The Predictors of Taxane Induce Peripheral Neuropathy as a Side Effect in Breast Cancer Patients among Iraqi Women

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ABSTRACT:

BACKGROUND:

Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death. Worldwide, breast cancer is the most frequently diagnosed cancer and the chief cause of cancer death among females.

The National Comprehensive Cancer Network Guidelines recommend taxanes for the treatment of early-stage and metastatic breast cancer. Peripheral neuropathy is a common non-hematological side effect of taxanes, which may result in chemotherapy delays, reductions, discontinuations and poor quality of life. Taxane-induce peripheral nerve damage can lead motor and sensory symptoms. Initial detection of peripheral neuropathy simplifies complete regression since an acute taxane induce peripheral neuropathy is both reversible and mild to moderate in severity.

Till now, there are no accepted preventive procedures or expectable parameters for chemotherapy induced peripheral neuropathy including taxanes, however duloxetine 60mg was official in large randomized phase 3 trials for treatment of chemotherapy induce peripheral neuropathy.

PATIENTS AND METHOD:

Single institution retrospective study started between November 2019 to December 2020, was conducted in Babil Oncology Center/Babil/Iraq which included 60 randomly selected patients with breast cancer, receiving chemotherapy including Taxane group and had undergone nerve conduction study. A collected multiple demographic parameters were compared by dividing the patients into two groups; patients who developed taxane induce peripheral neuropathy and patients who were not developed, these parameters were: patient age, body mass index , hormonal receptor status, human epidermal growth receptor 2 status, metastatic setting and duration and period of last cycle of taxane received. The clinical information, histological and immunohistochemistry laboratory results for each patient obtained from the Oncology Patients Archive Unit, then the statistical process was carried out on the collected information.

RESULTS:

Of 60 patients included in this study, 15 patients (25 %) developed taxane related peripheral neuropathy, of whom 13 (86.7%) developed mixed sensorimotor peripheral neuropathy and two (13.3%) patients developed sensory neuropathy. While the severity ranged from mild (one patient), mild to moderate (10 patients), moderate (4 patients) and there was neither sever nor life threatening peripheral neuropathy. The mean age of patients was 51.38 years and mean body mass index of patients was 26.24 Kg/m2. Peripheral neuropathy had statically significant association with age, body mass index and human epidermal growth receptor 2. Peripheral neuropathy was somewhat more in metastatic setting but statically insignificant.

CONCLUSION:

About one fourth of patients developed peripheral neuropathy after receiving taxane chemotherapy. Elderly, obese patients and patients who have human epidermal growth receptor 2 positive tumors are predictors for taxane induce peripheral neuropathy.

KEYWORDS: taxane induce peripheral neuropathy, human epidermal growth factor receptor 2

INTRODUCTION:

Breast cancer is the most common malignancy in females in the United States and is second only to lung cancer as a cause of cancer death, the American Cancer Society has assessed that 279,100 Americans will be identified with breast cancer and 42,690 will die of disease in the United States in 2020.[1]

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Worldwide, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death amongst females.[2] Breast cancer has become a major hazard to female health in Iraq, where it is the leading cause of death after cardiovascular illnesses among women, with a cancer-related mortality rate of 23%. [3] Tumors in the breast have long been classified according to their morphologic features,

histologic type and grade. Identification of molecular markers such as expression of estrogen and progesterone(ER, PR) and hormonal epidermal growth receptor 2 (HER2) has offered additional predictive value for the therapeutic assessment of women diagnosed with breast cancer. [4]

Microtubules are vital and energetic cytoskeletal polymers that show a perilous part in cell division, signaling vesicle conveyance, figure, and polarity, which marque them attractive boards in anticancer timetables and drug design. [5] Anti microtubule mediators are broadly classified as microtubule-stabilizing or microtubule-destabilizing agents according to their effects on tubulin polymerization.[6]

