Chula Med J Vol. 65 No. 2 April - June 2021;155-163 DOI : 10.14456/clmj.2021.21

Original article

Factors predicting chemotherapy induced peripheral neuropathy in breast cancer patients receiving neurotoxic chemotherapy

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Background: Cancer is a major cause of death worldwide. Chemotherapy is an effective treatment that is widely used to increase the numbers of cancer survivors. However, it often causes side effects such as nausea, vomiting, and lack of appetite. Chemotherapy induced peripheral neuropathy (CIPN) is one of the most serious side effect leading to fatal outcomes in these patients.
Objectives: To examine the influence of patient characteristics (body mass index: BMI, age, and physical activity), clinical characteristic (anemia) and treatment related factors (dosage of neurotoxic chemotherapy) on CIPN in cancer patients receiving neurotoxic chemotherapy.
Methods: One hundred and twenty Thai patients with breast cancer were recruited using the convenience sampling at a Chemotherapy and Blood Transfusion Unit at a university hospital in Bangkok. Research instruments included a personal information form, body mass index (BMI) record, physical activity questionnaire, and CIPN 20 questionnaire. Hemoglobin level was obtained from the laboratory records. The dosage of neurotoxic chemotherapy was obtained from each patients' medical record form. Data were analysed by using descriptive statistics, spearman's rho, and logistic regression analysis.
Results: The results showed that the patient characteristics (BMI, age, and physical activity), clinical characteristic (anemia), and treatment related factors (dosage of neurotoxic chemotherapy) could predict CIPN, but only physical activity and dosage of neurotoxic chemotherapy were most significant predictors of CIPN. Physical activity (OR = 0.99, 95%CI = 0.98 - 1.00, $P = 0.04$) and dosage of neurotoxic chemotherapy (OR = 1.01, 95%CI = 1.00 - 1.02, $P = 0.00$) were significant predictors of CIPN.
Conclusion: The findings recommend that health care providers should prepare to improve physical activity of breast cancer patients before receiving neurotoxic chemotherapy and closely monitor the patient receiving high dose of neurotoxic chemotherapy in order to prevent and reduce CIPN.

Keywords: Neurotoxic chemotherapy, chemotherapy induced peripheral neuropathy, predictor, breast cancer.

Cancer is a major leading causes of death worldwide. In Thailand, cancer is the first cause of death and tends to increase continuously. Approximately, 60.0% of cancers were breast, colorectal, liver and lung and the mortality rate represented about 63.1%.[1] Chemotherapy (CTX) is one of the major treatments in cancer patients. However, it often causes side effects, such as nausea, vomiting, loss of appetite, and peripheral neuropathy. Chemotherapy induced peripheral neuropathy (CIPN) is recognized as a side effect resulting from the administration of neurotoxic chemotherapeutic agents such as taxanes which is the main treatment for breast cancer.[2] The CIPN symptoms include tingling hands or feet and feeling numbness in the fingers and toes.[3] The mechanisms involve disruption of a dorsal root ganglion and axonal toxicity through transport deficits or energy failure.[4] These symptoms can affect physical function, psychological function and emotional status after chemotherapy treatment.

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Received: October 9, 2019
Revised: November 16, 2019
Accepted: February 20, 2020

Based on literature reviews, there were treatment related factors correlated to CIPN. For the example, the more cycles of chemotherapy, the more recurrences of CIPN.[3] Additionally, other factors related to CIPN include patients characteristics (such as body mass index (BMI), age, physical activity), clinical characteristics (such as anemia) and treatment related factors (such as dosage of neurotoxic chemotherapy). The findings of previous studies in breast cancer patients receiving taxane chemotherapy showed that higher BMI was associated with a higher incidence of CIPN.[5-7] Another study in breast cancer reported that the patients who were over 60 years old were significantly associated with severity of paclitaxel- induced peripheral neuropathy and persists longer in older patients.[8] Furthermore, some studies also found that age was a predictor of CIPN in breast cancer receiving paclitaxel chemotherapy.[9, 10] In contrast, a study in breast cancer patients treated with taxanes found that age was not a predictor of severity of CIPN.[11] Furthermore, recent studies physical activity could reduce CIPN,[12, 13] while some studies indicated that anemia was related to CIPN.[14, 15] In relation to the use of taxane for treatment, a previous study indicated that the incidence of chemotherapy induced peripheral neuropathy depended on dose per cycle of neurotoxic chemotherapy.[7] Similarly, a study also showed that more severity neuropathic symptoms had been found in cancer patients receiving high dose of neurotoxic chemotherapy.[16] There were still inconsistent findings about the relationship among these factors and the occurrence of CIPN. Moreover, there are limited studies in Thailand whether these factors impact CIPN in patients with breast cancer. The findings in the present study would yield a better understanding of the factors influencing CIPN in Thai patients with breast cancer, so as to further seek strategies to decrease or prevent it.

