



Frequency of Paclitaxel Induced Peripheral Neuropathy (PIPNe) in Iraqi Breast Cancer Patients: A QLQ-CIPN20 Analysis

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Abstract: Breast Cancer is a first leading cause of deaths in women worldwide. Many anticancer agents are used to treat the disease such as Taxol (Scientific name Paclitaxel). Taxol target the cell cycle dysfunction and prevent microtubules depolymerisation, leading to cell cycle arrest at the G2/M phase and cell death. This prospective cohort study evaluated the incidence and severity of Paclitaxel-Induced Peripheral Neuropathy (PIPNe) in 30 breast cancer patients receiving Taxol chemotherapy at Al-Yarmook teaching Hospital. PIPNe was assessed using the the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-CIPN twenty-item scale (QLQ-CIPN20). Patient-reported symptom questionnaires over a 10 weeks follow-up period. For sensory scale, patients score was ($6.42 \pm 3.73b$) at baseline to ($34.85 \pm 15.11a$) after treatment ($p < 0.0001$). For motor scale, patients score was ($5.58 \pm 3.21b$) at baseline to ($26.22 \pm 12.0c$) after treatment ($p < 0.0001$). For autonomic scale, patients score was from ($5.12 \pm 2.96b$) at baseline to ($14.37 \pm 11.09c$) after treatment ($p < 0.0001$). These findings highlight the high burden of PIPNe in breast cancer patients treated with Taxol and emphasize the need for close monitoring and early intervention to mitigate this adverse effect."

Keywords: cancer, Taxol, Sensory, motor, autonomic, neuropathy, CIPN

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Introduction

Breast cancer (BC) is still the most frequent type of cancer in world It constitutes the most commonly-diagnosed cancer and the leading cause of cancer death in women, worldwide, according to the International Agency for Research on Cancer (IARC)(1), Breast cancer (BC) is a complex disease encompassing multiple tumor entities, each characterized by distinct morphology, behavior and clinical implications(2) although the incidence of BC has

increased in the last 20 years, the prognosis and outcomes of those patients have changed dramatically, with survival rates increasing to about 78% for 10 years (3).

Many treating approaches uses to treat BC, Chemotherapy is a common treatment uses anti-cancer (cytotoxic) drugs to destroy cancer cells such as Paclitaxel (Taxol), The unique antitumor mechanism of Taxol is its ability to stabilize and prevent microtubules depolymerisation, leading to cell cycle arrest at the G2-M phase and cell

death (4) Paclitaxel used to treat a variety of types of cancer. This includes Kaposi's sarcoma, pancreatic, breast, lung, esophageal, ovarian, and cervical cancer (5). Despite the efficient effect, adverse side effect can accrue which may become challenging and result in chemotherapy modification or cessation. Taxol has many side effects such as Axonal transport disruption, mitochondrial dysfunction and Oxidative Stress, and Inflammation and Neuropathic Pain (6).

Neuropathic pain refers to the pain caused by the injury or disease of somatosensory system, Chemotherapy induced peripheral neuropathy (CIPN), a common side effect of anti-neoplastic agents, significantly decreases quality of life (QOL) in patients with cancer. CIPN symptoms include numbness, tingling, and pain especially in the hands and feet. This in turn is associated with inability to complete activities of daily living and falls (7). A meta-analysis involving over 4000 patients estimated CIPN prevalence to be about 68% by the end of the first month of chemotherapy and 30% at 6 months (8).

Paclitaxel-induced peripheral neuropathy (PIPN) is a side effect of cancer treatment, mostly sensory such as sensation of numbness, tingling, Pain and Cold stimuli in their hands and feet, the underlying cause is still unclear. Iraqi female breast cancer patients whom diagnosed with ductal breast carcinoma receive the drug as neoadjuvant in Her2-neu negative

Neuropathic pain is manifested as positive and negative symptoms. Positive symptoms include various painful symptoms e.g. spontaneous pain episodes such as tingling and prickling sensations as well as tactile and thermal allodynia or hyperalgesia. Negative symptoms usually include neurological sensory deficits such as numbness and

continuous feeling of wearing socks that diminishes the ability to feel ground properly that contributes to loss of balance and falls (9) Symptoms are generally symmetrical, but may start in an asymmetrical manner (10)

