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Effect of Menopausal Status on Chemotherapy-Induced Peripheral Neuropathy: Single-Institution Retrospective Audit

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Abstract

Introduction Paclitaxel can cause peripheral neuropathy in up to 60% of patients. Chemotherapy-induced peripheral neuropathy (CIPN) compromises quality of life and often leads to dose reduction or discontinuation of lifesaving chemotherapy. Preclinical models have suggested the possible neuroprotective effect of progesterone through remyelination and other mechanisms.

Objectives The aim of this study was to evaluate the incidence of CIPN for different menopausal status.

Materials and Methods We evaluated the effect of menopausal status, as a surrogate for circulating progesterone levels, on the risk of developing paclitaxel-induced peripheral neuropathy, in an audit of breast cancer patients. Data on CIPN (by clinical history and examination) and other variables were collected from the case charts of patients who had received paclitaxel-based chemotherapy for breast cancer at our institution.

Results Five hundred and fifty women were treated with either neoadjuvant or adjuvant paclitaxel in this period. Of these, 262 (47.6%) women were premenopausal, 49 (8.9%) were perimenopausal, and 239 (43.5%) were postmenopausal at the time of diagnosis. Forty-five (8.1%) women had pre-existing diabetes mellitus. Two hundred and fifty-six (82.31%) developed chemotherapy-induced amenorrhea (CIA).

CIPN was seen in 32.7% of women who continued to be premenopausal after receiving chemotherapy and 62.3% of postmenopausal women. Thirty-five (77.8%) out of forty-five diabetic women developed CIPN. On a multivariate logistic regression model, pre-existing diabetes mellitus (risk ratio [RR] = 2.64, 95% confidence interval [CI]:

Keywords
- breast cancer
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1.26–5.52, $p = 0.009$), postmenopausal (RR = 2.84, 95% CI = 1.48–5.45, $p = 0.002$), and CIA status (RR = 2.17, 95% CI = 1.14–4.12, $p = 0.018$) were significantly associated with the development of CIPN. Number of cycles did not appear to have an impact ($p = 0.819$).

Conclusions Postmenopausal status was independently associated with higher incidence of CIPN. One of the possible mechanisms could be lower circulating progesterone levels in these patients. A randomized controlled trial (CTRI/2015/11/006381) is ongoing to test this hypothesis.

Introduction

Breast cancer is the most common cancer among women worldwide, and also the leading cause of cancer death in over 100 countries.[1,2] Management of breast cancer involves multimodality treatment and taxanes have moved into first-line therapy with disease free and overall survival benefits.[3]

The antineoplastic activity of paclitaxel is accompanied by potentially debilitating side effects such as a peripheral neuropathy. Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting side effect of several first-line chemotherapeutic agents[4]. CIPN is a schedule and dose-dependent cumulative toxicity with dose being the most important risk factor for developing CIPN.[4–6] Other causal factors are prior/concomitant administration of platinum compounds or vinca alkaloids, age, pre-existing neuropathy of other causes, while common among them is diabetes.[7–10] The most widely accepted mechanism of paclitaxel-induced neuropathy is a "dying back" process starting from the distal nerve endings and eventually resulting in a disturbed cytoplasmic flow in the affected neurons.[4,11,12] Injury of neuronal and nonneuronal cells within the peripheral nervous system, macrophage activation in both the dorsal root ganglion and peripheral nerve, and microglial activation within the spinal cord are other plausible mechanisms behind taxane-induced neuropathy.[13] Various pharmacological and nonpharmacological agents have been tested for the management of CIPN. A systematic review investigating 18 agents, such as amifostine (WR-2721), glutamine, vitamin E, recombinant human leukemia inhibitory factor (AM424), acetyl-*l*-carnitine, among others, found that there are no agents that have shown consistent, clinically meaningful benefits for CIPN prevention.[14]

Progesterone has been evaluated for a neuroprotective effect in animal models of Alzheimer's disease, stroke, and traumatic brain injury via genomic and nongenomic pathways[15] but never evaluated for its possible role in preventing CIPN. We propound that progesterone with its neurotropic effect would be protective against clinically manifest peripheral neuropathy. In this audit, we evaluated the effect of menopausal status as a surrogate for circulating progesterone levels on the risk of developing taxane-induced peripheral neuropathy and therefore its potential use in its prevention of CIPN.