Purpose of the study

Body mass index, age, physical activity, anemia, and the dosage of neurotoxic chemotherapy could influence CIPN in cancer patients receiving neurotoxic chemotherapy.

Research hypotheses

Patients' characteristics (BMI, age, and physical activity), clinical characteristic (anemia) and treatment related factors (dosage of neurotoxic chemotherapy) can influence CIPN in cancer patients receiving neurotoxic chemotherapy.

Conceptual framework

The theory of Unpleasant Symptoms by Lenz ER, *et al*.[17] used as a conceptual framework to guide this study. It has three major components: 1) symptoms; 2) influencing factors; and 3) consequences of symptoms. In this study, CIPN is an unpleasant symptom perceived by cancer patients receiving neurotoxic chemotherapy. According to Lenz ER, *et al*. there are three types of influencing factors affecting the symptom experience and the consequences of the symptoms. These include physiologic, psychologic, and situational factors. Physiologic factors include functioning bodily systems, any pathology, and the person's energy level. Psychologic factors incorporate the individual's mental state and their reaction to their illness. Situational factors consist of aspects of the social, physical environment, employment status, marital and family status, health care resource and life styles behaviors. This study focused mainly on physiologic factors and situational factors as there are currently limited knowledge on these two factors. Specifically, BMI, anemia, age, and dosage of neurotoxic chemotherapy are considered as physiologic factors, whereas physical activity is considered as a situational factor (Figure 1).

Materials and methods

Sample selection

This research study design is the correlational predictive design. Populations were patients diagnosed with breast cancer, receiving neurotoxic chemotherapy at the Chemotherapy and Blood Transfusion Unit on the 7th floors of Outpatient Department, Siriraj Hospital. The subjects were those aged 18 years old and over, receiving taxanes chemotherapy (Paclitaxel and Docetaxel) as the Unit. The sample size was calculated by using the G power 3.1 program.[18] Power of test was 0.95, α probability error of 0.05; and odd ratio was 2.37.[5] As a result, minimum sample size of 120 was necessary. Therefore, 120 patients were approached to be recruited in this study.

***Inclusion criteria*:** 1) Having the first CTX cycle containing taxanes treatment; 2) Being able to speak and understand Thai language; and 3) Having no sign or symptoms of CIPN like a numbness hands or feet tested by using CIPN 20 questionnaire before receiving neurotoxic chemotherapy.

***Exclusion criteria*:** 1) Previously diagnosed with mental illness; 2) Passing a General Practitioner

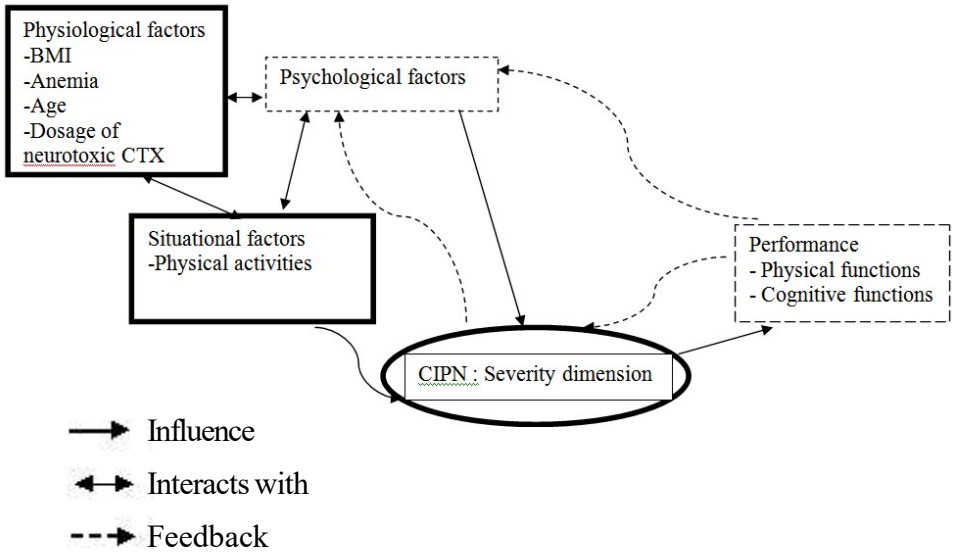

Figure 1. Conceptual framework of the study modified from theory of unpleasant symptoms.[17]