Grading systems of chemotherapy-induced toxicity

There are significant challenges to correctly assessing and interpreting chemotherapy-induced peripheral neurotoxicity (CIPN), primarily due to the differing perceptions of this clinically relevant toxicity by patients and physicians, Accurate grading of CIPN is essential for making informed decisions regarding the management of drug regimens during cancer treatment and assessing their long-term consequences:

1. Quantitative assessment of chemotherapy-induced peripheral neuropathy

Most medical oncology articles regarding chemotherapy related neurotoxicity use toxicity severity rating scales such as the WHO or the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), the last consider the most widely used scale in oncology for evaluating adverse events, including neurotoxicity. NCI-CTCAE's peripheral neuropathy scale emphasizes the impact of neurological symptoms on patients' functionality. However, the relationship between this clinical reported outcome (CRO) scale and patients' perception is not consistent, particularly in CIPN of intermediate severity (11). Furthermore, the interpretation of the origin of CIPN symptoms, even by experienced oncologists, often does not align with objective neurological impairment (12).

In contrast, neurologists have introduced the Total Neuropathy Scale-clinical version (TNSc), a scale specifically designed to address CIPN

severity (13). TNSc provides measurable detailed objective clinical neurological data and exhibits slightly better clinimetric properties (14).

However, quantitative test abnormalities frequently coincide with clinical symptoms and signs, and are not necessarily informative in addition to the clinical impression (15). Furthermore, the clinical severity is not necessarily reflected by quantitative test. Besides, nerve conduction velocity studies, electromyograms and, especially, sural nerve biopsy are not without discomfort for the patient.

Notably, neither the oncology gold nor the neurology gold standard are able to adequately capture the complex interplay between patients' experiences and the impact of neuropathy on their lives. This is particularly the case in intermediate toxicity grades (Grade 2), where crucial treatment decisions are made regarding treatment continuation, dose adjustments, or discontinuation, potentially determining long-lasting quality of life and survival outcomes (16).

2. Quality of life assessment

Patient-reported outcome tools, such as the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-CIPN twenty-item scale (QLQ-CIPN20), have been shown to be better measures of neuropathy than clinician determined CTCAE grading.

One may argue that subjective parameters are at least as important as objective parameters in grading of chemotherapy-induced neuropathy. Paresthesias, pain or impairment of function may interfere severely with quality of life (the patient's perspective) and may be, in that respect, more relevant than absent reflexes or elevated sensory detection thresholds. Furthermore, neuropathic symptoms and

signs may be judged by the patient to be not as important, or not interfering with quality of life, in the setting of potential curative chemotherapy. In other words: who scores the severity of paresthesias or the extent of functional abnormality? Who judges the severity of chemotherapy-induced peripheral neuropathy? The doctor or the patient? The doctor may assess the degree of sensory abnormality or muscle weakness, but it is the patient who experiences a handicap in daily life and the impact of peripheral neurotoxic symptoms such as pain or paresthesias on quality of life (QOL).

Quality of Life Questionnaire-CIPN twenty-item scale (EORTC QLQ-CIPN20), a validated instrument designed to elicit cancer patients' experience of symptoms and functional limitations related to chemotherapy-induced peripheral neuropathy.

The QLQ-CIPN20 consists of 20 items, rated by subjects on a 4-point Likert-type scale ranging from 1 (1=not at all, 2=a little, 3=quite a bit, and 4=very much) the final score was calculated in accordance with standard EORTC scoring procedures

It is becoming more and more widely accepted that the assessment of CIPN must rely predominantly on subjective perceptions as reported by the affected subjects. The most widely used PROs are based on simple questions referring to common daily activities, and they are intended to be useful for all types of CIPN, although it is well known that different neurotoxic drugs have remarkably diverse neurotoxicity profiles.

The aim of this study is to evaluate the CIPN QLQ-20 in Iraqi breast cancer patients before and after Taxol chemotherapy, with a focus on its association with PIPN development.

Methods

Study Design

This was a prospective observational study conducted to evaluate chemotherapy-induced peripheral neuropathy (CIPN) in breast cancer patients before and after Taxol (paclitaxel) treatment.

