# Peripheral Neuropathy Caused by Taxanes: A Study for Evaluation.

Abdel-Maksoud, Mohamed Yousef

Ain Shams Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt Hematology Oncology Department, Saad Specialist Hospital, Al-Khober, Saudi Arabia
myousof_72@yahoo.com

**Abstract: Purpose:** Taxanes are effective in the treatment of many common cancers, including lung, breast, prostate, and gynecological malignancies. Paclitaxel and docetaxelare the two most widely used chemotherapy drugs in the taxane family; however, the development of chemotherapy induced peripheral neuropathy (CIPN) often necessitates dose-reduction, which may hamper the effectiveness of the drug and compromise survival outcomes especially when used in the adjuvant setting. Limited literature is available on the prevalence and severity of dose reduction due to CIPN. We sought to determine the frequency and severity of neuropathy and CIPN-induced dose reduction in cancer patients who received taxane-based chemotherapy with study of risk factors. **Methods:** We conducted a prospective review of 64 cancer patients and treated with taxane-based neoadjuvant, adjuvant or palliative chemotherapy at Ain Shams Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt and Hematology Oncology Department, Saad Specialist Hospital, Al-Khober, Saudi Arabia between January 2013 and March 2015. Twenty-eight patients received paclitaxel (43.7%) while thirty-sex patients received decetaxel (56.3%). Doses were administered according to the standard doses/$m^2$ either weekly or every three weeks and patients were followed for manifestations of CIPN during the course of treatment and for 3 months after finishing it if possible. **Results:** Twenty of 64 (31.3%) patients developed neuropathy, with ten of those patients (35.7%) in the paclitaxel group and ten (27.8%) in the docetaxel group. Fourteen (21.9%) patients required dose reduction. Ten (15.6%) of these patients were dose-reduced specifically due to CIPN that developed during treatment and 4 (6.3%) had reductions due to other causes all of them were in the docetaxel group. The median relative dose intensity (received dose/planned dose) for the 14 CIPN-induced dose reduction patients was 80%. Age was a non-significant factor for the development of neuropathy, neither for the whole 64 patients ($p$-value = 0.441), nor for both subgroups ($p$-value = 0.919 for paclitaxel group and = 0.494 in docetaxel group). Patients with older age appeared to have a higher risk of taxane-induced dose reduction but was non-significant for the whole 64 patients(p-value = 0.134 for dose reduction in general and = 0.877 for dose reduction due to neuropathy) and for paclitaxel group (p-value = 0.106 for dose reduction in general and for dose reduction due to neuropathy as all dose reduction cases in paclitaxel group were due to CIPN).In docetaxel arm, age was significant for dose reduction in general ($p$-value = 0.0138) but was non-significant for dose reduction due to CIPN (p-value = 0.156). Patients treated with paclitaxel (rather than docetaxel) experienced a higher but non-significant risk of CIPN and neuropathy-induced dose reduction with p-values of 0.461 and 1.271 respectively, while in case of dose reduction in general, docetaxel had higher incidence but also non-significant ($p$-value = 0.939). Weekly paclitaxel protocol had higher but non-significant risk of CIPN or CIPN-induced dose reduction than 3-weekly protocol ($p$-values = 0.195 and 0.018 respectively).Finally, DM was assessed. For the whole 64 patients, there was significant increase of incidence of CIPN in diabetic patients (p-value = 0.003) and a highly significant dose reduction in the same group (p-value = 0), while there was non-significant increase in dose reduction due to CIPN compared to dose reduction due to other causes ($p$-value = 0.065). Similar results were elicited in the paclitaxel group with significant increase in CIPN and highly significant in dose reduction in general and non-significant in dose reduction due to CIPN compared to dose reduction due to other causes (p-values are 0.011, 0.00001, and 1 respectively).As regards the docetaxel group, the situation is slightly different. CIPN had a non-significant increase in diabetic patients ($p$-value = 0.179). For dose reduction, there was a highly significant increase among diabetic patients ($p$-value = 0.0003) but non-significant in dose reduction due to CIPN compared to dose reduction due to other causes ($p$-value = 0.428). **Conclusions:** In our study, the incidence of CIPN-associated dose reduction in our patient population was 21.9%. Older patients treated with docetaxel had a higher risk for dose reduction; while the diabetic subject shad a higher risk of dose reduction with diabetic patients treated with docetaxel had a higher risk of dose reduction only while diabetic patients treated with paclitaxel had a higher risk for both neuropathy and for dose reduction.

