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Original Research Article

A prospective observational study to assess peripheral neuropathy in patients receiving weekly paclitaxel chemotherapy

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ABSTRACT

Background: Peripheral neuropathies are disorders of peripheral nerve cells and fibres. Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of anticancer treatment, and it can affect the patient's long-term survival. The prevalence of CIPN is around 38%. Peripheral neurotoxicity (PN) is a side effect of paclitaxel that can lead to treatment discontinuation. The intensity and severity of neuropathy is more with patients receiving weekly paclitaxel chemotherapy.
Methods: 60 patients of CA breast receiving weekly paclitaxel monotherapy who fulfilled inclusion and exclusion criteria were enrolled in the study. Clinical examination and grading of neuropathy was done according to NCI-CTCAE version 4.0. All patient had undergone nerve-conduction studies at baseline and 3 months after baseline.
Results: 50% of patients, developed signs symptoms of peripheral neuropathy, out of which tingling sensation was the most common symptom (40%). The incidence of grade 1 peripheral neuropathy at 3 and 6 months were 35%, and 31.66%, while grade 2 neuropathy was noted in 18.33%, and 14.75% of patients, respectively. There was a significant difference in the SNAP value between baseline and 3 months for right ulnar nerve, right and left sural nerve and CMAP for right median nerve, right ulnar nerve, right and left tibial nerves which suggests development of neuropathy during 3 months of paclitaxel chemotherapy.
Conclusions: This study provides information on the incidence and severity of peripheral neuropathy in patients receiving weekly paclitaxel chemotherapy, which can help physician in further management.

Keywords: Paclitaxel dosage, Grades of neuropathy, CA breast

INTRODUCTION

Peripheral neuropathy is a group of diseases with a wide spectrum of etiologies. Diabetes, exposure to toxic substances such as alcohol and chemotherapeutics, immune-mediated conditions, and gene mutations are the most common causes.[1]

As chemotherapeutic agents have numerous targets and mechanisms of action aimed at eliminating rapidly dividing cancer cells, they can harm nervous system structures and can cause a variety of neuropathies, including large and small fibre neuropathies, sensory and/or motor neuropathies, demyelinating and axonal neuropathies, cranial and autonomic neuropathies.[2,3] Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of anticancer treatment, and it can affect the patient's long-term survival and quality of life.[4]

The prevalence of CIPN is around 38%, but it varies greatly depending on the anticancer drugs and treatment regimen used.[5] Previous research has primarily focused on

specific chemotherapeutic agents, with CIPN incidence rates ranging from 19 percent to over 85 percent.[6]

CIPN has been linked to a number of traditional chemotherapeutics like platinum drugs, particularly cisplatin and oxaliplatin, taxanes, vinca alkaloids, and bortezomib.[7]

In both early-stage and metastatic breast cancer, paclitaxel (PTX) is a key component of many therapeutic regimens. PTX, a microtubule-stabilizing agent, binds to microtubules and inhibits their dynamic behaviour, resulting in cell proliferation inhibition. Peripheral neurotoxicity (PN) is a side effect of the drug that can lead to treatment discontinuation and a poor quality of life.[8] The incidence of PTX-induced PN is known to be affected by a number of factors, including cycle dosages, treatment schedules, infusion durations, cumulative dosages, and comorbidities like diabetes.[9]

Sensory nerve action potentials (SNAP) are decreased or absent in nerve conduction studies, indicating axonal loss from sensory nerves; the sural nerve is particularly affected.[10]

The National Cancer Institute's common terminology criteria Adverse Reactions (NCICTCAE) is the most commonly used CIPN evaluation tool in clinical trials. It is a clinician reported outcome (CRO) that includes criteria and definitions for quantifying the severity of CIPN in both sensory and motor components, using a 5-point scale [grade 1 (asymptomatic) to grade 5 (death)].[11]

There are only a few studies from India that report on the incidence of peripheral neuropathy caused by it. As a result, it's critical to investigate the prevalence of peripheral neuropathy. This study proposed to address the co-relation of duration of therapy and incidence of peripheral neuropathy.

METHODS

The present prospective observational study was carried out in Department of Medicine, Bharati Vidyapeeth (DTU) Medical College, Pune between January 2021 to December 2022. 60 Patients receiving weekly paclitaxel monotherapy who fulfilled below inclusion and exclusion criteria were enrolled in the study.

Inclusion criteria

Patients with following criteria were included (a) female patients with age group of >18 years; (b) with established CA Breast by histopathological examination report; and (c) willing to give consent.

Exclusion criteria

Patients with following criteria were included (a) metastasis; (b) with diabetes mellitus or previously diagnosed neuropathy; (c) compromised organ function; (d) pregnant and lactating females; and (e) who received other chemotherapeutic agents which are established to cause neuropathy.