The unique mechanism of action for paclitaxel was initially distinct by ***Schiff et al*** in 1979, who showed that it bound to the interior surface of the microtubule lumen at obligatory locations totally distinct from those of colchicine, podophyllotoxin, and the vinca alkaloids.[7]

The main side effects of taxane are myelosuppression, hypersensitivity response, fluid retention and peripheral neuropathy, neuropathy is the core toxicity of taxane which is present as symmetric stocking glove dissemination, at first transient and then persistent .[8]

Peripheral neuropathy is a common dose-limiting toxicity crossways the antimicrotubule agents and possible as a result of their direct consequence on microtubules. Studies have shown that they hinder anterograde and/or retrograde fast axonal transport and can elucidate the demyelinating "dying back" pattern seen and the vulnerability of sensory neurons with the longest axonal projections. [9] The neuropathy phenotype in taxanes (paclitaxel and docetaxel) mainly varied sensorimotor axonal.[10] Total cumulative dose and dose intensity are considered the most important factors of incidence and severity of peripheral neurotoxicity, as in other chemotherapy-induced peripheral neuropathies. [11] Onset dosages for neuropathy of any grade range from 100–300 mg/m2 and 75–100 mg/m2 with paclitaxel and docetaxel, correspondingly. [12]

The gold standard for the impartial neurophysiological assessment of chemotherapy induce peripheral neuropathy (CIPN) involves the use of nerve conduction studies (NCS). [13]According to World Health Organization (WHO) rating scale, a grade 0 corresponds to no symptoms of neuropathy, grade 1 (mild) corresponds to paresthesias (a tingling, tickling or prickling sensation) and/or decreased tendon reflexes, grade 2 (moderate) parallels to severe paresthesias and/or mild weakness, grade 3 (sever) corresponds to insufferable paresthesias and/or marked motor loss and grade 4 (life threatening) corresponds to paralysis.[14]

Most forceful evidence for treatment of TIPN arised arose from a large randomized, double-blind, placebo-controlled phase III trial CALGB 170601 with duloxetine (60 mg/daily), which was shown to be modestly but significantly active in diminishing TIPN-related pain .[15]

AIM OF THE STUDY:

The aim of this study is to know how frequent does taxane group induce neurotoxicity in breast cancer patients and is it affected by age, body mass index (BMI), immune histochemistry (IHC) states of the tumor, metastatic or early stages of cancer, time and duration of taxane cycles?

PATIENTS AND METHODS:

This retrospective study, started on 3rd November 2019, ended on 10th December 2020, was conducted in Babylon Oncology Center in BABIL/IRAQ. The study included 60 randomly selected patients with breast cancer diagnosis, receiving chemotherapy including taxane group of medication. Nerve conduction study (NCS) were performed in Neurophysiology Department at Marjan Teaching Hospital at T0, T1 and T2 by the same neurophysiologist using Neuropack line device (NIHON KOHDEN, Japan). Inclusion criteria included female patients who initiated taxane-based chemotherapy (paclitaxel and docetaxel) in the neoadjuvant, adjuvant, or previously untreated metastatic setting.

Exclusion criteria included physical disabilities, pregnancy, diabetes and current exposure to neurotoxic agents like Navelbine and platinums. The Data collected included the patients' age at the time of diagnosis and BMI of them. Tumor specimens which were stained by immunohistochemistry for estrogen and progesterone receptor (ER, PR) and human epidermal growth receptor (HER2). The criteria of severity of peripheral neuropathy according to World Health Organization (WHO) rating scale, a grade 0 corresponds to no symptoms of neuropathy, grade 1 (mild) corresponds to paresthesias (a tingling, tickling or prickling sensation) and/or decreased tendon reflexes, grade 2 (moderate) parallels to severe paresthesias and/or mild weakness, grade 3 (sever) corresponds to insufferable paresthesias and/or marked motor loss and grade 4 (life threatening) corresponds to paralysis. The data was analyzed statistically to obtain the frequency of neuropathy and if related to metastatic state,

IHC states, whether duration and periodicity of cycles as well as patients' age and BMI increase their frequency.