assessment of Cognition (GPCOG) screening test < 9 scores for patients aged 60 years old and older [19]; 3) Previously received neurotoxic chemotherapy includes taxanes, vinca alkaloid, and thalidomide; and, 4) Previously received the treatment with radiation at the pelvic and whole spine or had bone marrow transplant.

The researcher got the ethical approval from the committee of research ethics in human subjects at the Faculty of Medicine Siriraj Hospital, Mahidol University for the data collection on 9th April 2018 (IRB-NS 2018/05.1501).

Research instruments

A demographic record forms: This was developed by the researcher to collect the data related to the subjects in 3 parts: personal characteristics, hemoglobin level as evidence of anemia, and dosage of CTX received. The personal characteristics record included age and body mass index. Age was measured by counting from birth date using the cut point of age as < 60 years old for adults and ≥ 60 years old as older person. Body mass index was calculated, and its categories were divided into four groups as underweight (< 18.5 kg/m^2), normal (18.5 - 24.9 kg/m^2), overweight (25 - 29.9 kg/m^2), and obese (≥ 30 kg/m^2).[20] The clinical record was used to report if any subject had anemia. The value of hemoglobin was less than 12 g/dL. [21] The treatment record was used to document the dosage of neurotoxic chemotherapy was the amount of dose per cycle of taxanes regimens (mg/m^2).

The physical activity questionnaires [22]***:*** it consisted of four items to measure physical activity which were then scores in metabolic equivalent of tasks (METs) unit. The METs are multiplied by the time used in each activity in hours per week. [20] The total scores were then calculated by summing the score of all activities to derive at the level of exercises with energy exertion to demonstrate physical activities each person had in MET hours/week. The physical activity levels were used as cut off point based on the mean of physical activity level scores of this study.

Chemotherapy induced peripheral neuropathy (CIPN) record form: The CIPN 20 questionnaire comprises 20-item questions was used to assess whether the peripheral neuropathic side effects of chemotherapy occurred in each subject. It includes three subscales assessing sensory, motor and autonomic symptoms. [23] Each item was measured on a Likert scale ranging from 1 = Not at all, 2 = A little, 3 = Quite a bit, and 4 = Very much. The individual items and multi-item scale be scored. The minimum scores were 20 and the maximum scores were 80, which 20 scores represented the subject without CIPN and 21 - 80 scores represented the subject with CIPN. The CIPN levels were categorized into four groups based on severity of symptoms: none = 20 scores, mild = 21 - 40 scores, moderate = 41 - 60 scores, and severe = 61 - 80 scores. The reliability Cronbach's alpha coefficient of CIPN 20 was 0.72.

Data collection

Baseline measures were collected from the subjects at the first week before receiving neurotoxic chemotherapy including age, weight, height, physical activity, hemoglobin value, and existence of CIPN at the Chemotherapy and Blood Transfusion Unit. The researcher interviewed each subjects about 15 - 20 minutes to complete the questionnaires. Three weeks after baseline measures, the subject were again interviewed at the Unit to obtain information about CIPN symptoms and record the dosage of CTX received. The interview took approximately 10 minutes to complete.

Statistical analysis

Data analysis was carried out by using SPSS version 18 (Mahidol University); a alpha level of .05 was set as the accepted level of significance of this study. All variables were analyzed and described by using percentage, frequency distribution, mean, range, standard deviation. Logistic regression analysis was used to examine the power of predicting factors.

Results

Patients characteristics

The findings of the study showed that all of the subjects were female, 60.0 % were married. Half of the subjects (54.2%) were diagnosed with breast cancer stage II. In terms of age, three-fourths of the subjects (75.8%) were younger than 60 years old and ranging from 20 to 77 years old, with the mean age of 51.97 (SD = 11.0). More than half of the subjects (55.0%) were considered having normal weight (BMI 18.5 - 24.9 kg/m^2), 27.5% were overweight (BMI ≥ 25 - 29.9 kg/m^2), 12.5% were obese (BMI ≥ 30 kg/m^2), and 5.0% were underweight (BMI < 18.5 kg/m^2). The mean scores of physical activity of the subjects was 138.4 MET hours/week (SD = 62.3), ranging from 33.8 to 387.3 MET hours/week. Furthermore, the mean dosage of neurotoxic chemotherapy was 208.2 mg/m^2 (SD = 82.1), with the range of 90 - 415 mg/m^2 (Table 1, 2).

