

## Incidence of Peripheral Neuropathy in Breast Cancer Women on Paclitaxel

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## 1. Abstract

**1.1. Background:** Breast cancer is the most prevalence cause of cancer death among women and the fifth largest cause of cancer death globally, treatment of breast cancer include hormonal that can be change to other chemotherapy when the response is poor, Paclitaxel is the one of the most chemotherapy used in this reason which include Peripheral neuropathy which is the most adverse effect encountered by paclitaxel which may affect targets tubulin, and impairs mitotic spindle assembly, chromosome segregation, and cell division and quality of life of patient. The aim of this study was to evaluate the incidence of peripheral neuropathy among breast cancer women on paclitaxel.

**1.2. Patient and Methods:** This is a cross sectional study of 100 postmenopausal women taken Paclitaxel-treated chemotherapy aged 45-75 years which admitted to oncology center of Imam Hussein teaching hospital in Kerbala city which presented in this study and clinical examination of the incidence and severity of peripheral neuropathy was done according to standard score, tumor marker Ca 15.3 was measurement of each patient as response mechanism to be associated with incidence of peripheral neuropathy.

**1.3. Results:** The incidence of peripheral neuropathy was 82% in total according to the scoring Schedule (3-13) a severity scoring making significant higher than standard normal a strong negative correlation between Ca 15-3 levels in breast cancer patients and incidence of peripheral neuropathy which abnormal R.value=0.821.

**1.4. Conclusion:** The incidence of peripheral neuropathy is Paclitaxel chemotherapy in taken to women have breast cancer was non response conduct relating a adverse effect with Ca 15.3 as

continuous and effective measurement and close following up are required to control situation.

## 2. Introduction

Breast cancer is the top cause of cancer death among women and the fifth largest cause of cancer death globally. Despite advances in identification and treatment, the illness is becoming more prevalent and deadly, especially in middle-income and low-income nations. Third of all female cancer diagnoses in Iraq are due to breast cancer [12], It is the cancer that occurs most frequently in women in developed nations, accounting for 23% of all cancers, and it is the disease that occurs most frequently in women between the ages of 20 and 79 [13].

Paclitaxel belongs to the family of cytoskeletal drugs that target tubulin. As a result, paclitaxel treatment leads to abnormality of the mitotic spindle assembly, chromosome segregation, and consequently defects of cell division. By stabilizing the microtubule polymer and preventing microtubules from disassembly, paclitaxel arrests cell cycle in the G0/G1 and G2/M phases and induces cell death in cancer, It has been known that inhibition of mitotic spindle using paclitaxel usually depends on its suppression of microtubule dynamics [16].

It is not known what the major site of pathophysiology is for the peripheral neuropathy that can occur as a result of paclitaxel treatment. In tissue culture, paclitaxel causes the creation of aberrant microtubule bundles inside the cytoplasm, which disrupts normal cell function and proliferation. Paclitaxel is used to treat various types of cancer. In patients, this results in the effect that was wanted on the tumor; however, this does not come without the risk of

damage to normal tissue [26].

Paclitaxel most frequently causes alopecia, nausea, vomiting, mucositis, neutropenia, leukopenia, anemia, hypersensitivity responses, arthralgia, myalgia, and weakness, patients with preexisting neuropathies may be at a higher risk for developing peripheral neuropathy, another often encountered adverse effect. Patients who get significant neuropathy should have their dosage decreased by 20% (Meitasari et al., 2021).

It was also recorded that using a Paclitaxel causes Flush, edema, hypotension, skin rash, stomatitis, thrombocytopenia, hemorrhage, elevated blood alkaline phosphatase and aspartate aminotransferase, local injection site reaction, elevated serum creatinine, and many more are among the less usual adverse effects (Gur et al., 2022).