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## 1. Introduction

Advances in chemotherapy have resulted in improvements in disease-free survival and overall survival for persons with cancer, and these improved outcomes are often associated the use of taxane-based regimens.[1]

Taxanes are plant derived and considered microtubule-stabilizing agents that block mitosis in the late G2 mitotic phase of the cell cycle, inducing cell death.[2]

Paclitaxel and docetaxel, the two most widely used chemotherapy drugs in the taxane family, are effective in the treatment of many common cancers, including lung, breast, prostate, and gynecological malignancies.[3]

Despite the benefits of taxane-based chemotherapy, patients frequently experience neuropathic symptoms associated with treatment known as chemotherapy induced peripheral neuropathy (CIPN), which is a common and potentially dose-limiting side effect of both paclitaxel and docetaxel.[4]

The risk of developing taxane-induced peripheral neuropathy is dependent on the drug, schedule, cumulative dose, and patient's risk factors for CIPN which include ethnicity, older age, history of alcoholism, diabetes mellitus (DM), inherited neuropathy, and prior therapy with neurotoxic medications.[5]

The precise pathogenesis through which taxanes exert their neurotoxic effects is unclear; however taxanes are believed to induce sensory and motor neuropathy by mitochondrial dysfunction, oxidative stress and vascular dysfunction. Also, there are associated structural changes in the form of neuropathy, axonopathy, and/or myelinopathy especially in the intra-epidermal nerve fiber (IENF) degeneration.[6]

Upon infusion, paclitaxel induces a rapid decline in axonal mitochondrial membrane, potential spontaneous neuronal firing and reactive oxygen species production resulting in functionally impaired and vacuolated axonal mitochondria in both myelinated and unmyelinated axons.[7]

Also, in experimental animals paclitaxel also causes reduction in the number of vasa nervosa, attenuated nerve blood flow and marked endothelial cell apoptosis.[7]

Few studies have compared CIPN caused by paclitaxel with those caused by docetaxel, although previous studies suggest that docetaxel-induced neuropathies may be less severe and occur with less frequency than paclitaxel-induced neuropathies.[8]

According to the National cancer Institute Common Toxicity criteria for Adverse events (CTCAE) has classified CIP Nintosensory and motor with four grades for each (table 1).[9]

**Table 1:National cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) for CIPN.**

| Neuropathy | Grade 1 | Grade2 | Grade 3 | Grade4 |
|---|---|---|---|---|
| **Peripheral sensory neuropathy** | Asymptomatic with loss of deep tendon reflexes (DTRs). | Moderate symptoms, activities of daily living are limited instrumental (ADL-I) e.g. preparing meals, shopping, using telephone, managing money, etc. | Severe symptoms, activities of daily living are limited self-care (ADL-SC) e.g. bathing, dressing, feeding self, using the toilet, taking medications, and not bed ridden. | Life-threatening consequences-urgent intervention indicated (LTC-UII). |
| **Motor neuropathy, Muscle weakness** | Asymptomatic, intervention not indicated (INI). | Moderate symptoms, activities of daily living are limited instrumental (ADL-I) e.g. preparing meals, shopping, using telephone, managing money, etc. | Severe symptoms, assistance device indicated, activities of daily living are limited self-care (ADL-SC) e.g. bathing, dressing, feeding self, using the toilet, taking medications, and not bed ridden. | Life-threatening consequences-urgent intervention indicated (LTC-UII). |

Clinically, manifestations include distal symmetrical sensory loss, impairments in vibration, loss of deep tendon reflexes (loss of ankle and knee jerk have been described as a characteristic sign associated with docetaxel induced peripheral neuropathy), reduced proprioception, and sensation of numbness, tingling, tickling, burning pain (paresthesia) in a stocking and glove pattern, and muscle weakness.[10]

These symptoms lead to loss of dexterity, gait disturbances, clumsiness, pain, disability and interference with routine daily activities and diminish their quality of life.[11]

CIPN usually develops after a cumulative dose of 135-200 mg/m2 (or after a single dose more than 250 mg/m2) in paclitaxel or a dose of more than 600 mg/m$^2$ in docetaxel. This is usually reached after two to four cycles but some patients experience the pain earlier.[12,13]

CIPN classically occurs within 24–72 hours following taxane administration. The symptoms improve in between cycles with gradual progression

of symptoms with subsequent cycles. In most patients, symptoms of CIPN usually resolve over a period of few weeks following discontinuation of taxanes.[14]

The relationship between weekly versus three-weekly administration of taxanes and neuropathy is uncertain, as the results have revealed conflicting results.[15]

Despite the prospect of poorer survival associated with dose reduction, the incidence and severity of dose reduction specifically due to CIPN has not been well-described and studied prospectively. [16]

Therefore, we conducted a prospective review evaluating the prevalence, severity, and risk factors associated with dose reduction required due to taxane induced peripheral sensory neuropathy among cancer patients at a medical center.