More than half of the subjects (52.5%) had hemoglobin value lower than 12.0 mg/dL. The mean hemoglobin value was 11.8 mg/dl (SD = 1.3) with the ranged of 8.8 to 15.1 mg/dl (Table 2).

The majority of the subjects (85.0%) received the three weekly regimens and 15.0% received the weekly regimens of taxanes. The mean dosage of neurotoxic chemotherapy was 208.2 mg/m^2 (SD = 82.1), with the range of 90 - 415 mg/m^2 (Table 1).

Table 1. Frequency, percentage, range, and mean of patients characteristic (n = 120).

Patients characteristics	Number (n = 120)	Percentage
Gender		
Female	120	100.0
Age		
< 60 years	91	75.8
≥ 60 years	29	24.2
BMI		
Underweight	6	5.0
Normal	66	55.0
Overweight	33	27.5
Obese	15	12.5
Breast cancer		
Stage I	11	9.2
Stage II	65	54.2
Stage III	34	28.3
Stage IV	10	8.3
Taxane regimens		
Three weekly regimens	102	85.0
Weekly regimens	18	15.0

Table 2. Frequency, percentage, range, and mean of participants, clinical characteristic, and treatment related factors (n = 120).

	Number (n = 120) (%)	Mean	SD	Min	Max
BMI (kg/m^2)		24.5	4.7	15.7	40.8
Age (years)		52.0	11.0	20.0	77.0
Physical activity					
MET hours/week		138.4	62.3	33.8	387.3
No (< 138.39)	84 (70.0)				
Yes (≥138.39)	36 (30.0)				
Anemia (Hb < 12 g/dL)		11.8	1.3	8.8	15.1
Hb < 12 g/dL	63 (52.5)				
Hb ≥ 12 g/dL	57 (47.5)				
Dosage (mg/m^2)		208.2	82.1	90.0	415.0
CIPN (scores)		24.5	4.7	20.0	43.0
No (20)	29 (24.2)				
Yes (21 – 80)	91 (75.9)				
Sensory symptoms	89 (74.2)	12.4	3.5	9.0	26.0
Motor symptoms	40 (33.3)	8.8	1.4	8.0	16.0
Autonomic symptoms	30 (25.0)	3.3	0.6	3.0	6.0

CIPN

The score of CIPN ranged from 20 to 43 scores, with the mean score of 24.5, (SD = 4.7). Three-fourths of the subjects (75.9%) reported CIPN and most of the subjects reported having sensory CIPN symptoms (74.2%), while less having motor (33.3%), and autonomic (25.0%) symptoms, respectively. In details, the majority of the subjects reported that they had some sensory symptoms; for example, 42.5% experienced numbness in fingers or hands and 31.7% had numbness in toes or feet and tingling fingers or hands. For those who reported quite a bit of sensory symptoms, 20.0% had numbness in fingers or hands, and 17.5% numbness in toes or feet (Table 3).

Table 3. Frequency, percentage, of participants reported CIPN symptoms (n = 120).

CIPN symptoms	1 (%)	2 (%)	3 (%)	4 (%)
Sensory symptoms				
(1) Tingling fingers or hands?	61.7	31.7	5.0	1.7
(2) Tingling toes or feet?	68.3	22.5	5.8	3.3
(3) Numbness in fingers or hands?	33.3	42.5	20.0	4.2
(4) Numbness in toes or feet?	45.8	31.7	17.5	5.0
(5) Aching or burning pain in fingers or hands?	91.7	6.7	0.8	0.8
(6) Aching or burning pain in toes or feet?	94.2	4.2	1.7	-
(9) Trouble standing or walking?	65.8	22.5	10.8	0.8
(10) Trouble distinguishing hot and cold water?	95.8	3.3	0.8	-
(18) Trouble hearing?	100.0	-	-	-
Motor symptoms				
(7) Cramps in hands?	95.8	4.2	-	-
(8) Cramps in feet?	88.3	10.0	1.7	-
(11) Trouble holding a pen making writing difficult?	80.8	13.3	5.8	-
(12) Trouble handing small objects (e.g. buttoning a blouse)?	80.0	15.8	4.2	-
(13) Trouble opening jar/bottle due to loss of strength in hands?	95.0	3.3	0.8	0.8
(14) Trouble walking because your feet come down to hard?	100.0	-	-	-
(15) Trouble walking stairs or standing up from chair due to weakness in legs?	99.2	0.8	-	-
(19) Only for those driving cars: trouble driving due to use of pedals?	100.0	-	-	-
Autonomic symptoms				
(16) Dizziness after standing up?	100.0	-	-	-
(17) Blurry vision?	94.2	5.8	-	-
(20) Only for males, trouble getting or maintaining an erection?	100.0	-	-	-