Data collection and ethical consideration:

The study protocol was approved by the scientific Iraqi Council of Medical Oncology. Agreement and permission of the director of the center was obtained. Data of the patients were kept confidentially and not disclosed to unauthorized persons. Any data or information that lead to identification of the participant were hided and replaced with specific serial codes.

Statistical analysis:

Statistical analysis was carried out using SPSS version 23. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Independent samples t-test was used to compare means between two groups. Pearson Chi-square test and Fisher- exact test were used to find the association between categorical variables. A *p*-value of ≤ 0.05 was considered as significant.

RESULTS:

Figure 1 shows distribution of patients according to taxane induce peripheral neuropathy including (positive and negative). Taxane induce peripheral neuropathy occurs in about (25.0%) of patients (N=15).

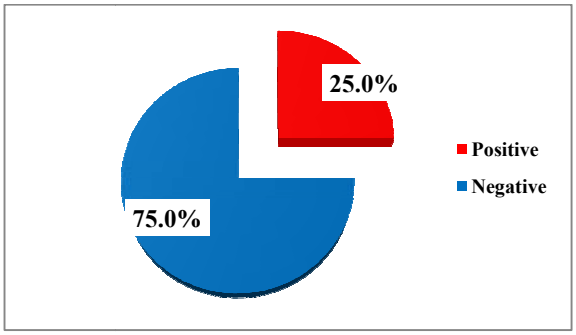

Figure1: Distribution of patients according to taxane induce peripheral neuropathy.

The Distribution of Patients with Taxane Induce Peripheral Neuropathy According to Type and Severity of Neuropathy

Table 1 shows distribution of patients with taxane induce peripheral neuropathy according to type and severity of neuropathy. Majority of patients with taxane induce peripheral neuropathy (86.7%) presented with mixed type of neuropathy (motor and sensory) and majority of patients with taxane induce peripheral neuropathy (66.7%) presented with mild to moderate neuropathy.

Table 1: The Distribution of patients with taxane induce peripheral neuropathy according to type and severity of neuropathy (N=60).

Study variables	N	(%)
Type of taxane induce peripheral neuropathy		
Sensory	2	13.3%
Motor	0	0.0%
Mixed (sensory and motor)	13	86.7%
Total	15	100.0%
Severity of taxane induce peripheral neuropathy		
Mild	1	6.7%
Mild to moderate	10	66.7%
Moderate	4	26.6%
Total	15	100.0%

Figure 2 : The mean differences of age (years) according to taxane induce peripheral neuropathy including (positive and negative). There were significant differences between means of age according to study group. **(t-test=3.132, P=0.003*).**

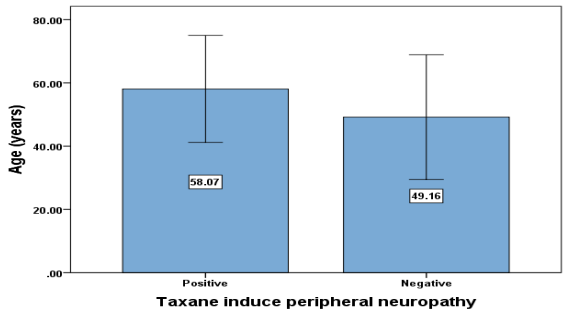

Figure 2: The mean differences of age (years) according to taxane induce peripheral neuropathy

Figure 3: The mean differences of body mass index (kg/m^2) according to taxane induce peripheral neuropathy including (positive and negative). There were significant differences between means of BMI according to study group. **(t-test=2.695, P=0.009*).**

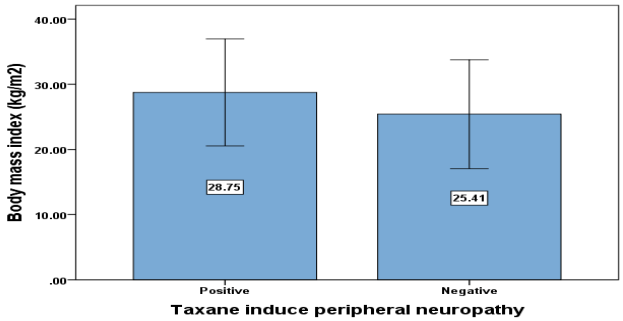

Figure 3: The mean differences of body mass index (kg/m^2) according to taxane induce peripheral neuropathy.

