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Assessment of Menopausal Status in Paclitaxel Induced Peripheral Neuropathy among Breast Cancer Women

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ABSTRACT

Breast cancer is a disease in which breast cells grows erratically and the most common presumptuous malignancy in women globally. The primary diagnostic screening of breast cancer is mammography due to its specificity and accuracy. Multiple risk factors are linked with breast cancer and its treatment is multimodality and extremely useful tool in inhibiting the progression of cancer. The most widely used chemotherapy is with taxanes which stabilizes microtubules .The most common side effect of taxanes is peripheral neuropathy .Paclitaxel induced peripheral neuropathy is a disabling pain and sensory indications may start within (24-72hrs) following the administration .This can be reduced by dose minimization or modification .**OBJECTIVE :** The main objective of the prospective observational study was to determine occurrence of PIPN in different menopausal stages and to identify other risk factors .To investigate the relationship between Health Related Quality of Life with paclitaxel induced peripheral neuropathy was the secondary objective .**STUDY LOCATION AND DURATION** : PSG multispeciality hospital under oncology department for 6 months. **SAMPLE SIZE** : 60 patients **RESULTS AND CONCLUSIONS** : All were treated with adjuvant and neoadjuvant therapy of paclitaxel. Of these, 58.3% were postmenopausal, 23.3% premenopausal and 18.3% peri menopausal at the time of study. Paclitaxel induced peripheral neuropathy was seen more in postmenopausal women due to declined reproductive hormones. It was also estimated that paclitaxel induced peripheral neuropathy and menopausal symptoms had a negative impact on health related quality of life of patients.

INTRODUCTION:

Breast cancer is the generally diagnosed malignant cancer in which erratic growth and proliferation of breast cells to other healthy surrounding lymph nodes among adult women universally (17). It is also identified as the primary cause of death from such tumors and fifth cause of cancer-related mortality(19,21). It was assessed that approximately 2.3million cases were reported annually all over the world. Out of all types of breast cancer, TNBC accounts for 15-20%. The widely used approach for screening breast cancer is mammography which showed a high success rate in women aged above 50 years due to its increased sensitivity and specificity (13,18,21). The risk factors contributing to breast cancer are various. The existence of micro metastases and isolated cancer cells in regional lymph nodes as well as extent of primary tumor have a prognostic importance (20). The treatment modality is multidisciplinary which includes locoregional therapy (surgical procedures and radiotherapy) and systemic therapy (chemotherapy, hormone therapy) with increased survival benefits (1).

The commonly used chemotherapy treatment for breast cancer patients is using taxanes which are microtubule stabilizing agents (14). The ordinarily used and studied taxane is paclitaxel that has been yielded from the bark of pacific yew tree Taxus brevifolia, but had restricted use due to severe hypersensitivity reactions(2). As a part of this study, a detailed explanation about paclitaxel induced peripheral neuropathy which is a non hematologic side effect involving dying back process slowly affecting distal nerve endings and eventually affecting a disturbed cytoplasmic flow in the affected neurons (2,31). For the reduction of PIPN commonly the physicians suggest dose reduction. In the current scenario, there is no effective symptomatic management for peripheral neuropathy (11). But due to some extent of success in controlling pain clinically, drugs such as tricyclic antidepressants, anticonvulsants, neuroprotective agents like antioxidants have been used and these agents promised to the management of neurotoxicity related to taxanes (1).

In late 40s of women, a natural decline in reproductive hormones causes certain psychological and physiological changes. the neuroprotective action of estrogen and progesterone also decreases (4,7). According to this, women in the study can be classified into premenopausal, peri menopausal, postmenopausal and chemotherapy -induced amenorrhea. This study discusses primarily the occurrence of PIPN in different menopausal stages for women with breast cancer and also evaluates the association between the severity of PIPN and HRQoL in patients with breast cancer.

MATERIALS AND METHODS:

STUDY DESIGN:

The study was conducted at PSG Hospital in Coimbatore, Tamil Nadu, and India which is a 1400 bedded tertiary care hospital. It is the first teaching hospital in Tamil Nadu and the third teaching hospital in India to get NABH accreditation. This study was conducted in the Medical Department of Oncology as a prospective observational study for a period of 6 months.

STUDY POPULATION:

60 patients participated in the study who has breast cancer with paclitaxel induced peripheral neuropathy and age above 20 years as inclusion criteria. Pregnant, Lactating women and patients undergoing ovariectomy were excluded from the study.

AIM AND OBJECTIVES:

The study aimed to determine the occurrence of paclitaxel induced peripheral neuropathy in different menopausal stages and also assess the HRQOL in patients with breast cancer.

OBJECTIVE:

❖ PRIMARY OBJECTIVE:

a. To determine the occurrence of paclitaxel induced peripheral neuropathy (PIPN) in different menopausal stages in patients with breast cancer.

b. To identify any other risk factors.

❖ SECONDARY OBJECTIVE:

a. Investigate the relationship between health-related quality of life (HRQoL) and paclitaxel induced peripheral neuropathy (PIPN) using questionnaires to patients with breast cancer.

