Incidence and Risk Factors Associated with Falls Among Women with Breast Cancer During Taxane-Based Chemotherapy

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Research Article

Keywords: Breast cancer, Fall incidence density, Physical performance test, Taxane-based chemotherapy

Posted Date: February 28th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1291231/v1>

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Abstract

Purpose

This study aims to evaluate the falling incidence density and examine the potential risk factors associated with falling among women with breast cancer during taxane-based chemotherapy.

Methods

One hundred and twenty-three women with breast cancers were participated in this study. The fall incidence density, taxane-induced peripheral neuropathy (TIPN) symptoms, and physical performance tests were evaluated at five time points throughout chemotherapy treatment. A fall diary was used to record fall incidence density during treatment. The fall incidence density was calculated by the number of first fall occurrence divide by person-time at risk. The risk factors associated with falls incidence density were analyzed using the Cox proportional hazard model. The Kaplan-Meier curve illustrated the probability to survive from fall during chemotherapy treatment.

RESULTS

Over the course of taxane-based chemotherapy, 29 (23.58%) women with breast cancer reported falls. In addition, the fall incidence density was 3 per 1000 person-day. This study discovered a significant link between age (HR = 1.06; 95% CI: 1.01-1.11), BMI (HR = 1.10; 95% CI: 1.01-1.20), and a 30-s chair stand test (HR = 0.82; 95% CI: 0.79-0.97) and falling.

CONCLUSIONS

As evidenced by the findings, the initial fall occurred after the first cycle of chemotherapy treatment and was found throughout the course of treatment. Furthermore, falls were associated with age, BMI, and a 30-second chair stand test. Early detection of TIPN symptoms and lower limb muscular weakness, particularly among older persons and those with a high BMI, may be essential to prevent falls.

Introduction

Breast cancer is one of the most frequently diagnosed malignancies in the world [1]. The incidence rate of breast cancer has risen dramatically in recent years [2]. Women with breast cancer who have undergone chemotherapy and/or hormonal therapy face a significant risk of falling, falling injuries, and higher expense for medicine and health treatment [3, 4].

The most common agents suggested for early as well as advanced stages of treatment include taxane-based chemotherapy [5]. However, the common adverse effects of taxane-based chemotherapy treatment

are taxane-induced peripheral neuropathy (TIPN) symptoms [6]. Several studies have suggested that breast cancer with TIPN symptoms is associated with physical performance impairments and increased risk of fall [7–9]. For cancer patients undergoing chemotherapy, falling can cause severe injuries, decreases in function, and higher mortality risk [4, 10, 11]. The risk of falling among older adult cancer patients was higher when compared against cancer-free individuals (adjusted odds ratio 1.16; 95% CI: 1.02-1.33) [12]. Moreover, several important factors increased the risk of falling, including age, obesity, and symptoms of TIPN, as well as the number of cycles in chemotherapy, balance, and poor physical performance [9, 13]. Impaired physical performance can be linked to decreased functionality, which is associated to fall risk [14]. Many studies have shown that patients undergoing neurotoxic chemotherapy are physically impaired in combination with having a greater risk of falls [15–18].

Although a recent systematic review found that several studies have investigated falls in different cancer patients receiving neurotoxic chemotherapy drugs, the majority of the studies were retrospective [19]. There have been few prospective longitudinal studies that revealed falling risk. Further, there is a lack of evidence on fall incidence density and the risk factors for falls among patients with breast cancer who underwent taxane-based treatment. The objectives of this study were to determine the incidence density of falling among women with breast cancer who received taxane-based chemotherapy and to investigate the possible risk factors associated with falling. We expected that falling among women with breast cancer undergoing taxane-based chemotherapy would have occurred after the first treatment cycle.

Materials And Methods

Design and setting

This prospective cohort study utilized convenience sampling of women with breast cancer. The study was performed to explore the incidence density of falls and evaluate the association between patients' characteristics, chemotherapy schedules and regimens, TIPN symptoms, and physical performances in women with breast cancer who received taxane-based chemotherapy. The participants were recruited from the National Cancer Institute of Thailand, King Chulalongkorn Memorial Hospital, and Bhumibol Adulyadej Hospital, Thailand, between October 2020 and July 2021.

