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Original Article

# Paclitaxel-Induced Peripheral Neuropathy Using NCI-CTC in Isfahan, Iran

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**Abstract**

Paclitaxel is a highly effective anticancer agent. It is active against a broad range of cancers that are generally considered refractory to conventional chemotherapy. Paclitaxel induces a peripheral neuropathy (PN) that is characterized by sensory symptoms such as numbness and paresthesia in a glove and stocking distribution. PN may be severe and dose limiting at initial doses above 275 mg/m$^2$. Our purpose was to evaluate the incidence, severity, dose dependency, and reversibility of paclitaxel-induced neuropathy. We studied 45 patients with breast cancer, treated with Paclitaxel (240, 270, 300 mg/m$^2$) in an average of 4 cycles of treatment. Paclitaxel was administered by a 3 h intravenous infusion every 3 weeks in all patients. We used National Cancer Institute-Common Toxicity Criteria (NCI-CTC) to evaluate peripheral neuropathy. The cumulative dose of paclitaxel in each patient was also measured. The severity of symptoms was graded. Incidence and reversibility of neuropathy was measured in an interview with the patient. Paresthesias appeared in 39 (86.6%) patients after an average cumulative dose of 394 mg/m$^2$. In most patients, PN was seen after the first or second dose (68%) of paclitaxel and then stabilized in 36%, improved in 36%, resolved completely in 24% and progressed in 4%. There was no need to discontinue Paclitaxel in any of the patients due to PN. In view of our experience in the present study, we found that Paclitaxel-induced neuropathy is a dose-dependent phenomenon, and most of the symptoms occurred after the first or second phase of treatment.

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## 1. Introduction

Taxol (Paclitaxel), a microtubule toxin derived from the western yew tree is

**Table 1.** Grading of neurologic symptoms according to the NCI-CTC criteria.

| | |
|---|---|
| 0 | Normal |
| 1 | Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function |
| 2 | Objective sensory loss or paresthesia (including tingling) interfering with function but not interfering with activities of daily living |
| 3 | Sensory loss or paresthesia interfering with activities of daily living |
| 4 | Permanent sensory loss that interferes with function |

particularly effective against solid tumors such as ovarian, breast, lung and head and neck cancers [1, 2]. This drug kills cancer cells reducing the size of tumor and prevents spreading of disease to distant sites [3]. Taxol acts intracellularly by stabilizing tubulin dimmers, thus interfering with microtubular disassembly causing the arrest in G2-M phase of the cell cycle followed by DNA fragmentation and morphological features of apoptosis [4, 5]. Major side effects of paclitaxel include myelosuppression, hypersensitivity, mucositis, and peripheral neuropathy (PN) [6].

PN is a major dose limiting complication of taxol at doses >275 mg/m$^2$ or when used in combination with other neurotoxic agents such as cisplatin [7]. Its neuropathy is characterized by degeneration of sensory axons, manifesting clinically as numbness, pain, and loss of balance [1]. The neurotoxicity studies of taxol have been mostly done on upper dose limits and little information is available on lower doses. Herein, National Cancer Institute-Common Toxicity Criteria (NCI-CTC) is used to evaluate and grade PN [8, 9].

## 2. Methods

All patients reviewed in the study had breast cancer. They were treated with 240, 270, 300 mg/m$^2$ of paclitaxel as a 3 h intravenous infusion single therapy or combination therapy with drugs other than those causing PN. In all patients, either dexamethasone or hydrocortisone was added to ranitidine, chlorpheniramine, and granisetron regimen. Seventy patients' charts were reviewed, though only forty-five agreed to provide the necessary additional information. These patients had received their chemotherapy regimen between June 2005 and Sep 2007 (median age 46 years, range 28-68 years).