STUDY GROUPS:

Details related to treatment and clinician reports were obtained from the hospital case sheets. Information like PIPN data while on chemotherapy and sensory neuropathic examination, menstrual history, and other variables was collected from patient records prospectively. In

this study women were classified based on their last menstrual cycle as premenopausal and postmenopausal prior to the chemotherapy cycle .Again the women were reclassified into 4 according to the levels of circulating progesterone.

a) Women who had continued menstrual cycle after completion of post-chemotherapy as premenopausal (sustained presence of progesterone).

b) Women who are nearing to menopausal age (progesterone levels starts to vary).

c) Women who attained chemotherapy-induced amenorrhea (CIA) after few days of chemotherapy (presence of progesterone levels for few cycles).

d) Women who were postmenopausal before initiation of chemotherapy (slight or no circulating progesterone).

National Cancer Institute -Common Toxicity Criteria (NCI-CTC)4.03 version for adverse events is a physician-based tool for assessing sensory neuropathy severity and gradings. To evaluate health related quality of life (HRQoL), EORTC QLQ-C30 ver.3.0 consisting of five functional scales, three symptom scales and a global health status / QOL scale and for the identification of quality of life in menopausal women Menopause Rating Scale (MRS) was used in this study.

STATISTICAL ANALYSIS:

To summarize baseline characteristics and treatment timelines IBM SPSS software was used for descriptive statistics. Pearson's correlations were used for the evaluation of association between PIPN and QOL, menopausal and QOL.

RESULT:

The study discussed primarily the occurrence of paclitaxel induced peripheral neuropathy in different menopausal stages for women with breast cancer. In this study,31.6% of 56-65 years age group and postmenopausal women 58.3% were reported more PIPN occurrence than 23.3% premenopausal, 18.3% perimenopausal and other age groups; due to decreased circulating progesterone and estrogen levels which showcased a risk of developing PIPN (4,7). All the subjects for the study were females because the breast cells of women are constantly exposed to reproductive hormones like estrogen, progesterone and have more fat fibrous breast tissues and fewer ducts and lobules (2). There was increased PIPN in breast

cancer patients who had BMI above 25(35%) due to reduced growth factor production with elevated body weight (5). The PIPN affects the quality of the work negatively in employed patients (3). The type and severity of comorbid conditions had contributed to the development of peripheral neuropathy requiring individualization of drugs. Here, receptor positivity and negativity play an important role in the occurrence of breast cancer. Women with hormone receptor positive (HER-47%)cancers tend to have better outcome in a short period of time and have high chances of recurrence after many years of treatment .Whereas HER negative(53%) BC have no involvement of estrogen and progesterone receptors and cancer cells do not develop in response to such hormones and more likely respond to treatment with drugs that target the HER 2 protein .ER/PR positive (38%, 31%) BC tend to grow more slowly than ER/PR negative (62%,68%)cancers and responds to hormone therapy .Higher doses of paclitaxel like greater than 350 mg are associated with severe neuropathy. Grade 2 occurred in 50% and grade 1 in 23% patients receiving paclitaxel were observed in postmenopausal women from the study and showed a true indicator of the correlation between hormonal status and PN grade. The severity of pain caused by PIPN depends on the comorbidities, age and the hormonal levels; it was assessed by pain scale and as the severity of nerve damage increased the level of pain and its scoring also elevated (14). The drugs usually given for the treatment of PIPN in the patients were 89% pregabalin, TCA 5%, SNRI 3% and NSAIDs 5% for the reduction of pain severity and symptoms. These drugs were used because they showed successful effects in clinical trials for PIPN prevention (19). This study also discussed the health related quality of life of breast cancer patients suffering PN. The highest EORTC QLQ scores range from 41-60 and lowest scores from 0-20 and 21-40. From these we understood that there was a clear association between PIPN and worsened HRQoL. So, the clinicians and patients need to carefully consider the benefits and risks of the treatment. By Menopausal rating scale we have seen that QOL of menopausal women is negatively affected by the occurrence of menopausal symptoms and also suggests that these symptoms were a contributing factor for peripheral neuropathy in breast cancer patients receiving paclitaxel chemotherapy. Overall, from this study it proved that the occurrence of PIPN was high in postmenopausal women due to declined levels of reproductive hormones. Secondly, the study suggested that HRQoL of breast cancer women decreased with the occurrence of PIPN. Even the severity of menopausal symptoms was also adversely associated with QOL in breast cancer patients.

CONCLUSION:

Due to neuroprotective effects of reproductive hormones a positive outcome was demonstrated. It also notes that paclitaxel-induced peripheral neuropathy was common among postmenopausal women who are likely to have low circulating progesterone levels. Peripheral neuropathy was more prevalent in breast cancer patients receiving paclitaxel and has detrimental impact on their physical function and overall quality of life. The study showcased the importance of identifying and effectively managing PIPN in breast cancer patients to enhance their well-being during cancer treatment.

Also, the devastating effects of PIPN can be minimized using progesterone hormone therapy by improving neuroprotective activity and thus alleviating PIPN severity and intensity. The modern novel therapies and molecular information can help to mitigate the adverse effects of PIPN in clinical settings. Consequently, the proposal suggests exploring progesterone's potential benefits further through a randomized trial to determine its role in protecting against PIPN.

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This project has no relevant external financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

CONFLICTS OF INTEREST:

We authors declare that there are no financial or non- financial competing interests during the conduct of study.

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