Table 2: Association between taxane induce peripheral neuropathy and study variables.

Study variables	Taxane induce peripheral neuropathy		Total	X^2	P-value	Odds ratio	95% CI
	Positive	Negative					
Hormonal state Positive Negative Total	6 (40.0) 9 (60.0) 15 (100.0)	25 (55.6) 20 (44.4) 45 (100.0)	31 (51.7) 29 (48.3) 60 (100.0)	1.09	0.296	0.533	0.162-1.751
HER-2 Positive Negative Total	13 (86.7) 2 (13.3) 15 (100.0)	22 (48.9) 23 (51.1) 45 (100.0)	35 (58.3) 25 (41.7) 60 (100.0)	6.60	0.01*	6.795	1.373-33.636
Metastatic state Positive Negative Total	12 (80.0) 3 (20.0) 15 (100.0)	24 (53.3) 21 (46.7) 45 (100.0)	36 (60.0) 24 (40.0) 60 (100.0)	3.33	0.068	3.5	0.868-14.11
Period of last taxane received < 6 months > 6 months Total	7 (46.7) 8 (53.3) 15 (100.0)	22 (48.9) 23 (51.1) 45 (100.0)	29 (48.3) 31 (51.7) 60 (100.0)	0.022	0.881	0.915	0.284-2.95
Dose period of taxane Every week Every Three weeks Total	7 (46.7) 8 (53.3) 15 (100.0)	23 (51.1) 22 (48.9) 45 (100.0)	30 (50.0) 30 (50.0) 60 (100.0)	0.089	0.766	0.837	0.26-2.699

*P value ≤ 0.05 was significant.

Table 2 shows the association between taxane induce peripheral neuropathy including (positive and negative) and study variables including (hormonal state, HER-2, metastatic state, period of last cycle of taxane received and dose period between two cycles of taxane (either every week or every 3 weeks). There was significant association between taxane induce peripheral neuropathy and HER-2. Peripheral neuropathy is more common in metastatic tumor but statically insignificant.

DISCUSSION:

The National Comprehensive Cancer Network Guide- lines recommend taxanes for the treatment of early-stage and metastatic breast cancer.[16] Peripheral neuropathy is a common non-hematological side effect of taxanes, which may result in chemotherapy delays, reductions, discontinuations and poor quality of life [17] Taxane-induce peripheral nerve (TIPN) damage can lead to motor and sensory symptoms such as bilateral par aesthesia manifested as numbness, tingling and burning pain. [18]

In the current study, the incidence of taxane induce peripheral neuropathy (TIPN) is about 25 % (n: 15), this incidence may go with ***Song SJ et al*** , a large Korean retrospective study, the incidence of TIPN in this Korean study was 21.9 %.[19] While ***Nellowe Candelario et al***, an American retrospective trial found that 69 % developed taxane induce peripheral neuropathy most of them are grade 1.[20] The difference in incidence of taxane induce peripheral neuropathy may belong to variation of geographic areas of world and race. In the current study; mean age of patients was (51.38 ± 10.22), increase mean age contributed with increase taxane induce peripheral neuropathy and statically significant **(P=0.003)** that showed in figure (1). These results correspond with ***Song SJ et al***, a Korean study that mention above previously.[19] ***Ghoreishi Z et al,*** an Iranian retrospective control study found same result that elderly patient exposed to increase risk of taxane induce peripheral neuropathy. [21] ***Molassiotis A et al;*** a large prospective study for possible taxane induce peripheral neuropathy risk factors found same result and association between age and taxane induce peripheral neuropathy. [22]