Peripheral neuropathy which is the most adverse effect of paclitaxel can be defined as the damage, inflammation, or degeneration of the peripheral nerves, -related peripheral neuropathy frequently results in a reduction or withdrawal of therapy, which has an effect on the treatment's efficacy and response, as well as a significant impact on the patient's quality of life.

The first evaluates the degree to which chemotherapy causes damage to sensory and motor peripheral nerves, and the second analyzes the neuropathies and dysfunctions that are linked with sensory, motor, and hearing neurotoxicity. Both of these analyses are performed by the neurotoxicity subscale [14].

The total neuropathy score, often known as TNS, is another technique of evaluation. It is a comprehensive evaluation that takes into account the patient's symptoms, electrophysiology, ability aspects, and signs The TNS may be decreased or used simply for clinical purposes [9].

The most symptoms of peripheral neuropathy, which include paresthesia, numbness, a burning sensation, and weakness, typically have a low intensity and are only rarely debilitating or fatal [22].

The aim of this study was to evaluate the incidence of peripheral neuropathy among breast cancer women on paclitaxel, measure the concentration of tumor marker in these patients and clarify if there any association between demographic data, tumor marker and incidence of peripheral neuropathy.

### 3. Patient, Materials and Methods

A total number of one hundred postmenopausal patients women (age 45 to 75 years old) with breast cancer gave their approval to take part in this study, forms of informed consent with participants' signatures were collected from everyone who took part in the study in accordance with the protocols that were authorized by the ethical research committee of the College of Pharmacy at the University of Kerbala, the study included women who were using Paclitaxel chemotherapy.

Demographic and clinical information, including age, illness stage, chemotherapy dosage, and treatment duration, were collected, and then abstracted from a clinical database sheet.

#### 3.1. Inclusion Criteria

Women with histologically confirmed breast cancer and postmenopausal, They were required to be non-pregnant, all patients were required to have clinically or radiographically measurable disease and to have adequate renal and hepatic function normal and postmenopausal women aged range (45-75 years)

#### 3.2. Exclusion Criteria

Patients were ineligible if they had diabetic mellitus or any other underlying medical condition that would hinder study participation, those with child-bearing potential who did not implement adequate contraceptive measures were also ineligible

The study was conducted at the labs of the College of Pharmacy at the University of Kerbala as well as in Oncology Center in Kerbala during the period of July 2022 and December 2022.

The degree of sensory neuropathy that was received during therapy for cancer was utilized to establish whether or not Chemotherapy-Induced Peripheral Neuropathy (CIPN) was present. This information was depend on the National Cancer Institute Common Toxicity Criteria. Patients were classified as having chronic idiopathic pain in the extremities (CIPN) if they had a grade 2 or higher score for sensory neuropathy.

Patients were randomly assigned to weekly paclitaxel intravenous injection over 1 or 3 hours, The study's primary endpoint, peripheral neuropathy (PNP), was measured by sensory symptoms, strength, musculotendinous reflexes, and vibratory sensation (range 0-12; PNP >3 points) [20].

The clinician identified neuropathy according to total neuropathy score based on the patient's symptoms which include sensory and motor symptom, autonomic symptom, vibration sensibility, strength and tendon reflex, burning or prickling feeling in the hands, arms, legs, or feet (Paresthesia), loss of sensation or feeling nerve ending (Numbness) and fatigue [19], (Figure 1).

#### 3.3. Ca 15-3 concentration in postmenopausal women

Intravenous blood was collected from each of the patients, which included affected women with breast cancer. After allowing the samples to coagulate at room temperature, the serum was extracted from them by centrifuging them for 15 minutes at a speed of 2000 revolutions per minute. After that, the serum was kept in a freezer at a temperature of -20 C until it was required.

The Enzyme Linked Fluorescent Assay (ELAF) method, based on the quantitative sandwich principle, was used to assess CA 15.3 concentrations in human serum, with all procedures carried out in accordance with the manufacturer's guidelines (Biomérieux/France).