The study included 30 female patients diagnosed with breast cancer who were scheduled to receive Taxol-based chemotherapy and 30 female control (apparently healthy and did not receive any drug). There is no demographic differences between the two groups. Assessments for patients were performed at two time points: baseline (before Taxol treatment) and post-treatment (after completion of Taxol chemotherapy) and assessment for control.

- **Inclusion Criteria:** Female patients aged 18 years or older. Histologically confirmed diagnosis of breast cancer and Scheduled to receive Taxol-based chemotherapy.
- **Exclusion Criteria:** Pre-existing peripheral neuropathy due to other causes (e.g., diabetes, alcohol abuse, or other neurological disorders).

Ethical approval

Code of Ethic in research approved by ministry of health and read by patients, vocal approval has been taken from patients.

Data Collection

1. Demographic and Clinical Data:

Demographic information and clinical characteristics (treatment regimen, etc.) were collected from medical records.

2. Chemotherapy Regimen

All patients received Taxol (paclitaxel) as part of their chemotherapy regimen. The dose, frequency, and duration of treatment were recorded.

3. Assessment Tool

The EORTC QLQ-CIPN20 questionnaire was used to assess

chemotherapy-induced peripheral neuropathy.

Higher scores indicating greater symptom severity

The questionnaire was administered for patients at two time points:

Baseline: Before the initiation of Taxol treatment.

Post-Treatment: After the completion of Taxol chemotherapy.

4. Calculations

Understand the Scoring System

Each item in the EORTC QLQ-CIPN20 is scored on a 4-point Likert scale:

1 = Not at all

2 = A little

3 = Quite a bit

4 = Very much

Calculating Raw Scores for Each Subscale

The questionnaire is divided into three subscales:

- Sensory Scale: Items 31–36, 48, 49 (8 items)
- Motor Scale: Items 37–43 (7 items)
- Autonomic Scale: Items 44–47 (4 items)

Transform Raw Scores to a 0–100 Scale

Using the following formula to transform the raw scores into a scale of 0 to 100:

$$\text{Transformed Score} = \left(\frac{\text{Raw Score} - \text{Minimum Possible Score}}{\text{Maximum Possible Score} - \text{Minimum Possible Score}} \right) \times 100$$

Minimum Possible Score: The lowest possible sum of the items in the subscale (e.g., if all items are scored as 1).

Maximum Possible Score: The highest possible sum of the items in the subscale (e.g., if all items are scored as 4).

Statistical Analysis

The Statistical Analysis System –SAS (2018) program by paired T-test was used to detect the effect of difference groups in study parameters (Sensory, Motor and Autonomic). LSD-Least significant difference was used to

significant compare between means in this study.(17)

Results and discussion:

In this study, post-treatment QLQ-CIPN20 scores were significantly higher than pre-treatment scores across all subscales (sensory, motor, and autonomic), indicating a worsening of chemotherapy-induced peripheral neuropathy (CIPN) symptoms after treatment.

It's important to notice that Item 20 rates male impotence; this is non-informative in female patients and frequently not provided by male patients.

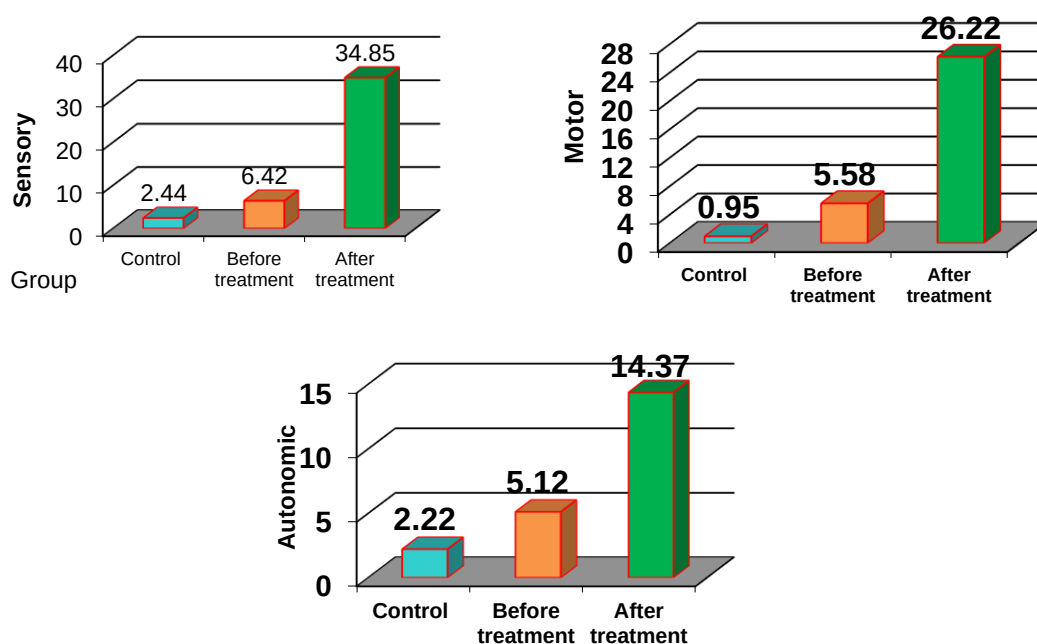
As a consequence, this item was excluded.