Sampling technique

Every consecutive patient receiving paclitaxel chemotherapy who fulfilled the selection criteria.

Methodology for data collection

All the patients enrolled received weekly paclitaxel monotherapy. Detailed clinical assessment and neurological evaluation were done monthly till 3 months and at 6 months.

Grading of neuropathy

It was done according to NCI-CTCAE version 4.0 into 5 grades (grade 1 to 5) (a) grade 1: asymptomatic; loss of deep tendon reflexes or paraesthesia; (b) grade 2: moderate symptoms; limiting instrumental activities of daily living; (c) grade 3: severe symptoms; limiting self-care activities of daily living; (d) grade 4: life-threatening consequences; urgent intervention indicated; and (e) grade 5: death.

Nerve-conduction studies

All patient had undergone nerve-conduction studies at baseline and 3 months after baseline. In sensory nerve conduction studies, sensory nerve action potentials (SNAPs) and in motor nerve conduction studies, compound muscle action potential were assessed.

Statistical analysis

All statistical analysis was done using SPSS software with version 26.0. Continuous variables result was shown by descriptive statistics and categorical variables result was shown by frequency and percentage. Group comparison of categorical variable was done using Chi-square test. Paired t-test was used to test the significant mean difference between continuous variables. Throughout results, 5% level of significance was used. All results were shown 95% of confidence. P value <0.05 was considered as significant.

RESULTS

The present study was carried to assess peripheral neuropathy in female patients receiving weekly paclitaxel chemotherapy for CA breast. A total of 60 patients were included in the present study with mean age of 50.77±10.15, ranging between 28 to 75 years (Figure 1). There were total 30 (50%) patients out of 60, having symptoms of peripheral neuropathy. Majority [12 (40%)] of the patients had tingling sensation as symptom followed by numbness in 10 (33.3%) patients, 3 (10%) patients had paraesthesia and hypoesthesia, and 2 (6.7%) had muscle wasting. The grades of neuropathy among study

population were recorded at baseline and after 1-, 2-, 3-, and 6-months follow-up. At baseline all the 60 patients had neuropathy grade of '0'.

The number of patients with grades 1 neuropathy were 4, 15, 21 and 19 at 1-,2-, 3- and 6 months respectively and with grade 2 neuropathy were 1, 3, 11 and 9 at 1-,2-, 3- and 6 months respectively. Among these patients, for 3 patients' chemotherapy with Paclitaxel was stopped before completion of 12 weeks. The distribution of patients according to grade of neuropathy at different follow ups is presented graphically (Figure 2).

The sural sensory nerve action potential (SNAP) was evaluated for all patients at baseline and at 3 months. The means of SNAP values at baseline and 3 months for all nerves were calculated and compared using student 't' test. We reported significant difference in the SNAP value between baseline and 3 months for right ulnar nerve, right and left sural nerve. The mean values of SNAP with respective P values are shown in Table 1.

Compound motor action potential (CMAP) at baseline and 3 months for various nerves with respective p values are shown in table number 2 and presented graphically. There was a significant difference in the means of CMAP for right median nerve ($p<0.001$), right ulnar nerve ($p=0.03$), right ($p<0.001$) and left ($p<0.001$) tibial nerves (Table 2).

The association between paclitaxel dosage in milligrams and the grades of neuropathy was assessed using Chi-square test at different follow-ups. The distribution of patients according to treatment with paclitaxel and grades of neuropathy at different follow-ups at 1, 2, 3 and 6 months is shown in table number 3 and presented graphically. There was no significant difference in distribution of patients according to grades of neuropathy and dosage of paclitaxel was noted in the present study (Figure 3).

The patient distribution according to the type of symptom and grade of neuropathy at each follow up is depicted in Table 3.

Table 1: Evaluation of sensory nerve action potential (SNAP).

Parameters		Mean	SD	P value
Right median nerve	At baseline	27.33	4.71	0.16
	At 3 months	26.09	5.25	
Left median nerve	At baseline	25.99	4.18	0.95
	At 3 months	25.93	5.28	
Right ulnar nerve	At baseline	20.36	4.12	<0.001
	At 3 months	22.74	4.92	
Left ulnar nerve	At baseline	20.39	4.50	0.75
	At 3 months	20.12	4.42	
Right sural nerve	At baseline	18.61	3.01	0.01
	At 3 months	20.41	5.08	
Left sural nerve	At baseline	20.95	3.87	<0.001
	At 3 months	17.49	4.79	

Note: *Significant p value.

Table 2: Evaluation of CMAP.

