. Thus, generalization of the findings from our study to patients with other diseases, in which also a proportion are overweight and obese, should be made with caution. Finally, because this study design is cross-sectional, it is impossible to determine the nature of the CIPN symptoms change during chemotherapy treatment. Only the relationship between exposure and outcome was investigated. As a result, more research with a prospective study design is needed to confirm our findings.

Conclusions

The present study revealed that cancer survivors who have undergone chemotherapy with CIPN symptoms have lower physical performance, sensory perception, and functional ability when compared with cancer survivors without CIPN symptoms. In addition, these results indicate that patients with CIPN symptoms may be at increased risk of falling and disability. For cancer patients with CIPN symptoms, customizing rehabilitation program to prevent and reduce physical impairment and functional limitation could improve patient health and survivorship care plans.

Declarations

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Authors' contributions

The authors have contributed in the following ways: NR provided the concept/research design, data collection, and manuscript writing. CS and NP provided the concept/research design and data collection. PW contributed to the concept/research design, data analysis and manuscript writing. All authors read and approved the final manuscript.

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Availability of data and material: The data that support the findings of this study are available on request from the corresponding author (Pooriput). The data are not publicly available due to the ethical restrictions.

Conflicts of interest: No potential conflict of interest was reported by the authors

Ethics approval: The study was approved by the Human Research Ethics Committee of Chulabhorn Research Institute (028/2560). All included patients provided signed informed consents prior to participation in the study.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: All of the authors read the final version of the paper and approved its submission for publication.

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