## 2. Materials and methods

Patient clinical information was recorded. From January 2013 to March 2015, a prospective review of 64 cancer patients and treated with taxane-based neoadjuvant, adjuvant or palliative chemotherapy at Hematology Oncology Department, Saad Specialist Hospital, Al-Khober, Saudi Arabia in collaboration with Ain Shams University Clinical Oncology Department, Cairo, Egypt.

Patients were treated per standard of care recommendations and treatment decisions and dose reductions or delays were made based on routine standard of care recommendations. Eligible patients were over 18 years of age and had an established diagnosis of cancer. Data collected included: demographics (age, and gender), taxane received (paclitaxel, or docetaxel), history of diabetes, pre-existing peripheral neuropathy, administration of neurotoxic medications, and alcohol history. Progress notes were reviewed to determine whether patients developed peripheral neuropathy during their chemotherapy course and whether dose reductions were instituted at the discretion of the treating physician.

### Statistical analysis

Patients' demographic and clinical characteristics were assessed and compared between two distinct cohorts of subjects, those who experienced a dose reduction due to any reason and those who did not. In addition we conducted further analyses only among those who experienced a dose reduction, comparing those who had a dose reduction due to CIPN versus those with dose reductions for other reasons.

We assessed the following potential risk factors for CIPN and dose-reduction: age, diagnosis of diabetes mellitus, and type of taxanereceived. History of alcohol intake and prior history of peripheral neuropathy were not assessed as they were negative in all patients. Also, administration of neurotoxic medications was not assessed due to low number of patients (only four patients). Also, among paclitaxel arm, weekly paclitaxel was compared with three-weekly protocol.

Patient and disease characteristics were analyzed using descriptive statistics, and expressed as either relative frequency [percentages] for discrete variables and for continuous variables mean with standard deviation (SD) or median are used. The association between qualitative variables was tested by the Pearson Chi-Square test or when the sample sizes were small, Fisher exact test was used, while the association between quantitative variables was tested by unpaired Student t-test with p-value was calculated for both being significant if less than 0.5 and highly significant if less than 0.001. The SPSS (version 17.0) statistical program was used for all analyses.

## 3. Results

### Patient characteristics

Patient characteristics are shown in Table 2. Of the 64patients, 28 patients were included in paclitaxel group (group A, 43.8%) and 36 patients were included in decetaxel group (group B, 56.2%). Fifty-six(87.5%) were women (26 in group A (92.9%) and 30 in group B (83.3%)) and eight(12.5%) were men (2 in group A (8.1%) and 6 in group B (16.7%)).

The median age was 46.5 years (range, 28–69) with median age in group A was 44.5 years (range, 34–60) and median age in group B was 50.5 years (range, 28–69).Among the paclitaxel group, eighteen patients (64.3%) had weekly protocol and 10 patients (35.7%) had three-weekly protocol, while in the docetaxel group all patients had three-weekly protocol.

Doses were given according to standard protocol regimens with dose of paclitaxel 175 mg/m2 in three-weekly protocol and 80 mg/m2 in weekly protocol for 12 weeks and dose of docetaxel was 80 mg/m2 in 16 patients (44.4%) and 100 mg/m$^2$in 20 patients (55.6%) whose were breast cancer cases treated with adjuvant or neoadjuvant AC (doxorubicin and cyclophosphamide) followed by docetaxel.[17]

None of the patients had a prior history of alcohol or history of previous neuropathy, while only four patients had a prior history of neurotoxic medications (2 in each group). The medications were carboplatin (2 patients) and gemcitabine (2 patients). Finally, sixteen patients (25%) had a diagnosis of diabetes mellitus with 8 patients in group A (28.6%) and 8 patients in group B (22.2%).