Participants

One hundred and twenty-three women with breast cancer participated in this prospective cohort study. The study protocols were approved by the Ethics Review Committee for Research Involving Human Projects, Chulalongkorn University (COA No. 209/2020), National Cancer Institute of Thailand (COA No. 025/2020), King Chulalongkorn Memorial Hospital (COA No. 001/2021), and Bhumibol Adulyadej Hospital (under study ID: 13/63) before data collection.

The inclusion criteria included: (a) aged between 35-65 years, (b) received taxane-based chemotherapy, and (c) possessed good communication skills as well as the ability to understand the Thai language. Participants were excluded if they had serious medical conditions including musculoskeletal or

neurological conditions with peripheral neuropathic signs, had received other neurotoxic chemotherapy agents, and had already fallen before the study started.

Procedures

In order to assess the incidence density and related fall factors, a longitudinal prospective study was conducted. Before participating in the study, all individuals were informed of the study aims and testing procedures, after which informed consent was acquired. The fall incidence density and factors associated with fall incidence were measured five times: (1) before chemotherapy was initiated to create a baseline, (2–4) before chemotherapy cycles began, and (5) within 30 days after the final taxane-based chemotherapy cycle had been received.

Fall incidence density

Fall incidence density was an interesting outcome in the current study. A fall was described as an occurrence that led to an inadvertent rest on the ground or any other lower level not caused by an intrinsic event (like stroke) or overwhelming threat [20]. These criteria included trips and slips, as defined in previous research [21]. At the baseline, each participant and caregiver had a detailed description of falls. In addition, participants were given a diary and told to record their falls over the study period. Then, the researcher gathered the fall diary at each measuring point. Participants were prompted to always report falls in the diary by weekly telephone calls.

TIPN symptoms measurement

All participants reported TIPN symptoms with the EORTC QLQ-CIPN20. The EORTC QLQ-CIPN20 self-reported questionnaire included 20 items that assessed chemotherapy-induced peripheral neuropathy, containing TIPN symptoms. Each item was rated on a 4-point scale (1 = “not at all,” 2 = “a little,” 3 = “quite a bit,” 4 = “very much”), with higher scores indicating high severity of TIPN symptoms [22]. Many studies suggested that the self-reported questionnaire was valid and reliable to evaluate peripheral neuropathy complications from neurotoxic agents [22–24]. Patients with TIPN symptoms were identified in this study if they reported sensations of numbness or tingling in their fingers/toes in four items [25].

Physical performance test

All patients were asked to perform physical performance tests including the Romberg test, the Sharpened Romberg test, the unipedal stance test, and the 30-s chair stand test after completing the self-reported questionnaire. The order of the physical performance test was randomized by drawing lots. For the Romberg test, patients were asked to stand with their feet approximately 6–8 inches apart and their hands at their sides. Then, they closed their eyes and stood still for 60 seconds. The timing was stopped if patients opened their eyes or lost their balance [26]. For the Sharpened Romberg test, patients were asked to stand in a tandem position with one leg in front of the other and their hands at their sides. Then, they closed their eyes and stood still for 60 seconds. The timing was stopped if patients opened their eyes or lost their balance [27]. For the unipedal stance test, patients were asked to stand on a preferred

leg without support and remain still for 30 seconds. Time was stopped when a raised leg touched down or balance was lost [28]. For the 30-s chair stand test, participants had to sit in the center of a chair with arms crossed, feet flat on the floor, and back straight. Participants were instructed with "ready to go." The participants then stood up and sat down as many times as they could in 30 seconds [29]. Three trials per physical performance test were allowed. The average values were used for analysis.

Data Analysis

Data were analyzed using SPSS Statistic version 23 for Windows (IBM, Armonk, NY). The data were tested for normality using the Kolmogorov-Smirnov test. Demographic and characteristics data were presented as frequencies, mean, and standard deviation. The differences in demographic and characteristics at baseline between faller and non-faller were evaluated using t-tests and Mann-Whitney U tests for continuous data with normal and non-normal distribution, respectively. Only age, weight, high, BMI, and cumulative dose were distributed normally. In addition, the χ^2 test or Fisher exact test was used to compare the categorical data for demographic characteristics at baseline. Only the line of therapy and regimen were tested with the χ^2 test.