Parameters		Mean	SD	P value
Right median nerve	At baseline	11.69	2.82	<0.001
	At 3 months	13.21	3.38	
Left median nerve	At baseline	11.13	2.68	0.29
	At 3 months	11.72	3.80	
Right ulnar nerve	At baseline	12.91	2.04	0.03
	At 3 months	14.03	3.37	
Left ulnar nerve	At baseline	13.54	2.79	0.14
	At 3 months	14.35	3.55	
Right peroneal nerve	At baseline	7.26	1.22	0.08
	At 3 months	6.83	1.88	
Left peroneal nerve	At baseline	7.28	1.49	0.53
	At 3 months	7.47	1.62	
Right tibial nerve	At baseline	18.46	3.17	<0.001
	At 3 months	14.55	3.66	
Left tibial nerve	At baseline	19.37	3.42	<0.001
	At 3 months	14.26	3.38	

Note: *Significant p value.

Table 3: Distribution of patients as per grades of neuropathy and each follow-up and type of sign and symptoms.

Grade of neuropathy		Symptom types					Total
		Muscle wasting	Numbness	Paraesthesia	Hypoesthesia	Tingling	
At 1 month	Grade 0	1	5	2	2	9	19
	Grade 1	1	0	1	1	1	4
	Grade 2	0	1	0	0	0	1
At 2 months	Grade 0	0	2	0	2	2	6
	Grade 1	2	3	2	1	7	15
	Grade 2	0	1	1	0	1	3
At 3 months	Grade 0	0	0	0	0	0	0
	Grade 1	2	2	2	3	4	13
	Grade 2	0	4	1	0	6	11
At 6 months	Grade 0	0	1	1	0	1	3
	Grade 1	1	2	1	3	5	12
	Grade 2	1	3	1	0	4	9

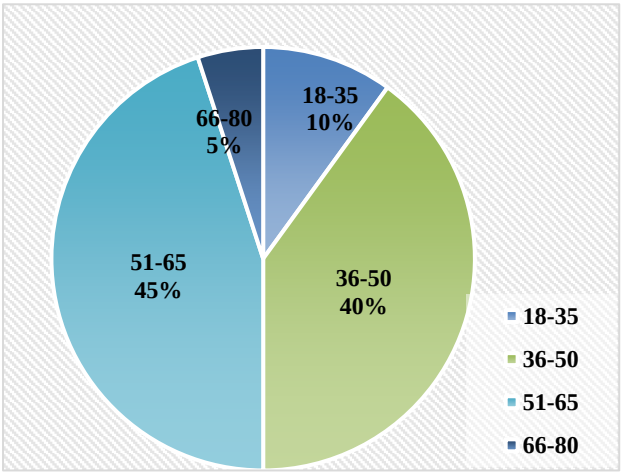

Figure 1: Age distribution of study participants (in years).

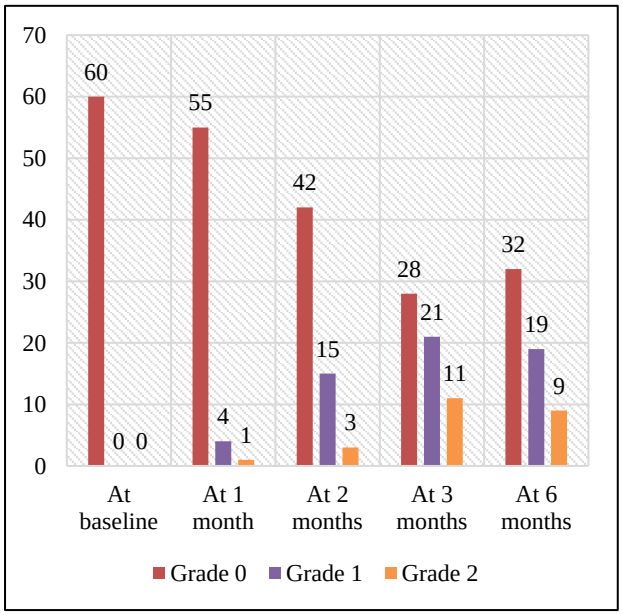

Figure 2: Grades of neuropathy.