Twenty patients (31.3%) developed CIPN, with ten of those patients (35.7%) in the paclitaxel group and ten (27.8%) in the docetaxel group. Fourteen patients (21.9%) required dose reduction during the

course of their treatment (6 patients in group A (21.4%) and 8 patients (22.2%) in group B). Ten of these (15.6%) had dose reductions due to CIPN (6 patients in group A (21.4%) and 4 patients (11.1%) in group B) and 4 (6.3%) had reductions due to other causes (no patients in group A (0%) and 4 patients (11.1%) in group B).

The median relative dose intensity (received dose/planned dose) for the patients that required dose reduction was 80% (range, 75–85) with 20% reduction of dose in all patients who received docetaxel and 25% reduction in patients who received weekly paclitaxel and 15% reduction in those who received three-weekly paclitaxel including those with CIPN-induced dose reduction. In addition to CIPN, the other causes for dose reduction included, myelosuppression (n=2), namely grade IV neutropenia, and poor intolerance (n=2).

**Table 2: Main demographic and baseline patient characteristics in 64 patients**

| Characteristics | N (%) | | |
|---|---|---|---|
| | Total | Group A | Group B |
| **Age** | | | |
| Median | 46.5 | 44.5 | 50.5 |
| Range | 28-69 | 34-60 | 28-69 |
| **Sex** | | | |
| Male | 8 (12.5%) | 2 (8.1%) | 6 (16.7%) |
| Female | 56 (87.5%) | 26 (92.9%) | 30 (83.3%) |
| **Taxane received** | | | |
| Paclitaxel | 28 (100%) | 28 (100%) | 0 (0%) |
| Docetaxel | 36 (100%) | 0 (0%) | 36 (100%) |
| **History of diabetes** | | | |
| | 16 | 8 | 8 |
| **History of alcoholism** | | | |
| | 0 (0%) | 0 (0%) | 0 (0%) |
| **History of pre-existing neuropathy** | | | |
| | 0 (0%) | 0 (0%) | 0 (0%) |
| **Administration of neurotoxic medications** | | | |
| | 4 | 2 | 2 |
| **CIPN** | | | |
| Total | 20 (31.3%) | 10 (35.7%) | 10 (27.8%) |
| Without dose reduction | 10 | 4 | 6 |
| With dose reduction | 10 | 6 | 4 |
| **Dose reduction** | | | |
| Total | 14 (21.9%) | 6 (21.4%) | 8 (22.2%) |
| Without CIPN | 4 (6.3%) | 0 (0%) | 4 (11.1%) |
| With CIPN | 10 (15.6%) | 6 (21.4%) | 4 (11.1%) |

Age was compared as a risk factor as regards CIPN and dose reduction (table 3 and table 4). The mean age of the whole 64 patients was 48.5 years while the mean age for patients who developed CIPN was a slightly younger 46.8 years but that was non-significant ($p$-value = 0.441). The mean age for dose reduction in general (included cases due to CIPN or cases due to other causes) was older 53.3 but it was non-significant also ($p$-value = 0.134), while the mean age of dose reduction due to CIPN was 49 years and again it was non-significant ($p$-value = 0.877).

When the patients were classified into paclitaxel and docetaxel groups, the situation changed a little. In paclitaxel arm, the mean age was 44.9 years while for the CIPN patients it was 44.6 years (non-significant, $p$-value = 0.919) and for dose reduction subgroup it was 43 years for both dose reduction in general and dose reduction due to CIPN as all dose reduction cases in paclitaxel group were due to CIPN (non-significant, $p$-value = 0.106).

In docetaxel arm, the mean age was older 51.3 years while for the CIPN patients it was 49 years (non-significant, $p$-value = 0.494) and for dose reduction subgroup it was 61 years for patients with dose reduction in general (significant, p-value = 0.0138) and 58 years for those with dose reduction due to CIPN (non-significant, $p$-value = 0.156). So, age was a significant factor as regards dose reduction in general in patients received docetaxel only.

**Table 3: Patients' age characteristics (mean and standard deviation)**

| | Age | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | | CIPN | | Dose Reduction due to CIPN | | Dose Reduction in General | |
| | Mean | ±SD | Mean | ±SD | Mean | ±SD | Mean | ±SD |
| Total | 48.5 | 9.57 | 46.8 | 9.67 | 49 | 9.95 | 53.3 | 11.21 |
| Paclitaxel | 44.9 | 6.19 | 44.6 | 9.08 | 43 | 2.36 | 43 | 2.36 |
| Docetaxel | 51.3 | 10.83 | 49 | 10.21 | 58 | 10.39 | 61 | 8.41 |

CIPN: Chemotherapy Induced Peripheral Neuropathy. SD: Standard Deviation.