Fall incidence density referred to the probability of fall occurrence among women with breast cancer during taxane-based chemotherapy treatment. The fall incidence density is the number of first fall occurrences divided by the total person-day at risk. The day of observation on which the patients experienced their first fall incident, the date of loss of follow-up, death, or the end of the trial were totaled. Cox's proportional hazard model was performed to determine the association between the interested risk factors and fall incidence density. The fall incidence density was shown as the function of time by the Kaplan-Meier (KM) curve. The log-rank test was used to compare the survival function of falls among women with breast cancer, with or without TIPN symptoms. The significance level was set at $p < 0.05$.

Results

Demographic characteristics

A total of 262 women with breast cancer who received taxane-based chemotherapy were invited to enroll in this study. One hundred and twenty-seven patients met the inclusion criteria. However, four patients dropped out of the study. Thus, one hundred and twenty-three women with breast cancer participated in the study. Table 1 presents the demographic and clinical characteristics of participants. The results showed that 29 individuals reported falls (fallers), and 94 did not (non-fallers) over the course of three months of taxane-based chemotherapy treatment. Significant differences in age, height, and BMI between faller and non-faller groups were observed at baseline. Accordingly, most of the patients who fell did so at home ($n = 21$, 72.41%), with about one-third tripping on the stairs, one-fourth falling in the bedroom, and most of them falling in the bathroom. While one-third of the fallers fell outdoors, the majority of them slipped or tripped on the street (Table 2).

Table 1
Demographic and Clinical Characteristics of the Participants

Baseline characteristics	Total (n = 123)	Fallers (n = 29)	Non-fallers (n = 94)	p-value
Age (yrs.), mean (SD)	50.11 (9.04)	54 (7.09)	48.91 (9.27)	0.01*
Weight (kg), mean (SD)	60.67 (12.17)	62.04 (11.80)	60.24 (12.32)	0.48
Height (cm), mean (SD)	155.76 (6.47)	152.81 (4.84)	156.66 (6.66)	0.001*
BMI (kg/m ²), mean (SD)	24.94 (4.39)	26.49 (4.37)	24.46 (4.30)	0.03*
Line of therapy, (%)				
Adjuvant	94 (76.40)	26 (89.65)	68 (72.34)	0.06
Neoadjuvant	29 (23.60)	3 (10.35)	26 (27.66)	
Cumulative dose (mg), mean (SD)	1125.34 (278.56)	1199.51 (278.07)	1102.46 (276.17)	0.11
Number of tablets usually taken, (%)				
None	76 (61.80)	13 (44.83)	63 (67.02)	0.10
1	22(17.90)	6 (20.70)	16 (17.01)	
2	17 (13.80)	8 (27.59)	9 (9.56)	
3	6 (4.90)	1 (3.44)	5 (5.31)	
4	2 (1.60)	1 (3.44)	1 (1.10)	
TIPN symptoms, (%)				
TIPN	110 (89.43)	26 (89.65)	84 (89.36)	0.96
No-TIPN	13 (10.57)	3 (10.35)	10 (10.64)	
Physical function performance, mean (SD)				
Romberg test	60 (0)	60 (0)	60 (0)	1.00
Sharpened Romberg test	53.31 (15.11)	54.17 (14.34)	48.76 (18.41)	0.29
Unipedal stance test	27.41 (7.64)	28.26 (5.95)	28.81 (7.41)	0.65
30-s chair stand test	12.94 (3.74)	14.48 (3.84)	14.70 (4.62)	0.43
^a n = 54, fallers: n = 14, non-fallers: n = 40, *Statistically significant.				