Of note, item 19 rates difficulty using the pedals and is only applicable to patients who drive a car. This item can be excluded from the sum scores where the majority of patients do not drive so item 19 was included in the sum score for this analysis.

In addition to a sum score, the items in CIPN20 have been divided into three subscales. The sensory subscale consists of items 1, 2, 3, 4, 5, 6, 9, 10, and 18; motor: items 7, 8, 11, 12, 13, 14, 15, and 19; and autonomic: items 16, 17, and 20.(18).

Table (1): Comparison between difference groups in Sensory, Motor and Autonomic/ EORTIC

Parameters	Groups	Mean $\pm$ SD	L.S.D.(P-value)
Sensory	Control	2.44 $\pm$ 1.60 c	4.329 ** (0.0001)
	Before treatment	6.42 $\pm$ 3.73 b	
	After treatment	34.85 $\pm$ 15.11 a	
Motor	Control	0.95 $\pm$ 0.88 c	2.877 ** (0.0001)
	Before treatment	5.58 $\pm$ 3.21 b	
	After treatment	26.22 $\pm$ 12.0 a	
Autonomic	Control	2.22 $\pm$ 0.01 c	2.803 ** (0.0001)
	Before treatment	5.12 $\pm$ 2.96 b	
	After treatment	14.37 $\pm$ 11.09 a	
Means having with the different letters in same column differed significantly. ** (P $\leq$ 0.01).			



Figure(1): Comparison between different groups in (sensory, motor and autonomic)

- **sensory Subscale**

The mean sensory score increased from (**6.42 ± 3.73b**) at baseline to (**34.85 ± 15.11a**) after treatment ($p < 0.0001$), against control ($2.44 \pm 1.60c$) indicating a significant worsening of sensory symptoms such as numbness, tingling, and pain in the hands and feet. (Fig-1).

- **Motor Subscale**

Motor scores also increased significantly from (**5.58±3.21b**) at baseline to (**26.22±12.0c**) after treatment ($p < 0.0001$), against control ($0.95 \pm 0.88 c$) reflecting greater difficulty with tasks requiring fine motor skills and muscle strength. (Fig-1).

- **Autonomic Subscale**

Autonomic scores showed a smaller but still significant increase from (**5.12±2.96b**) at baseline to (**14.37±11.09c**) after treatment ($p < 0.0001$), against control ($2.22 \pm 0.01c$) suggesting mild worsening of symptoms such as dizziness. (Fig-1).

The significant increase in sensory, motor and autonomic scores (Table-1) highlights the substantial burden of CIPN on patients' quality of life, particularly in terms of daily functioning and physical comfort. worsening of CIPN symptoms after treatment is consistent with the known neurotoxic effects of Taxol, which can damage peripheral nerves and lead to sensory, motor, and autonomic dysfunction. The higher cumulative dose of Taxol received by some patients may also contribute to the severity of symptoms.(19)

The clinical implications of these findings are significant. The worsening of CIPN symptoms highlights the need for close monitoring and early intervention, such as dose modification or the use of neuroprotective agents (20).

Conclusion:

Compared to previous studies, our results align with reports of high CIPN

incidence in breast cancer patients receiving Taxol. The chemotherapy effects sensory more than motor and autonomic and symptoms are worsening near the time of regime ends.

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Recommendation:

Future research should explore strategies to prevent or manage CIPN, particularly in high-risk patients.

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