**Table 4: Significance of age as regards CIPN and dose reduction**

| | Age | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | | CIPN | | Dose Reduction due to CIPN | | Dose Reduction in General | |
| | Mean | ±SD | t | *P*-value | t | *P*-value | t | *P*-value |
| Total | 48.5 | 9.57 | - 0.785 | 0.441(NS) | 0.158 | 0.877(NS) | 1.596 | 0.134(NS) |
| Paclitaxel | 44.9 | 6.19 | - 0.104 | 0.919(NS) | - 1.966 | 0.106(NS) | - 1.966 | 0.106(NS) |
| Docetaxel | 51.3 | 10.83 | - 0.711 | 0.494(NS) | 1.664 | 0.156(NS) | 3.259 | 0.0138(S) |

t: Student t-test. NS: Non-significant. S: Significant.

Type of taxane received was also tested for significance (Table 5). For CIPN and dose reduction due to CIPN, paclitaxel had non-significant higher risk with *p*-values of 0.461 and 1.271 respectively, while in case of dose reduction in general, docetaxel had higher risk but also non-significant (*p*-value = 0.939).

**Table 5: Significance of taxane used**

| | Taxane used | | | | | |
|---|---|---|---|---|---|---|
| | Paclitaxel | | Docetaxel | | Chi-square | |
| | N | % | N | % | $X^2$ | *P*-value |
| Total | 28 | 100% | 36 | 100% | - | - |
| CIPN | 10 | 35.7% | 10 | 27.8% | 0.461 | 0.496(NS) |
| Dose Reduction due to CIPN | 6 | 21.4% | 4 | 11.1% | 1.271 | 0.259(NS) |
| Dose Reduction in General | 6 | 21.4% | 8 | 22.2% | 0.005 | 0.939(NS) |

**$X^2$: Pearson Chi-Square test.**

Among the paclitaxel group weekly protocol was compared to three-weekly protocol as regards incidence of CIPN and dose reduction. It was found higher non-significant incidence of Both CIPN and dose reduction in weekly paclitaxel patients with p-value 0.195 and 0.018 respectively (table 6).

**Table 6: Weekly paclitaxel versus three-weekly protocol**

| | Paclitaxel Weekly versus Three-Weekly | | | | | |
|---|---|---|---|---|---|---|
| | Weekly | | Three-Weekly | | Chi-square | |
| | N | % | N | % | $X^2$ | *P*-value |
| Total | 18 | 64.3% | 10 | 35.7% | - | - |
| CIPN | 8 | 44.4% | 2 | 20% | 1.673 | 0.195(NS) |
| Dose Reduction | 4 | 22.2% | 2 | 20% | 0.018 | 0.890(NS) |

Finally, DM was assessed for the whole 64 patients and for each subgroup (table 7). For the whole 64 patients, there was significant increase of incidence of CIPN in diabetic patients who received taxanes (*p*-value = 0.003) and a highly significant dose reduction in the same group (p-value = 0), while there was non-significant increase in dose reduction due to CIPN compared to dose reduction due to other causes (*p*-value = 0.065). Similar results were elicited in the paclitaxel group with significant increase in CIPN and highly significant in dose reduction in general (*p*-values are 0.011, and 0.00001 respectively). Dose reduction due to other causes was not assessed in that group as that group lacked patients who had dose reduction due to other causes.

As regards the docetaxel group, the situation is slightly different. CIPN had a non-significant increase in diabetic patients (*p*-value = 0.179). For dose reduction in general, there was a highly significant increase among diabetic patients (*p*-value

= 0.0003) but non-significant in dose reduction due to CIPN compared to dose reduction due to other causes (*p*-value = 0.428).