Materials and Methods

Study Design

At a tertiary cancer center in Mumbai, we conducted a retrospective audit of data collected on 550 women on follow-up treated with taxanes for breast cancer. In 2013, data was recorded of incidence of CIPN among women presenting to the follow-up clinic and had received taxane-based chemotherapy for nonmetastatic breast cancer. We performed a retrospective audit of that cross-sectional cohort.

Study Population

The inclusion criteria were all women who presented in that month to the follow-up clinic, having been treated at our institute for nonmetastatic breast cancer and having received taxane-based chemotherapy. Women were in varying stages of 2 to 4 years of follow-up from adjuvant therapy.

Objectives

The primary aim of the audit was to evaluate if there was any difference in the incidence of CIPN in our patient cohort by menopausal status. The secondary aims were to evaluate any other factors that play a role in the same.

Study Groups

Treatment-related details and clinician reports documenting CIPN were obtained from the hospital case records. Clinical information such as data on CIPN (by clinical history including CIPN while on chemotherapy and sensory neuropathy examination if available), menstrual history, and other variables were also collected from patient's records seen in the follow-up outpatient department. Women were considered pre/perimenopausal if their last menstrual period was within the previous 1 year. We have reviewed the data as premenopausal and postmenopausal at presentation prior to chemotherapy. We have reclassified patients based on surrogate markers for circulating progesterone into three groups:

1. Those patients who continued to have menstrual cycles post-chemotherapy completion as premenopausal (a surrogate for sustained cyclical presence of progesterone).
2. Those patients who achieved chemotherapy-induced amenorrhea (CIA) after a few chemotherapy cycles

(surrogate for presence of progesterone levels for few cycles).
3. Those patients who were postmenopausal prior to chemotherapy (no or negligible circulating progesterone).

Neuropathy (sensory) was evaluated on a score of 1 to 4 using the National Cancer Instiutue -Common Toxicity Criteria (NCI-CTC) 2.0 version (4) for adverse events.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics and treatment timelines. Univariate and multivariate cox regression analysis was used to evaluate factors affecting CIPN. For descriptive analysis and cox estimates, IBM SPSS Statistics for Windows, Version 21.0, IBM Corp, Armonk, New York, United States, was used.

Ethics Approval

The study (Project no: 900774) was approved by the institutional ethics committee on February 18, 2021 and a waiver of consent was granted as it was a retrospective audit of data collected in the clinic. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with Helsinki Declaration of 1964, as revised in 2013.

Results

We evaluated women who were seen in the breast follow-up clinic. Of the 550, median age was 48 years (range: 22–77 years); 490 women were less than 60 years of age, whereas 60 women were above the age of 60. Two hundred and sixty-two (47.6%) women were premenopausal, 49 (8.9%) were perimenopausal, and 239 (43.5%) were postmenopausal.

Table 1 Menopausal details

	Premenopausal ($n = 262$)	Perimenopausal ($n = 49$)
CIA and did not resume menses (256)	210 (80.1%)	46 (93.8%)
No CIA or those who resumed menses post CIA (55)	52 (19.8%)	03 (6.1%)

Abbreviation: CIA, chemotherapy-induced amenorrhea.

Two hundred and fifty-six (82.31%) women gave history of having developed CIA. Of the 262 premenopausal women, 52 (19.8%) and 3/49 (6.1%) perimenopausal women did not develop CIA or resumed their menstrual cycle while on treatment (►**Table 1**). Forty-five out of 550 (8.1%) women were diabetics on treatment prior to starting treatment for breast cancer. Paclitaxel-based chemotherapy was administered either in the neoadjuvant or the adjuvant setting. Dosing schedules were either weekly, biweekly (dose dense with granulocyte colony stimulating factor [GCSF] support), or triweekly (►**Table 2**).