Another predictor for TIPN is body mass index (BMI); in the current study, the mean of body mass index for patients who developed TIPN was (28.75 kg/m2) and was statically significant (P=**0.009)** higher than those who had no TIPN. That means obese women with breast cancer are more likely to develop TIPN than slim patients with same disease. These results were consistent with the two previous mentioned studies; ***Song SJ et al*** and ***Ghoreishi Z et al***. [19,21] In the current study, hormonal status estrogen and progesterone receptor (ER, PR) had no association with TIPN, these results are corresponded with ***Song SJ et al*** retrospective study that explained hormonal status was negative predictive value for TIPN.[19] While ***Ghoreishi Z et al*** found that a positive hormonal status was a predictor for occurrence of TIPN.[21] The concordance between results may due to race and hormonal positivity percentage among them and the effects of environment on it.

The current study found that TIPN was more common in metastatic breast cancer (MBC) but was statically insignificant (P = 0.068). This result agrees with ***Song SJ et al*** that mentioned previously. In USA, ***Rivera E et al***; found that TIPN were increase in MBC. [23]***Lichtman SM et al*** ; a combined analysis from Cancer and Leukemia Group B. (CALGB) that shows paclitaxel efficacy and toxicity in older women with metastatic breast cancer: combined analysis of CALGB 9342 and 9840 shows increase TIPN in both old age and MBC.[24] Hormonal epidermal growth receptor 2(HER-2) positivity breast cancer in the current study have statistically significant predictor for TIPN occurrence (P = 0.01) and odds ratio (6.795) that's meaning every HER-2 positive breast cancer have > 6 times occurrence risk of TIPN than HER-2 negative breast cancer. In ***Carlson, Robert H. et al;*** in San Francisco, USA informed that HER-2 + breast cancer patients are at higher risk of TIPN and statistically significant with odds ratio (2.11),[25] According to ***Carlson, Robert H. et al,*** factors not predictive of the development or severity of chemotherapy-induced peripheral neuropathy were age, body mass index (BMI) which is against the results of current study; these differences may belong to geographic disturbance, habits, race and environmental effects.

In the current study, we assessed two doses schedules of paclitaxel (weekly and tri weekly) and every 3 weeks of docetaxel, also assessed the duration of the last taxane received if it was ended before 6 months ago or the patient had received the last taxane cycle less than 6 months ago or is still receiving chemotherapy currently; none of these parameters above predicted increase incidence of TIPN. There were conflicting data about which dose duration (weekly versus tri weekly) predispose to TIPN more than the other one; in ***Sedman AD et al***, a final result of Cancer and Leukemia Group B

protocol 9840, found that the weekly schedule was associated with increase neurotoxicity than tri-weekly regimen.[26] In the current study, the severity of peripheral neuropathy ranging from mild (grade1) to moderate (grade2) and no documented sever (grade3) or life threatening (grade4), this was due to reversible and healing by time effect. The majority of cases (66.7%) in current study were mild to moderate severity according to nerve conducting study reports of patient's examination (table 1).

These results are comparable with several studies such ***as Cassier et al.,2008*** which show that only 6.8 % have grade 3 or more for patients received paclitaxel and only 0.9 % have grade 3 or more for patients received docetaxel; in this study, sensory versus motor was not delineated.[27] ***Albain et al ., 2008*** study 521 MBC received paclitaxel every three weeks; the percentage of patients who developed grade 2 was 17.7_18.4 % and only 3.9_5.3 % developed grade 3 and only 0.4 developed grade 4.[27]

CONCLUSION:

According to these results; older age, increase BMI, HER 2 positivity tumor are predictors for TIPN and these parameters may give hints about the future risk of peripheral neuropathy especially if more than one parameter or collectively take place in the same patient. Further studies with a larger sample size in study and longer period of follow up to early detection of peripheral neuropathy as well as further studies needed to evaluate multiple management strategies if peripheral neuropathy was taken place.

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