Table 2
Characteristics of Falls (n = 29)

Characteristic	N (%)
Location of fall	
Home	21 (72.41)
Outside the home	8 (27.59)
Place of fall at home (n = 21)	
On stairs	7 (33.33)
On flat ground	1 (4.76)
In the bathroom	8 (37.91)
In the bedroom	5 (24.00)
Place of fall outside the home (n = 8)	
On the street	7 (87.5)
In the yard	1 (12.5)
Caused of fall	
Tripped or slipped	21 (72.41)
Lower muscle weakness	4 (13.8)
Loss of balance	4 (13.8)

Incidence density of falls

Out of a total of 123 women with breast cancer, 29 participants (23.58%) reported falls. Of these, 110 (83%) reported TIPN symptoms over the course of three months. Moreover, the fall incidence density was 3 per 1000 person-day, or 3 per 1000 who fell in the course of 1 day of observation. The first fall occurred after the first cycle of taxane-based chemotherapy. In addition, it was found the highest number of women with breast cancer (18 persons) reported first fall occurrence before receiving the third cycle, which decreased gradually before receiving the fourth cycle (16 persons) and follow up (9 persons).

Risk factors associated with fall incidence density

The results demonstrated a significant association between age (HR = 1.06; 95% CI: 1.01-1.11), BMI (HR = 1.10; 95% CI: 1.01-1.20), a 30-s chair stand test (HR = 0.82; 95% CI: 0.79-0.97) and fall incidence (Table 3).

Table 3
Cox Multivariate Model for Factors Associated with Falls

	HR _{adj}	95% CI	P-value
Age	1.06	1.01 – 1.11	0.01*
BMI	1.10	1.01 – 1.20	0.02*
30-s chair stand test	0.82	0.79 – 0.97	0.05*
*Statistically significant.			

The Kaplan-Meier (KM) curve of fall incidence density according to TIPN symptoms

Figure 1 demonstrates the probability of first fall occurrence during 3 months of chemotherapy treatment among women with breast cancer, with or without TIPN symptoms. Based on the survival analysis and KM curve, the overall survival rate of fall was 76.4%. In addition, the overall survival rate of patients with or without TIPN symptoms were 74.5% and 85.7%, respectively. There were no statistically significant differences in the probability of fall occurrence between breast cancer patients who had TIPN symptoms and those without TIPN symptoms ($p < 0.17$).

Severity of TIPN symptoms

Women with breast cancer reported the severity of TIPN symptoms using the EORTC QLQ-CIPN20 questionnaire. In the beginning, all patients reported “not at all” (100%). At cycle 2, about half of the patients indicated that their TIPN symptoms were “a little”. At cycle 3 follow up, the TIPN symptoms worsened progressively (Figure 2).

Discussion

This study was the first to evaluate the fall incidence density among women with breast cancer treated with taxane-based chemotherapy. The results showed that 29 participants (23.58%) reported falls over the course of three months. The fall incidence density was 3 per 1000 person-day over the course of taxane-based chemotherapy treatment. In addition, age, BMI, and a 30-second chair stand test were found to be relevant factors in fall incidence density.

Our findings revealed that the initial fall occurred after the first round of taxane-based chemotherapy and continued throughout treatment. The possible cause appears to be related to an alteration in postural stability. Previous studies suggested that patients with breast cancer experienced changes in their postural stability following the first taxane-based chemotherapy cycle [7, 30]. The probable explanations for this observation related to the modification of TIPN symptoms which were due to poor postural control triggered to fall [15, 16, 18]. TIPN symptoms caused by reduced somatosensory feedback from the feet lead to walking difficulties and feeling unsteady on the feet induced abnormal gait patterns [15,

31, 32]. Moreover, loss of sensation and muscle weakness were associated with fall risk in patients with cancer and diabetic neuropathy symptoms [33, 34].

The present study also found that most fall patients fell at home compared to outside; falls at home usually involved stairs and bathrooms. Our results were in agreement with a previous study that suggested most patients with cancer (75%) who fell did so at home [35]. A systematic review study suggested that home assessment and home modification interventions were linked to reduced fall risks [36]. Similar to previous studies, the causes of falls in most patients who had undergone neurotoxic chemotherapy included tripping or slipping while walking, muscle weakness, and loss of balance [4, 35]. These findings indicated that health providers should be educated concerning basic hazards in home environments and help patients to evaluate and modify their homes for hazards to reduce the risk of fall, especially among patients with TIPN symptoms.