Overall, 306/550 (55.6%) women gave history suggestive of having developed varying grades of CIPN, with 48/306 (15.6%) women reported having grade III to IV neuropathy, more prevalent in the lower limbs. The incidence of neuropathy was 157/311 (50.5%) in premenopausal women compared to 149/239 (62.3%) in postmenopausal women ($p = 0.006$). CIPN history was noted in 18/55 (32.7%) women who continued to be premenopausal after receiving chemotherapy and 149/239 (62.3%) postmenopausal women.

Table 2 Overall study group

	Persistently Pre/perimenopausal	Chemotherapy-induced amenorrhea	Postmenopausal
n	55 (10%)	256 (46.5%)	239 (43.4%)
Median age	37	44	55
CIPN incidence	18 (32.7%)	139 (54.2%)	149 (62.3%)
Grade III CIPN	2 (11.1%)	18 (12.9%)	28 (18.7%)
DM, yes	0	15 (5.8%)	30 (12.5%)
Adjuvant taxanes	51 (92.7%)	244 (95.3%)	228 (95.3%)
Neoadjuvant taxanes	4 (7.2%)	12(4.6%)	11 (4.6%)
Total no of cycles of taxanes			
≤ 4	46 (83.6%)	188 (73.4%)	177 (74.0%)
>4	09 (16.3%)	68 (26.5%)	62 (25.9%)
Schedule of taxanes			
Weekly	7 (12.7%)	53 (20.7%)	57 (23.8%)
Triweekly	48 (87.2%)	203 (79.3%)	182 (76.1%)
Chemotherapy stopped due to CIPN	01 (5.5%)	10 (7.2%)	16 (10.7%)

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DM, diabetes mellitus.

Table 3 Multivariate logistic regression analysis for incidence of CIPN

Variable	RR	95% CI	*p*-Value
Diabetes	2.648	1.26–5.52	0.009
Menopausal status			
Premenopausal (ref)			
Chemotherapy-induced amenorrhea	2.17	1.14–4.12	0.018
Postmenopausal	2.84	1.48–5.45	0.002
No of cycles (> 4)	1.00	0.948–1.07	0.819

Abbreviations: CI, confidence interval; CIPN, chemotherapy-induced peripheral neuropathy; RR, risk ratio.

Among those who developed CIA, 139/256 (54.3%) women reported symptoms suggestive of neuropathy (►**Table 2**). Thirty-five (77.8%) out of forty-five diabetic women developed CIPN. Other factors that were evaluated were grade of neuropathy, extremities involved, and number of women in whom chemotherapy was discontinued due to neuropathy. Premenopausal (persistently premenopausal and CIA) women reported less grade III (15/129 [11.7%] vs. 13/177 [7.3%]) compared to postmenopausal women in the upper limbs and lower limbs (15/129 [11.7%] vs. 30/177 [16.9%]). One premenopausal and four postmenopausal patients experienced only joint pain as a side effect of paclitaxel chemotherapy.

Chemotherapy was discontinued in 27 patients due to CIPN.

On a multivariate logistic regression model, pre-existing diabetes mellitus (DM) (risk ratio [RR] = 2.64, 95% confidence interval [CI] = 1.26–5.52, $p = 0.009$), postmenopausal (RR = 2.84, 95% CI = 1.48–5.45, $p = 0.002$) and CIA status (RR = 2.17, 95% CI = 1.14–4.12, $p = 0.018$) were significantly associated with the development of CIPN. Number of cycles did not appear to have an impact ($p = 0.819$) (►**Table 3**).