1= not at all, 2 = a little, 3 = quite a bit, 4 = so much

Table 4. Logistic regression analyses among BMI, anemia, age, physical activity, and dosage of neurotoxic chemotherapy and CIPN.

Variables	B	SE	Wald statistic	*P*-value	OR	95%CI
BMI normal (ref)			1.80	0.61		
Underweight	0.38	0.98	0.15	0.69	1.47	0.21 - 10.17
Overweight	0.09	0.57	0.02	0.87	1.09	0.35 - 3.40
Obese	- 0.91	0.77	1.39	0.23	0.39	0.08 - 1.82
Anemia (Hb <012) (ref : Hb ≥ 12)	- 0.26	0.49	0.29	0.58	0.76	0.29 - 2.00
Age ≥ 60 (ref : Age < 60)	- 0.29	0.57	0.26	0.6	0.74	0.24 - 2.28
Physical activity	- 0.00	0.00	4.19	0.04*	0.99	0.98 - 1.00
Dosage	0.01	0.00	15.99	0.01*	1.01	1.00 - 1.02
Constant	- 0.03	0.84	0.00	0.97	0.96	

* = $P < 0.05$

As mentioned before, the logistic regression analysis and an enter method was used to run the analysis to determine predictive factors. The results found that the patient characteristics (body mass index, age, and physical activity), clinical characteristic (anemia), and treatment related factors (dosage of neurotoxic chemotherapy) could predict CIPN, but only physical activity and dosage of neurotoxic chemotherapy were most significant predictors of CIPN (Table 4).

Discussion

This study revealed that the majority of the subjects (75.8%) reported CIPN within the first month after receiving neurotoxic chemotherapy. This finding was similar to the report from a previous systematic review. [24], which found that 68.1% of various cancer patients reporting CIPN symptoms in the first month. Additionally, the sensory CIPN symptom was a predominant clinical characteristic in 74.2% of the subjects. The finding in the present study was also consistent with the study conducted in Thai cancer patients receiving neurotoxic chemotherapy which found that 93.3% experienced sensory symptoms.[25] Also, a systematic review[24] in overseas also indicated that 19.0% to 85.0 % of the patients receiving taxanes had sensory neuropathy symptoms. The reason for these symptoms might be due to the fact that paclitaxel could cause sensory CIPN symptoms as it induces a bilateral, distal, symmetrical axonal neuropathy which is represented by sensory symptoms. [16] In addition, most of the subjects reported having numbness as 42.5% had numbness in fingers or hands, and 31.7% experienced numbness in toes or feet and tingling in fingers or hands. The experience of numbness in this study was similar to the findings of a study which indicated that 87.0% of Thai cancer patients reported numbness in fingertips after receiving the first taxanes chemotherapy session. [25] In determining the influencing factors on CIPN in cancer patients, the findings partially supported the hypotheses in this study. First, age, BMI, and anemia could not predict CIPN in the present study. In relation to age, the finding was consistent with previous research indicating that CIPN symptom severity of breast cancer patients was not associated with age. [26] One possible explanation is that most of the subjects (75.8%) in the present study were younger than 60 years old. As a result, compensatory mechanisms, such as reduced energy requirements, terminal sprouting and expansion of target territory or enhanced neuronal excitability, might be sufficient to overcome the CIPN symptom as the neuronal tissue aging process was less in those with less advanced age. [27]