Among them were 2 patients with hypertension, 1 patient with hyperthyroidism and 2 patients with hyperlipidemia. Forty-four patients had received four cycles of cyclophosphamide- antracycline combination

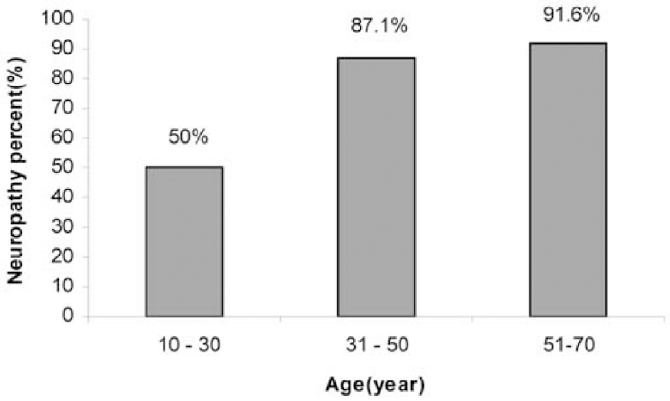


**Figure 1.** Percentage of the patients suffering from neuropathy according to age categories.

**Table 2.** Age distribution and incidence of neuropathy.

| Age | Neuropathy cases |
|---|---|
| 10-20 | 0 |
| 21-30 | 1 |
| 31-40 | 11 |
| 41-50 | 16 |
| 51-60 | 9 |
| 61-70 | 2 |

initially and then four cycles of paclitaxel, while one patient had received six cycles of paclitaxel-gemcitabine. Also, 14 of all patients underwent treatment with tamoxifen after completing the above regimens. Neurologic symptoms were assessed in detail, on a scale of 0 to 4 as shown in table 1 [8].

## 3. Results

Thirty-nine (86.66%) patients developed symptoms of peripheral neuropathy after an average of 1.42 cycles (Range 1-4) of paclitaxel and an average cumulative dose of 394 mg/m$^2$ (Range 240-1080 mg/m$^2$). Symptoms occurred after the first, second, third and fourth dose in the number of 23(58.9%), 8(20.5%), 7(17.9%) and 1(2.5%) patients, respectively. Reversibility of PN was only measured in 25 patients as the rest were still going through their medication protocols. Symptoms stabilized in 9 (36%), improved in 9 (36%), resolved completely in 6 (24%) and progressed in 1 (4%) patients, despite continued treatment at the same dose. The most common manifestations of PN were paresthesia (including tingling and numbness) seen in both feet and hands in 23 (58.9%) patents, feet in 5 (12.8%) and in hands in 11 (28.2%). In terms of grading the PN, 6 (13.3%) had a score of 0, 22 (48.8%) had a score of 1, 10 (22.2%) had a score of 2 and six (13.3%) had a score of 3. One patient got worse during treatment and her grading score changed from one to two. Table 2 shows the number of neuropathies in each age category. Figure 1 shows the frequency of neuropathy in various age categories in percentages.

## 4. Discussion

Paclitaxel-induced neuropathy is a dose-dependent phenomenon. PN may begin as soon as 24 to 72 hours after treatment with high doses (>250 mg/m$^2$) but usually occurs only after multiple courses at conventional doses (135 to 250 mg/m$^2$). Severe neurotoxicity precludes the administration of taxol doses above 250 mg/m$^2$ over a period of 3 or 24 h, but is rare at conventional doses (<200 mg/m$^2$) even in patients who have previously received other new toxic agents, such as cisplatin[10-12].

Another study found that taxol-induced PN may be severe and dose limiting at initial doses >275 mg/m$^2$ [7].

In our study, paclitaxel at doses <300 mg/m$^2$ did not cause dose limiting PN, but produced a mild PN in 86.6% of patients. We also observed a rise in incidence of PN as the age increases.

In a study on taxol-induced PN utilizing QST [7] (quantitative sensory testing), PN appeared in 84% of patients after an average of 1.7 cycles and an average cumulative dose of 371.5 mg/m$^2$ while in our study using NCI-CTC criteria, PN appeared in 86.6% patients after an average of 1.42 cycles and an average cumulative dose of 394 mg/m$^2$. These results are comparable. Because of high incidence of paclitaxel induced PN was seen in the first and second cycles of treatment, vitamin E supplementation may be recommended during early stages of treatment [13, 14]. Acetyl-L-carnitine has also been recommended as prophylaxis against chemotherapy induced neuropathy [15, 16]. To extend our experience with PN in our patients we suggest a study of motor neuropathies to be done prospectively.

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