Discussion

The incidence of CIPN has been reported to range from 30%[16] to as high as 66.6%.[17] The incidence of CIPN in our audit was reported to be 56% for varying grades of CIPN. Higher cumulative doses[18] especially more than 1000 mg/m^2 are associated with severe neuropathy. Grade III or IV sensory neuropathy can occur in 33% of patients receiving paclitaxel at a dose of 250 mg/m^2.[19] We, however, found no association with increasing number of cycles of chemotherapy and thus no association with higher cumulative dose.

Weekly paclitaxel[20,21] and a shorter duration of the drug infusion[20] (1–3 hours) are also associated with increased rates of CIPN. In this audit, the most common grades of neuropathy seen across all three menopausal groups were grade I to II. The incidence of grade III to IV neuropathy in our study population was less than 20%, which could be attributed to the predominant use of triweekly regimens as compared to weekly dosing schedules. Triweekly regimens were used in 41.7 and 80% in the neoadjuvant and adjuvant settings, respectively.

Various studies have evaluated numerous pharmacological and nonpharmacological options to prevent CIPN.[14] However, currently few agents that have been evaluated have failed to show consistent and clinically meaningful benefits for CIPN prevention.

Mechanisms involved in paclitaxel-induced CIPN include immune-mediated processes, loss of peripheral fibers, demyelination and axon degeneration, altered retrograde and anterograde transport, as well as mitochondrial dysfunction.[22] Progesterone has been reported to exert neuroprotective effects in animal models via genomic and nongenomic pathways[15] but never evaluated for its possible role in preventing CIPN. Circulating progesterone levels are predictive of ovulatory cycles and steadily decrease in perimenopause and menopause.[23] We used menstrual history as a surrogate for circulating progesterone in this study. Published studies have not looked at menopausal status and CIPN, though some studies have looked at an increased incidence of CIPN with increasing age.[9] In our study, postmenopausal CIA status was significantly associated with the development of CIPN.

We found postmenopausal status (RR = 2.84, 95% CI = 1.48–5.45, $p = 0.002$), decreasing levels of cyclical progesterone as in amenorrhea after a few chemo cycles (CIA) (RR = 2.17, 95% CI = 1.14–4.12, $p = 0.018$), and pre-existing DM (RR = 2.64, 95% CI = 1.26–5.52, $p = 0.009$) to be significantly associated with risk of CIPN, thus hypothesizing the possible preventive action of progesterone in development of CIPN.

The obvious shortcomings of the study are that it is a retrospective audit with an inherent recall bias. The women were interviewed for CIPN history on follow-up (not during chemotherapy) that may have led to a recall bias. To reduce this bias, clinician assessments, while on chemotherapy, were included in the analysis wherever available. Also, the absence of use of a validated questionnaire further weakens the study. Additionally, CIPN is dose-related; however, standard dosing was reported in both groups, till onset of neuropathy. Any dose modification to chemotherapy in response to neuropathy and/or other toxicities and any imbalances between the two groups will be after the onset of symptoms. One potential concern is that the circulating progesterone levels were not measured at the time of receiving chemotherapy. However, since circulating

progesterone levels steadily decrease in perimenopause and menopause, we used menstrual history as a surrogate for circulating progesterone in this study.

In spite of these shortcomings, the findings of our audit provide food for thought possibly pointing to an untapped resource like progesterone in preventing CIPN. There is a need for conducting clinical trials, using pharmacological and nonpharmacological approaches for evaluating and preventing CIPN.[24] We, thus, propose that progesterone may be of potential benefit and is being investigated in a randomized trial (CTRI/2015/11/006381) for its neuroprotective role in CIPN.

Conclusion

Progesterone has shown benefit in traumatic brain/spinal cord injury and ischemic stroke. The incidence of CIPN in our audit was highest in postmenopausal women with presumably low circulating progesterone levels. Thus, we propose that progesterone may be of potential benefit and would need to be investigated in a randomized trial for its neuroprotective role in CIPN.

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Conflict of Interest
None declared.

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