**Table 7: Significance of Diabetes Mellitus**

| | | | DM | | No DM | | Fisher Exact test | |
|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | value | *P*-value |
| Total | CIPN | CIPN | 10 | 15.6 | 10 | 15.6 | 0.003 | S |
| | | No CIPN | 6 | 9.4 | 38 | 59.4 | | |
| | D/R | D/R | 12 | 18.8 | 2 | 3.1 | 0 | HS |
| | | No D/R | 4 | 6.3 | 46 | 71.8 | | |
| | D/R with CIPN | D/R with CIPN | 10 | 15.6 | 0 | 0 | 0.065 | NS |
| | | D/R with no CIPN | 2 | 3.1 | 2 | 3.1 | | |
| Paclitaxel | CIPN | CIPN | 6 | 21.4 | 4 | 14.3 | 0.011 | S |
| | | No CIPN | 2 | 7.1 | 16 | 57.2 | | |
| | D/R | D/R | 6 | 21.4 | 0 | 0 | 0.00001 | HS |
| | | No D/R | 2 | 7.1 | 20 | 71.5 | | |
| | D/R with CIPN | D/R with CIPN | 6 | 21.4 | 0 | 0 | - | - |
| | | D/R with no CIPN | 0 | 0 | 0 | 0 | | |
| Docetaxel | CIPN | CIPN | 4 | 11.1 | 6 | 16.7 | 0.179 | NS |
| | | No CIPN | 4 | 11.1 | 22 | 61.1 | | |
| | D/R | D/R | 6 | 16.7 | 2 | 5.6 | 0.0003 | HS |
| | | No D/R | 2 | 5.6 | 26 | 72.1 | | |
| | D/R with CIPN | D/R with CIPN | 4 | 11.1 | 0 | 0 | 0.428 | NS |
| | | D/R with no CIPN | 2 | 5.6 | 2 | 5.6 | | |

**DM: Diabetes Mellitus. D/R: Dose reduction. HS: Highly significant.**

## 4. Discussion

In this prospective analysis of patients treated with taxanes, we sought to determine the frequency and severity of neuropathy and CIPN-induced dose reduction in cancer patients who received taxane-based chemotherapy with study of risk factors. These results add to a sparse body of literature pertaining to the frequency of taxane-associated CIPN and dose reduction.

In our study, twenty of 64 (31.3%) patients developed neuropathy, with ten of those patients (35.7%) in the paclitaxel group and ten (27.8%) in the docetaxel group. Fourteen (21.9%) patients required dose reduction. Ten (15.6%) of these patients were dose-reduced specifically due to CIPN that developed during treatment and 4 (6.3%) had reductions due to other causes all of them were in the docetaxel group. Those other causes for dose reduction included, myelosuppression (n=2, 3.15%), namely grade IV neutropenia, and poor intolerance (n=2, 3.15%).

**Bhatnagar and colleagues, 2014** conducted a retrospective single-institution breast cancer clinic chart review of 123 newly diagnosed breast cancer patients and treated with taxane-based neoadjuvant/adjuvant chemotherapy at the University of Maryland Greenebaum Cancer Center between January 2008 and December 2011. Forty-six patients received paclitaxel and 70 patients received docetaxel while the remaining seven patients received multiple agents. Forty-nine (40%) patients required dose reduction. Twenty-one (17%) of these patients were due to CIPN that developed during treatment while in the remaining 28 patients (23%) dose was reduced due to other causes as diarrhea (10 patients), infection (5 patients), myelosuppression (3 patients), hypersensitivity reaction (3 patients) and other causes (5 patients).[18]

Another study, **Shimozuma *et al.*, 2012** evaluated CIPN and health-related quality of life in the first 300 patients enrolled in a larger (1,060 total) multicenter phase III trial randomized to one of four adjuvant chemotherapy regimens: (1) anthracyclinecyclophosphamide (AC) followed by paclitaxel, (2) AC followed by docetaxel, (3) paclitaxel alone, or (4) docetaxel alone. CIPN was assessed by the Patient Neurotoxicity Questionnaire and the National Cancer Institute Common Toxicity Criteria. CIPN and health-related quality of life scores were compared between paclitaxel alone vsdocetaxel alone, AC paclitaxelvs paclitaxel alone, AC docetaxel vs. docetaxel alone, and AC paclitaxel and paclitaxel alone vs. AC docetaxel and docetaxel alone.[19]