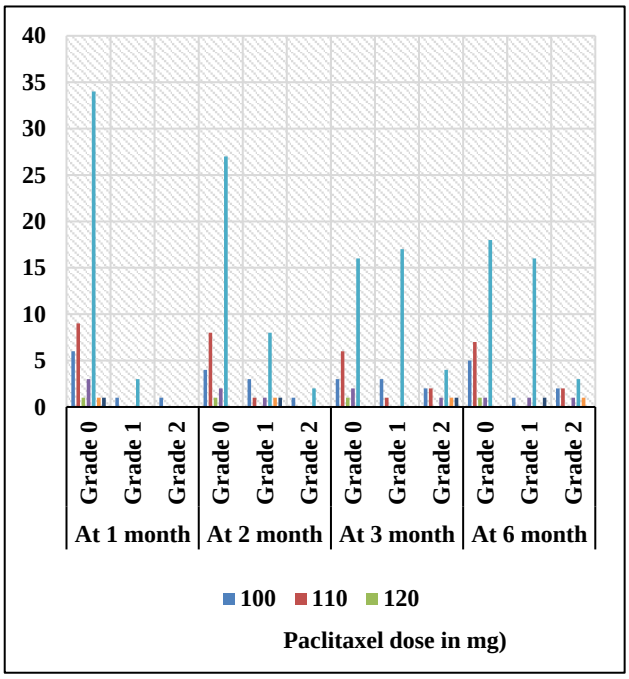

Figure 3: Association of grades of neuropathy and paclitaxel dosage.

DISCUSSION

Peripheral neuropathy is only a significant and frequent dose-limiting side effect for a select few medications, such as paclitaxel. CIPN is estimated to occur in up to 80% of paclitaxel-treated patients with breast cancer.[12-14]

The present study was carried out to assess peripheral neuropathy in CA breast patients receiving weekly paclitaxel chemotherapy. A total of 60 patients undergoing weekly paclitaxel chemotherapy regimen were included, with a mean age of 50.77±10.15, ranging between 28 and 75 years. Molassiotis et al evaluated the 343 samples over the course of a year. They ranged in age from 33 to 79, with a mean age of 55.15 (SD=9.4; range=33-79).[15]

In our study, there were no patients at baseline with peripheral neuropathy; the incidence of grade 1 peripheral neuropathy at 1, 2, 3, and 6 months was 6.7%, 25%, 35%, and 31.66% of patients, respectively, while grade 2 neuropathy was noted in 1.7%, 5%, 18.33%, and 14.75% of patients, respectively. Molassiotis et al observed that upto 23.1% patients with grade 2 sensory neuropathy and 7.7% with grade 2 motor neuropathy at cycle 6 which increased to 25.9% and 18.5% at 6 months' follow-up.[15]

A total of 30 (50%) patients showed symptoms of peripheral neuropathy. Tingling was the most common symptom (40%), followed by numbness in 10 (33.3%), paresthesia and hypoaesthesia in 3 each (10%), and muscle wasting in 2 patients. According to Molassiotis et al study, patients with paclitaxel had a higher incidence of tingling in the hands/fingers (42.9%), tingling in the feet/toes (42.9 %); burning pain (23.8%); dizziness (19%); blurred vision (38.1%) or muscle cramps (28.6%).[15]

The SNAP for the right ulnar nerve and the right and left sural nerve differ significantly between baseline and 3 months. CMAP differed significantly at baseline and at 3 months for the right median nerve, right ulnar nerve, and right and left tibial nerves. Molassiotis et al. demonstrated a marked reduction in SNAP (sensory) amplitudes of the upper limbs in comparison to the lower limbs.[15] In contrast to the upper limbs, the lower limbs' CMAP (motor) amplitudes significantly decreased at the end of the NCS.

With potential neuroprotective agents, numerous attempts have been made to prevent chemotherapy-induced neuropathy. However, a requirement for the use of any such agent is that it should not change the pharmacokinetic profile of the agent or diminish the antitumor activity of the antineoplastic therapy.[11]

Limitation

The study has been done with a small sample size and in women suffering from carcinoma breast which may limit the generalizability of results.

CONCLUSION

The present study was conducted to assess peripheral neuropathy in patients receiving weekly paclitaxel chemotherapy. A total of 60 patients receiving weekly paclitaxel chemotherapy were included in the present study. The mean age of 50.77±10.15, ranging between 28 to 75 years. There was total 30 (50%) patients out of 60, having signs symptoms of peripheral neuropathy, whereas 30 (50%) patients were asymptomatic. Majority (12 (40%)) of the patients had tingling sensation as symptom followed by numbness in 10 (33.3%) patients, 3 (10%) patients each had paraesthesia and hypoesthesia, and 2 had muscle wasting. At baseline all the 60 patients had no neuropathy. The incidence of grade 1 peripheral neuropathy at 3 and 6 months was 35%, and 31.66%, while grade 2 neuropathy was noted in 18.33%, and 14.75% of patients, respectively. There was a significant difference in the SNAP value between baseline and 3 months for right ulnar nerve, right and left sural nerve and CMAP for right median nerve, right ulnar nerve, right and left tibial nerves which suggests development of neuropathy during 3 months of paclitaxel chemotherapy.

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