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Pre-treatment anxiety is associated with persistent chemotherapy-induced peripheral neuropathy in women treated with neoadjuvant chemotherapy for breast cancer

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ABSTRACT

Objective: Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent adverse reaction caused by chemotherapeutic agents, especially the taxanes. CIPN can persist from months to years after completion of chemotherapy, decreasing quality of life for cancer survivors. The aim of this study was to explore the incidence and risk factors of persistent CIPN among women with breast cancer receiving neoadjuvant chemotherapy.

Methods: In this prospective study, we recruited women with breast cancer receiving neoadjuvant chemotherapy, including four cycles of docetaxel. Participants reported neuropathic symptoms of tingling/numbness at baseline, at the end of chemotherapy treatment, and at 8 months after completion of chemotherapy. Candidate factors associated with CIPN were assessed before chemotherapy.

Results: Among 111 participants, 50 (45.0%) experienced CIPN during chemotherapy, and 21 (18.9%) reported persistent CIPN after chemotherapy. Univariate logistic regression analysis revealed that development of CIPN was significantly associated with pre-treatment numbness (odds ratio [OR], 4.02; 95% confidence interval [CI], 1.09–7.40; p = .033), and persistent CIPN was significantly associated with pre-treatment numbness (OR, 3.60; 95% CI, 1.12–11.61; p = .032) and pre-treatment anxiety (OR, 5.02; 95% CI, 1.84–13.70; p = .002). Multivariate analysis indicated that pre-treatment anxiety remained significantly associated with persistent CIPN (OR, 4.01; 95% CI, 1.25–12.87; p = .020).

Conclusion: Our results suggested that pre-treatment anxiety might be related to a patient's risk for persistent CIPN in women with breast cancer undergoing neoadjuvant chemotherapy. Further research is required to investigate if interventions targeting pre-treatment anxiety could provide prevention and management for persistent CIPN.

1. Introduction

Breast cancer is the most common cancer in women worldwide and the second most common cancer after thyroid cancer in Korea [1]. As a result of early detection and improved treatment strategies, survival rates have improved remarkably in most developed countries, with a 92% 5-year relative survival rate in Korea [2]. The increased number of breast cancer survivors highlights the need to focus on the persistent burden of the disease, especially related to cancer treatment, which has an enormous potential to impact quality of life.

Neoadjuvant chemotherapy with taxanes has been commonly recommended for locally advanced breast cancer in order to improve surgical outcomes and to increase the opportunity for breast-conserving intervention [3,4]. Peripheral neuropathy is one of the most frequent

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adverse reactions induced by chemotherapeutic agents, especially the taxanes [5]. Chemotherapy-induced peripheral neuropathy (CIPN) predominantly involves the sensory peripheral nervous system and leads to symptoms characterised by numbness, tingling, paresthesia and sensory loss [6]. The incidence of CIPN in patients receiving chemotherapy ranges from approximately 30 to 40% [7]. Importantly, CIPN can persist from months to years after completion of chemotherapy, causing significant distress and decreasing the quality of life for cancer survivors [5].

Demographic variables such as health status, obesity, and age are considered predisposing factors for occurrence and duration of CIPN [8,9]. In addition, the chemotherapeutic regimen, cumulative dose and pre-existing neuropathy (related to diabetes or alcohol consumption or idiopathic) were also suggested to increase the risk of developing CIPN [10–12]. However, the identification of which patients will develop CIPN is still rather controversial, and most of these previous studies refer to adjuvant chemotherapy, and not specifically to neoadjuvant chemotherapy [13,14]. Furthermore, we are not aware of other studies that have investigated psychiatric factors including anxiety, depression, and sleep disturbance as risk factors for CIPN. Considering that antidepressant agents, for example, duloxetine and amitriptyline, have been shown to be helpful for CIPN [15–17], it is necessary to explore which psychiatric factors in the pre-treatment period could be potentially associated with the development and persistence of CIPN.

Consequently, a prospective study with a standardised clinical assessment conducted for a 1-year period before, during, and after neoadjuvant chemotherapy may contribute to a better understanding of the pre-treatment factors associated with this neurological complication. The aim of this study was to explore the prevalence of CIPN in women with breast cancer receiving neoadjuvant chemotherapy and to identify these risk factors, including psychiatric factors that contribute to the development and persistence of CIPN.