The results of the present study demonstrated a significant link between age, BMI, and a 30-s chair stand test and the fall incidence density. There were several risk factors involving falls in the elderly, including physiological, musculoskeletal, and functional decline [37]. Ageing is associated with a decline in peripheral nervous system structure and functions including a decline in the number of sensory and motor neurons as well as the impairment of sensorimotor integration capacity [37, 38]. Many studies have found an association between age and the risk of TIPN symptoms [8, 39, 40]. Elderly people with neuropathy symptoms seem to have an abnormal gait, muscle weakness, and functional decline which increases the risk of falls [15, 18, 41]. In addition, the literature indicated that patients with neuropathy symptoms seem to increase the risk of falls [42]. Furthermore, previous study explored the association between overweight and obese individuals and the risk of falls. The results suggested that obese individuals have an increased risk of falls [43]. The possible reason might be related to the levels of physical function and activity in a person with a high BMI. A person with a high BMI had an increased risk of functional limitation [44]. Patients with cancer who had undergone neurotoxic chemotherapy agents and had functional limitations seemed to be at increased risk of fall [18]. Although previous studies suggested that the Romberg test, Sharpened Romberg test, unipedal stance test were associated with falls, only the 30-s chair stand test was found to have a significant link to fall [26–28, 45]. Due to the ease of the testing method, a physical performance test with a time of quiet posture may fail to evaluate individual postural stability related to falls. The dynamic physical performance assessment involving body motions may be a more valuable source of information on postural stability [46, 47]. Several studies have suggested the lower muscle strength test as a predictor for falls [18, 29, 48]. A 30-s chair stand test is a common physical performance test for assessing lower muscle strength [45]. Women who have received neurotoxic chemotherapy agents seem to have low scores on the repeated chair stand test and are associated with a risk of fall [18]. Moreover, patients with CIPN reported muscle weakness appear to be at high risk of falls [33]. As a result, early screening using a 30-second chair stand test should be performed during taxane-based chemotherapy, particularly in older women with a high BMI.

Our results found no statistically significant differences in the probability of fall occurrence between breast cancer who had TIPN symptoms and those without TIPN symptoms. One possible explanation

was whether TIPN symptoms were detected when individuals reported sensory neuropathy symptoms in their fingers/toes but did not report motor neuropathy symptoms. However, motor neuropathy appears to be linked to a higher chance of falling [11].

A few limitations need to be considered. Only the fall incidence density throughout the treatment period and within a 30-day follow-up was provided in the present study. It was unable to express the fall incidence density over a long period. Another flaw in this study was the use of a self-reported assessment to evaluate the TIPN symptoms, which failed to observe motor neuropathy. Moreover, our findings suggested that the fall incidence density and risk factors associated with falls might be unique to breast cancer. Hence, the results of the present study cannot be applied to other cancer populations. Further studies should be performed on the sensory and motor neuropathy screening activity with combined patient self-reported and objective assessment tools. Follow up should also be conducted concerning fall incidence density continuing for at least 6 -12 months after finishing chemotherapy treatment.

In conclusion, the findings showed that the first fall occurrence after the first cycle of taxane-based chemotherapy treatment and found throughout over the course of treatment, as shown by the findings. Furthermore, falling was associated with age, BMI, and a 30-second chair stand test. These findings imply that early detection of TIPN symptoms and lower limb muscular weakness, particularly in older persons and those with a high BMI, may be essential to prevent falls.

Declarations

Funding This study was supported by the 90th Anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund) Grant Number: GCUGR1125632112D.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The study protocols were approved by the Ethics Review Committee for Research Involving Human Projects, Chulalongkorn University (COA No. 209/2020), National Cancer Institute of Thailand (COA No. 025/2020), King Chulalongkorn Memorial Hospital (COA No. 001/2021), and Bhumibol Adulyadej Hospital (under study ID: 13/63) before data collection.

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

Consent for publication Not applicable.

Code availability Not applicable.

Conflict of interest The authors declare no conflict of interest.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Nida Rattanakrong. The first draft of the manuscript was

written by Nida Rattanakrong and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

A Kaplan-Meier Curve for First Fall Incidence among Women with Breast Cancer during Received Taxane-based Chemotherapy. a) Total breast cancer. b) Breast cancer with TIPN and without TIPN symptom.

Figure 2

Severity proportions of TIPN among women with breast cancer during received taxane-based chemotherapy