A third study, **Speck *et al.*, 2013** included 488 women who received docetaxel (209 patients) or paclitaxel (279 patients with 49 of them received weekly paclitaxel and 230 received biweekly paclitaxel). Those eligible for this retrospective cohort study were women with non-metastatic breast cancer

with an adjuvant or neoadjuvant treatment plan including docetaxel or paclitaxel between June 1, 2009, and December 31, 2011, administered at the Rena Rowan Breast Center of the Abramson Cancer Center, part of the University of Pennsylvania Health System. Patients were excluded if they had metastatic disease (stage IV), previous neurotoxic chemotherapy, or pre-existing clinically documented neuropathy. Women were also excluded if they were pregnant or within 3 months postpartum or if they had a prosthetic limb or amputation, because these conditions would result in altered weight and affect body mass index (BMI) and body surface area (BSA) calculations. The primary outcome was a dose limiting (DL) event (dose delay, dose reduction, or treatment discontinuation) attributed to CIPN (DL CIPN). A total of 150 unique DL events occurred in 120 women (24.6%). More than one third (37.3%; n=56) of the events were attributed to CIPN. The 56 DL CIPN events occurred in 50 women (10.2%), with five out of 209 in docetaxel group (2.4%) and forty-five out of 279 in paclitaxel arm (16.1%). Dose reduction or treatment discontinuation attributed to CIPN was detected in 35 patients (7.2%) with 9 patients had dose reduction (1.8%, seven in paclitaxel group five of them in weekly arm and two in biweekly arm and two patients in docetaxel group) compared to 26 patients who had treatment discontinuation (5.4%, twenty-four in paclitaxel group seventeen of them in weekly arm and seven in biweekly arm and two patients in docetaxel group).[20]

In our analysis, the median relative dose intensity (received dose/planned dose) for the 14 CIPN-induced dose reduction patients was 80% (range, 75–85) compared to 73.4% (range, 68.0-94.0%) in **Bhatnagar *et al.*, 2014** while in **Speck *et al.*, 2013** The average dose intensity for patients that had their dose reduced and those who had their treatment discontinued was 76.5% (90.6% in dose reduction patients and 71.6% in treatment discontinuation patients).

In our study, the mean age of the whole 64 patients was 48.5 years while the mean age for patients who developed CIPN was a slightly younger 46.8 years but that was non-significant (p-value = 0.441). The mean age for dose reduction in general (included cases due to CIPN or cases due to other causes) was older 53.3 years but it was non-significant also (p-value = 0.134), while the mean age of dose reduction due to CIPN was 49 years and again it was non-significant (p-value = 0.877). When the patients were classified into paclitaxel and docetaxel groups, in paclitaxel arm, the mean age was 44.9 years while for the CIPN patients it was 44.6 years (non-significant, p-value = 0.919) and for dose reduction subgroup it was 43 years for both dose reduction in general and dose reduction due to CIPN as all dose reduction cases in paclitaxel group were due to CIPN (non-significant, p-value = 0.106). In docetaxel arm, the mean age was older 51.3 years while for the CIPN patients it was 49 years (non-significant, p-value = 0.494) and for dose reduction subgroup it was 61 years for patients with dose reduction in general (significant, p-value = 0.0138) and 58 years for those with dose reduction due to CIPN (non-significant, p-value = 0.156). So, age was a significant factor as regards dose reduction in general in patients received docetaxel only.

In **Bhatnagar *et al.*, 2014** similar results were obtained. The mean age of the whole 123 patients was 53 years (range, 32-78) while the mean age for patients who needed dose reduction in general (included cases due to CIPN or cases due to other causes) was older 53 years (range, 35-75) but it was non-significant (p-value = 0.23). When the mean age of dose reduction due to CIPN (55 years, range 35-67) was compared to dose reduction due to other causes (55 years, range 42-75) it was also non-significant (p-value = 0.84).

When the type of taxane received was tested for significance in our analysis,paclitaxel had non-significant higher risk for CIPN and dose reduction due to CIPN with p-values of 0.461 and 1.271 respectively, while in case of dose reduction in general, docetaxel had higher risk but also non-significant (p-value = 0.939).

The results obtained in **Bhatnagar *et al.*, 2014** were slightly different as paclitaxel had higher but non-significant risk than docetaxel as regards dose reduction in general (p-value = 0.57), but when dose reduction was divided into dose reduction due to CIPN and dose reduction due to other causes, paclitaxel was significantly higher than docetaxel in dose reduction due to CIPN (p-value = 0.001). Also, there was a third arm comprising patients who received multiple taxane agents. When both paclitaxel and docetaxelarms were collectively compared with multiple agents arm as regards dose reduction in general, the later was significantly higher (p-value = 0.02). When dose reduction was divided into dose reduction due to CIPN and dose reduction due to other causes, the multiple agents arm was non-significantly higher (p-value = 0.68).

In **Shimozuma *et al.*, 2012** the incidence of CIPN was significantly higher in taxanemonotherapy when compared to AC followed by taxane (p-value = 0.03), but more importantly, when paclitaxel was compared to docetaxel as regards the incidence of CIPN, paclitaxel was non-significantlyhigher (p-value = 0.669), which is similar to our study.