2. Methods

2.1. Study design and setting

Participants were enrolled in this prospective observational study in a tertiary general hospital in Seoul, Korea, between November 2013 and March 2016. Participants were women with breast cancer, aged 18 to 70 years, and were enrolled while they awaited neoadjuvant chemotherapy. The participants' treatment plan consisted of four cycles of anthracyclines and cyclophosphamide, followed by additional four cycles of docetaxel. Patients were excluded if they had a history of another cancer or another significant medical condition. Patients who had a history of psychiatric disorders and received treatment for > 1 month before enrolment were excluded, because that could affect the mood and sleep of the patients. Patients who participated in shift work in the preceding 6 months were also excluded, because that could result in short-term circadian disruption and sleep problems. This study is a secondary analysis of data from a protocol to investigate genetic effects of circadian disruption on adverse reactions of chemotherapy and cancer progression [18]. Written informed consent was obtained from all participants. Eligible participants completed baseline questionnaires before the first cycle of chemotherapy, recording socio-demographic data and possible variables that may affect CIPN. The occurrence of CIPN was recorded during the preparation of the last cycle of chemotherapy and 8 months after the completion of chemotherapy. Clinical data including the cancer stage and additional treatments were obtained via review of patient medical records. The present study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1308-038-511). The clinical trial registration number is NCT02011815 (www.ClinicalTrials.gov).

2.2. Measures

2.2.1. CIPN

Participants reported their neuropathic symptoms of numbness or tingling during the previous 24 h using a 0–10 numerical rating scale. A score of 0 indicated no symptoms, while 10 indicated severe symptoms that were intolerable. Consistent with other studies of cancer-related pain and numbness, we found that moderate neuropathy symptoms were indicated at a grade of 3 or higher on the numerical scale [17,19]. Persistent CIPN was defined as numbness or tingling sensation occurring in the last chemotherapy cycle and persisting over 8 months after completion of chemotherapy.

2.2.2. Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) was used to assess psychological adjustment caused by physical illness. It included an anxiety sub-scale and a depression sub-scale, both containing seven questions each. To prevent overlap with physical disease in the hospital setting, the developers of the HADS removed items of physical symptoms related to anxiety or depression, including dizziness, headaches, insomnia, anergia, and fatigue [20]. Cut-off scores with appropriate sensitivity and specificity were determined based on a score of ≥8 on each of the sub-scales [21].

2.2.3. Sleep disturbance

The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and disturbance. The PSQI was used as a screening tool to evaluate “good” and “poor quality” sleepers. The possible range for total PSQI score was from 0 to 21 points. A higher score indicated a poorer quality of sleep and a lower score indicated a better quality of sleep. In the general population, a cut-off score of > 5 has been used to indicate poor quality sleep [22]. However, for cancer patients, a score > 8 has been recommended to be an appropriate cut-off [23]. In the current study, we analysed poor sleepers using a score of > 8.

2.3. Statistical analysis

Socio-demographic and clinical characteristics were compared between all participants and participants who experienced CIPN, as well as between all participants and those who experienced persistent CIPN. We examined the bivariate correlations between numerical numbness scale for CIPN and other continuous variables. Bivariate correlations were conducted separately in all participants for analysis of CIPN occurrence, and in participants who experienced CIPN for sub-analysis of persistent CIPN occurrence. Univariate logistic regression analyses were conducted to examine the variables associated with the development of CIPN and persistent CIPN separately. A multivariate logistic regression model was created to identify the independent risk factors predicting the development and persistence of CIPN. Variables with $p < .1$ in the univariate analyses were retained as covariates in the multivariate analysis. We also evaluated the model using theoretically-based predictors. For persistent CIPN, additional logistic analyses were performed among the participants who experienced CIPN at the end of chemotherapy. All statistical procedures were performed with IBM SPSS statistical software for Windows, version 22.0 (SPSS, Inc., an IBM Company, Chicago, IL). All statistical tests were two-tailed with a 5% significance level.

3. Results

3.1. Sample characteristics

We approached 328 patients scheduled to receive chemotherapy before surgery. Of these, 63 patients were ineligible (due to metastasis, 24; changed treatment plan, 9; psychiatric treatment, 9; shift work, 10; low literacy, 3; and other medical conditions, 8). Among the remaining 265 eligible participants, 122 patients declined to participate.