Parameter	SCORE				
	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to finger or toes	Symptoms extends to ankle or wrist	Symptoms extends to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Autonomics symptoms	0	1	2	3	4 or 5
Pin sensibility	Normal	Reduced in finger/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Vibration sensibility	Normal	Reduced in finger/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflex	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Vibration sensation (QST vibration)	Normal to 125% of ULN	126-150% of ULN	151-200% of ULN	201-300% of ULN	>300% of ULN
Sural amplitude	Normal/reduced to <5% of LLN	76-95% of LLN	51-75% of LLN	26-50% of LLN	0-25% of LLN
Peroneal amplitude	Normal/reduced to <5% of LLN	76-95% of LLN	51-75% of LLN	26-50% of LLN	0-25% of LLN

QST = Quantitative Sensory Test; ULN = Upper Limit of Normal; LLN = Lower Limit of Normal  
 Note: In addition to the TNS, parameters written in italics are used only in full-length TNS, underlined ones in TNSr.  
 Adapted from the original versions.<sup>10,11</sup>

\* Pain in the upper and lower extremities, difficulty in standing (Hertz et al., 2018)

**Figure 1:** Total Neuropathy Score (TNS) and related reduced versions.

**3.4. Statistical Analysis**

Specifically, the statistical evaluation included Means of patient response and non-response group-collected variables were compared using the T-test, which was performed using the SPSS statistical package. Numbers are shown as the mean + standard deviation (SD). Results were considered statistically significant if the P value was less than 0.05.

**4. Result**

The current study included 100 women suffering from breast cancer who were using Paclitaxel chemotherapy, their average age was (54.36± 4.21), and (24.22 3.26 kg/m<sup>2</sup>) for body mass index, out of 100 Postmenopausal women, there were 90% and 72% women have breast feeding and delivery normal, respectively. It was found 30% for all women have history breast cancer. The demographic characteristics of all postmenopausal women are shown in tables 1 as follow:

The present study was found patients with CA15-3 > 30 U/mL are at risk of non-responses compared to those with CA15-3 (< 30 U/mL), according to the table (1), the findings demonstrated a statistically significant rise in the amount of Ca 15-3 found in breast cancer patients response (22.45 ± 9.28) group in comparison to the level found in the non-response (86.93± 11.34) group for patient taken Paclitaxel chemotherapy.

Concerning all patients were physical examination by the medical neurologist, our result clarified some clinical features for patient with score neuropathy as following table 2.

The results of the current study showed that there is a significant decrease in the concentration of Ca 15.3 levels with a significant increase in the score of neuropathy, that is, the higher the score, the greater the significant decrease in the concentration of Ca 15.3, we

found reverse negative correlation value (-0.821) between concentration of Ca15.3 and grade score of peripheral neuropathy in the response of paclitaxel treatment, the result was reflected with what was shown by patients with breast cancer and there is a response to treatment by Paclitaxel chemotherapy table 3.

Figure 3, showed that there is an inverse relationship in the response of chemotherapy between Tumor marker and incidence of neuropathy, as we observed a response to chemotherapy with a rate of up to 62% of incidence neuropathy. In contrast, we observed a decrease in the number of patients who had a high concentration of Ca15.3 Tumor marker in the their blood, vice versa.

On the other hand, we noticed in Table 4, that there are some menopausal women (13%) who have signs of neurological adverse effects and at the same time they have an increase in the concentration of Ca 15.3 in their blood, We also noticed that there are some women who do not have neurological adverse affect and at the same time it noticed a decrease in the concentration of Ca 15.3 in the blood.