In **Speck and colleagues study, 2013** results coincided with **Bhatnagar study**. In this study, dose limiting (DL) event (dose delay, dose reduction, or treatment discontinuation) attributed to CIPN (DL

CIPN) in paclitaxel arm was 8-times higher than (DL CIPN) in docetaxel arm (significant, p-value = 0.001).

When weekly paclitaxel protocol was compared to three-weekly protocol as regards incidence of CIPN and dose reduction, weekly protocol was found to have higher non-significant incidence of Both CIPN and dose reduction with p-value 0.195 and 0.018 respectively. Those results are comparable to results elicited in **Speck *et al.*, 2013** where DL CIPN obtained in weekly paclitaxel arm was nearly two-fold to DL CIPN elicited in bi-weekly arm but it was non-significant (p-value = 0.8).

Finally, DM was assessed for the whole 64 patients and for each subgroup. For the whole 64 patients, there was significant increase of incidence of CIPN in diabetic patients who received taxanes (p-value = 0.003) and a highly significant dose reduction in the same group (p-value = 0), while there was non-significant increase in dose reduction due to CIPN compared to dose reduction due to other causes (p-value = 0.065). Similar results were elicited in the paclitaxel group with significant increase in CIPN and highly significant in dose reduction in general (p-values are 0.011, and 0.00001 respectively). Dose reduction due to other causes was not assessed in that group as that group lacked patients who had dose reduction due to other causes. In the docetaxel group, CIPN had a non-significant increase in diabetic patients (p-value = 0.179). For dose reduction in general, there was a highly significant increase among diabetic patients (p-value = 0.0003) but non-significant in dose reduction due to CIPN compared to dose reduction due to other causes (p-value = 0.428).

In **Bhatnagar *et al.*, 2014** diabetes was assessed for the whole 123 patients as regards dose reduction in general then dose reduction due to CIPN and due to other causes were compared with DM. Diabetes mellitus was associated with a two-fold risk for taxane-associated dose reduction and was found to be a significant risk factor for dose reduction in general in patients received taxanes (p-value = 0.02), while DM was a non-significant factor when dose reduction due to CIPN was compared to dose reduction due to other causes(p-value = 0.51). Those results coincide with the results obtained in our analysis.

From our study and other similar studies we can conclude the following; the incidence of peripheral neuropathy due to taxanesvaries and is based largely on several predisposing risk factors such as age, race, type of taxane used, dose per cycle, concurrent therapy with other neurotoxic agents, treatment schedule, cumulative dose, duration of infusion and pre-existing neuropathy from other medical conditions such as diabetes.

CIPN remains an important toxicity of taxane administration. A recently published study demonstrated that CIPN, in and of itself, has no effect on disease free survival, progression free survival or overall survival [21], however, the potential consequences of dose reduction as a result of CIPN on PFS and OS remain unknown. In its most severe form, CIPN greatly impairs quality of life and can potentially lead to secondary consequences such as increased risk of recurrent falls [22]. Most importantly, as demonstrated in our report as well as in several others, it can be severe enough to warrant discontinuation of a highly effective class of chemotherapy agents, prompting further investigation for potential risk-factors.

The limitations of this study include relatively small sample size, which could result in bias in the determination of cause of dose reduction. In addition, when examining risk factors for CIPN-specific dose reduction, we compared those with CIPN dose reductions to patients who had dose reductions for other reasons. Thus associations may be due to factors that relate to taxane administration, development of CIPN, or other causes. Because CIPN dose reduction is directly related to the severity of CIPN, other comparison groups, such as those who experienced CIPN without dose reduction, would only provide indicators of CIPN incidence or severity. Further elucidation of additional factors for CIPN dose reduction may therefore prove to be problematic. Furthermore, many other risk factors were not assessed in our study such as race, alcoholism, history of intake or administration of other neurotoxic medications, and history of neuropathic disorders other than DM.

The strengths of this study include the fact that this is one of the few studies to report incidence and risk factors for dose reduction, as well as the magnitude of dose reduction.

In conclusion, CIPN is significant dose-limiting toxicity of taxane use. Elucidation of risk factors will be valuable in identifying patients at risk for developing CIPN and tailoring their treatment accordingly so as to avoid dose reductions of effective chemotherapy agents.

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