Furthermore, BMI could not significantly predict CIPN either in this study. This was supported by the study which showed that BMI was not a predictor of the development and severity of CIPN in breast cancer patients treated with taxanes. [11] In addition, more than half of the subjects (55.0%) in the present study had normal BMI revealing less of the excess body fat. Therefore, neurotoxic chemotherapy could not be stored, and CIPN symptoms would less occur. On the contrary, a longitudinal study has shown that BMI was associated with more severe and persistent CIPN symptoms. [6] The reason might be that there were more obese patients recruited in the previous study. These characteristic led to higher body surface areas

and the doses of chemotherapy were higher than those of normal weight patients, and this could cause CIPN symptoms. [28]

Also, anemia was not a significant predictor of CIPN. This was inconsistent with a recent study in breast cancer patients treated with eribulin, another anticancer drug, demonstrating a significant relationship between CIPN and anemia (Hb < 11.5 g/dL). [29] Previously, there was no the study about correlation between breast cancer patients treated with taxanes and anemia. The possible explanation would be that difference CTX may assume different effect on clinical status of the patients, and hence might not influence CIPN. In addition, the majority of the subjects in the present study were adults who had normal BMI. These age and BMI figures might also contribute to less occurrence of CIPN in this study.

However, physical activity and dosage of neurotoxic chemotherapy were statistically significant predictors of CIPN. The physical activity could significantly predict CIPN (OR = 0.99, 95%CI = 0.98 - 1.00, $P = 0.04$). There were similar studies of breast cancer patients similarly treated with neurotoxic chemotherapy that also showed the same results. One study found that those who met the amount of recommended physical activity level less CIPN symptoms.[30] Moreover, a prospective cohort study also reported that low Moderate Vigorous Physical Activity was associated with more severe and persistent CIPN symptoms.[6] One possible explanation is the exercises may result in fewer neuropathic symptoms by increasing mitochondrial energy production and blood flow to the peripheral nervous system.[31] Moreover, due to the mechanisms of exercise, it has a local effect on peripheral nerves, inducing changes in the vasculature and metabolic systems.[30] In terms of dosage of neurotoxic chemotherapy, a higher dosage reported more CIPN symptoms than those who had a lower dosage of neurotoxic chemotherapy. If the dosage was increased by one cycle, it could increase the risk of CIPN by 1.0% (OR = 1.014, 95%CI = 1.007 - 1.021, $P = 0.00$). The subjects in the study (74.2%) developed grade 1 of CIPN symptoms. The severity of CIPN in this study was in accordance with the result of a study in Japan showed that almost all of Japanese breast cancer patients (97.0%) developed grade 1 of CIPN symptoms. In this Japanese study, the taxanes regimens were treated with 80 (mg/m^2) for weekly regimens and 175 (mg/m^2) for three weekly regimens. The results showed that an increase in the dosage of neurotoxic chemotherapy led to more CIPN symptoms.[8] The finding in the present study yielded support to findings of previous studies that a high dosage of neurotoxic chemotherapy induced CIPN symptoms.[16] It might be explained with the mechanisms of neurotoxic chemotherapy especially paclitaxel, which an effect on small nerve fibers and un-myelinated nerve fibers, and damaged neurological structures. In brief, a high dosage of taxanes can increase CIPN.[16]

Overall, nurses should take into consideration the necessity to screen breast cancer patients with high risk of CIPN symptoms, especially the patients who receive the high dosage of neurotoxic chemotherapy. They should develop suitable physical activities or exercise programs for these patients prior to the course of CTX in order to prevent or reduce CIPN symptoms before breast cancer patients receiving neurotoxic chemotherapy. Furthermore, nurses should closely and constantly monitor breast cancer patients who receive high doses of neurotoxic chemotherapy in order to timely detect CIPN and offer nursing care assistance to help these patients relieve CIPN symptoms. Further studies should be carried out to examine other predictive factors of CIPN. The routine to research on CIPN prevention and management strategies should also be conducted to assist breast cancer patients to get less or better cope with CIPN.

Conclusion

The results of this study are useful for the health care team to prepare and care for breast cancer patients before and during receiving neurotoxic chemotherapy. They should seek strategies to encourage and improve physical activity of breast cancer patients before receiving CTX. They should also closely monitor CIPN in these patients, especially those receiving high dose of taxane chemotherapy in order to prevent and reduce the occurrence of CIPN.

Acknowledgements

The first author was grateful for the scholarship from Siriraj Hospital. Appreciation also goes to all co-authors for suggestion and feedback for completion of this study.

Conflict of interest

The authors, hereby, declare no conflict of interest.

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