**Table 1:** Demographic characteristics of control & patients.

Parameters	Postmenopausal women Mean ± SD	
Number	100	
Age (years)	54.36 ± 4.21	
BMI kg/m <sup>2</sup>	24.22 ± 3.26	
Number of birth	3 ± 1	
Breast feeding	Yes	90 (90%)
	No	10 (10%)
Normal vaginal delivery	Ye s	72 (72%)
	No	28 (28%)
Family history	Yes	30 (30%)
	No	70 (70%)

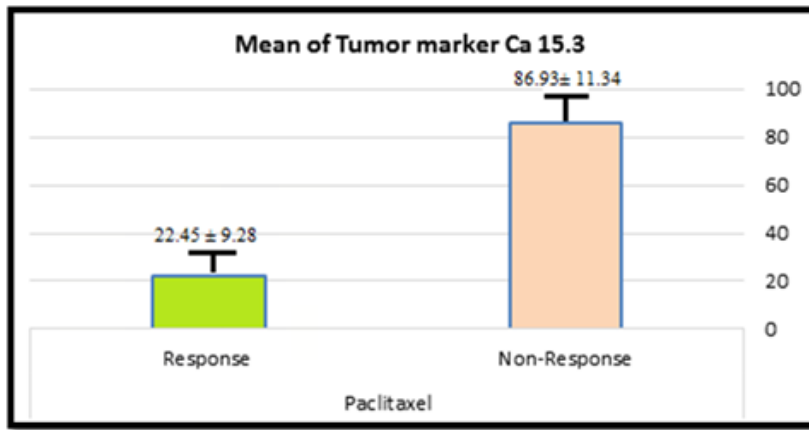


Figure 2: Concentration of tumor markers Ca 15.3 in the patients have breast cancer

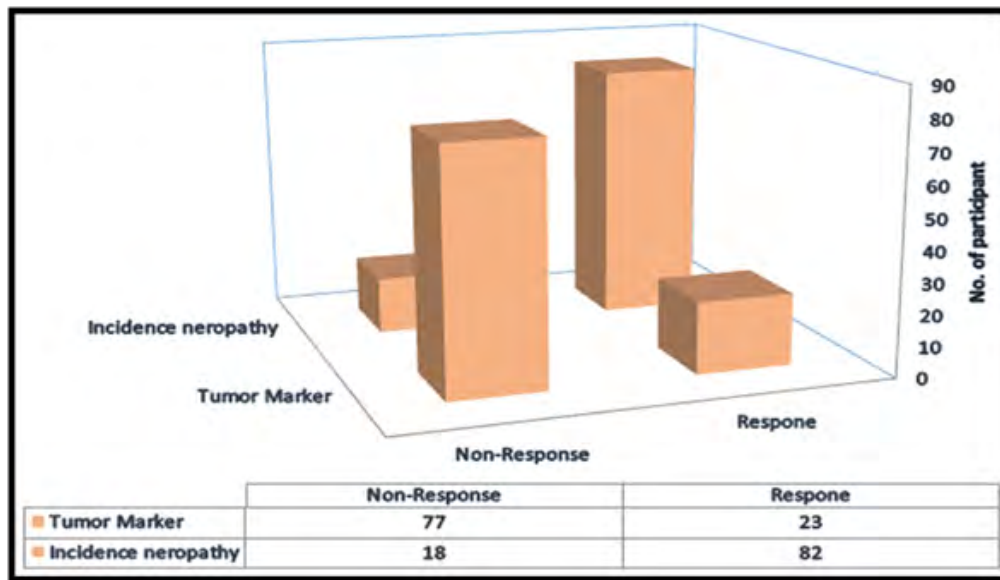


Figure 3: Relationship between response with Tumor marker and incidence neuropathy.

Table 2: Clinical feature of patient with score peripheral neuropathy

Clinical features	Percentage
Parasthesia	67%
NeuroPain	55%
Sensory motor	41%
Difficult Movement	37%
Numbness	28%
Tremors	2%

\*: represented score of peripheral neuropathy according to (Mielke et al., 2003)

Table 3: Correlation of Ca15.3 tumor marker with of peripheral neuropathy in patient response and non-response treatment.

		Grade	Ca 15.3 levels	
			Response	Non-Response
Grade		1		
Ca.15.3 levels	Response	-0.821	1	
	Non-Response	0.478	0.456	1

Table 4: Relationship between tumor marker with adverse effect of neuropathy.

Tumor Marker Ca15.3	Adverse effect	Non-adverse effect
< 30 U/mL	69%	31%
> 30 U/mL	13%	87%

## 5. Discussion

In this study, the relationship between CA15-3 and breast cancer response was investigated in 100 patients, and it was suggested that patients with CA15-3  $\geq 30$  U/mL are at risk of non-responses compared to those with CA15-3 ( $< 30$  U/mL), our results found 54 cases have non response (54%) while 46 cases have response to Paclitaxel chemotherapy, this study was disagreement with [27] who was demonstrated that serum CA 15.3 concentrations in Iraqi women breast cancer were within the normal range in about 88.23%, while the remaining 11.77% were above the normal value. Cancer antigen 15-3, also known as CA 15-3, is analyzed to determine how well a patient is responding to treatment for breast cancer and whether or not the illness has returned. Less than 30 U/mL is considered to be the reference range for serum CA 15-3 [21]. On the other hand, the present results corroborate those of the previous study, which found an elevated level of Ca 15.3 in patients with metastatic breast cancer. Cancer growth, progression, and metastasis are all influenced by a broad range of oncogenes and suppressor genes, as shown in the histology investigation [11]. Despite being readily available in the serum, the utility of CA 15-3 as a biomarker is limited, the sensitivity and specificity of CA 15-3 are low. Because some organ like Pancreatic, lung, ovarian, colon, and liver cancers may all be detected with it, as well as benign liver and breast disorders, which explains why it is employed in cancer screening [10]. CA 15-3 may also be an indicator of liver disease or benign breast problems, therefore, it would most likely do additional tests to validate the results [22].

Although paclitaxel's ability to stimulate microtubule assembly has many useful applications, it also has the undesirable effect of being neurotoxic. It has been shown that the dose, infusion intensity, and administration schedule all play a role in whether or not paclitaxel causes peripheral neuropathy in clinical settings [23].

One of the reasons for the difference that occurred in the score of neuropathy of the patients is due to the presence of the basic structure of the nervous structure, namely microtubules, neurons rely on microtubules for proper growth and function. Neuronal microtubules play a crucial role in mediating axonal transport by contributing to neurite outgrowth via interactions with the growth cone [24].

The reason for the high score of nervousness (10-13) in women with breast cancer who do not respond to treatment is due to axons and Schwann cells dysfunction, In a rat model, paclitaxel formulated in Cremophor-ethanol (Taxol®) distributed in the CNS and PNS, Paclitaxel accumulates in dorsal root ganglia and enters the brain at low amounts. Sciatic nerve and spinal cord had intermediate paclitaxel concentrations, possibly due to trafficking along dorsal root ganglion neuron axons [25].

According to the findings of some studies, a higher age is associated with a greater risk of paclitaxel-induced peripheral neuropathy

(PIPNe) in patients who have breast cancer; however, the effect of age on PIPNe in patients who have non-gynecologic cancers, such as bladder cancer, is unknown. Taking into consideration the findings of a preclinical study in which ovariectomized mice exhibited hyperalgesia that was reversed by estrogen treatment, it is likely that the high PIPNe risk in older females could be associated with low estrogen levels. This hypothesis is supported by the observation that PIPNe risk increases with age [17].

## 6. Conclusion

The result discovered that the probability of neuropathy and the response following chemotherapy had an inverse relationship, with the response to chemotherapy exhibiting an incidence neuropathy rate of up to 62%, as well as considerable negative correlation (R value; -0.821) between the concentration of Ca15.3 levels and the neuropathy adverse effect, the result of present study of PN is indicated that chemotherapy is paclitaxel sensory loss and correlation with Ca15.3 this will give important role to follow up patient on Paclitaxel chemotherapy.

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