Evaluation of Paclitaxel Induced Neurotoxicity and its Impact on the Quality of Life in Breast Cancer Patients

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Abstract

Objective: To determine the incidence as well as the grade of neurotoxicity due to taxanes in breast cancer patients. Further goal was to determine the effect of neurotoxicity with taxanes on quality of life (QOL). Additionally, another one of our aims was to look at the effect of treatment setting on the grade of neuropathy as well as on the quality of life.

Methods: This is a prospective open-labeled study. Breast cancer patients were enrolled through the outdoor-patient-department. Neurotoxicity was monitored clinically by questioning and physical examination at baseline and then after 6th cycle of Paclitaxel. Neuropathy was graded using NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) guidelines into grade 1 through 4. Patients having pre-existing neuropathy were excluded from the study. Quality of life was measured using FACT-Taxane scale and was classified into two groups. 0-100 score (low QOL) group and 101-172 (high QOL) group). The results of these variables were presented as mean values, frequencies and percentages. Chi-square test was used to assess correlation of these variables with each other and various demographic factors like age, treatment setting and stage of the disease. $p<0.05$ was considered significant.

Results: A total of 92 (n=92) patients took part in the study with ages ranging from 25 to 70. All 100% of the patients were females. Peripheral neuropathy was present in 88 (95.7%) patients. Among these 88 cases, according to NCI-CTCAE guidelines, 29 (33%) had Grade 1 neuropathy, 31 (35.2%) had Grade 2 neuropathy and the remaining 28 (31.8%) had Grade 3 neuropathy. No patient (0%) had Grade 4 neuropathy. According to FACT-TAXANE, quality of life was low (1-100 score) in 47 (51.1%) patients whereas 45 (48.9%) patients had high (101-172 score) quality of life. The grade of peripheral neuropathy had a significant impact on the quality-of-life scores ($p<0.05$). There was a significant impact of diabetes, hypertension and high BMI on both the grade of neuropathy and the quality-of-life. No significant impact of other risk factors (age, stage, treatment setting, other comorbid conditions and ER/PR/HER2neu status) on the grade of neuropathy or on the quality of life was seen.

Conclusion: Treatment with Paclitaxel is associated with significantly low quality of life due to its neurotoxic effects. Benefits and risks should be properly evaluated before commencing patients on any neurotoxic drugs.

Keywords: breast cancer, taxanes, neuropathy

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Introduction

Taxanes are being widely used in the treatment of breast cancer, ovarian cancer, lung cancer and other solid tumors. The first taxane introduced in the field of oncology was paclitaxel. It acts by interfering with the normal structure of microtubules, promoting polymerization and resulting in cell death,[1] Besides the hematological adverse effects of paclitaxel, patients also suffer from non-settling peripheral neuropathies. Where it provides the overall survival (OS) benefit,

these neuropathies have negative impact on the quality of life (QOL) of patients.[2,3] Paclitaxel causes neuromuscular symptoms involving both sensory and motor in nature that is actually due to nerve damage. It can be acute, mild or chronic depending upon the dose of paclitaxel. Sensory signs and symptoms may include persistent burning, pain, tingling, numbness, reduced sense of touch, ataxia. Motor symptoms include balance disturbances, absent deep tendon reflex.[4] Risk factors of paclitaxel induced peripheral neuropathy include a higher single dose of 250mg/m^2, a cumulative dose of 1000mg/m^2, rapid infusion time (less than 24 hours), comorbidity like diabetes, previous or concomitant antineoplastic drug causing neuropathy.[5] This undesired effect of chemotherapy can be avoided by dose reduction or withdrawing medicine.[2,6]

Many different grading scales have been used by the researchers to grade the neurotoxic effect of paclitaxel including National Cancer Institute Common Terminology Criteria (NCI-CTCAE),[7] The World Health Organization (WHO),[8] Eastern Cooperative Group (ECOG)[9] criteria. Each of these scales have grade 0 to grade 4 rating system indicating no neuropathy to permanent sensory loss or paralysis.[10] Quality of life (QOL) has been measured using FACT-TAXANE which is a detailed questionnaire comprising of FACT-General (FACT-G) and a 16 item taxane subscale for patients receiving taxanes.[2]

Material & Methods

An informed consent was taken from all the participants of the study. Neuropathy was monitored clinically by questioning and physical examination at baseline and then 3 weekly starting from 1st cycle of Paclitaxel. Neuropathy was graded using NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) guidelines into grade 1 through 4 with higher grades representing worse signs and symptoms. Quality of life (QOL) has been measured using a translated version (local language) of FACT-TAXANE which is a detailed questionnaire comprising of FACT-General (FACT-G) and a 16 item taxane subscale for patients receiving taxanes. FACT-G has questions that deal with different forms of well-being, including Physical Well-Being (PWB), Social Well-Being (SWB), Emotional Well-Being (EWB) and Functional Well-Being (FWB). FACT-Taxane has a maximum of 172 score with higher scores representing better quality of life. For feasibility, we have classified it into two groups. 0-100 score (low QOL) group and 101-172 (high QOL) group. This is a prospective open-labeled study. After taking approval from Hameed Latif Hospital (Lahore) ethical committee, patients coming through the outdoor-patient-department of Oncology department, who fulfilled the criteria were enrolled and written informed consent was taken. Data was collected in the form of patient-clinician interviews and physical examinations. After data collection, it was analyzed using SPSS ver.26. Quantitative variables like age and all the scale scores have been described in terms of mean values and standard deviations. Other variables like stage of the disease, treatment setting etc. have been assessed in terms of percentages and frequencies and have also been compared with variables like grades of neuropathy and QOL using chi square test ($p \leq 0.05$).

Results

A total of 92 (n=92) patients were included in this study with ages ranging from 25 to 70 years (mean age= 48.78$\pm$/-11.69 SD). 100% of the participants were females with a mean height of 154.36 cm $\pm$/-5.89 SD and a mean weight of 70.17 kg $\pm$/- 11 SD. Out of the 92 patients, 52 (56.5%) had breast cancer in their right breast while the remaining 40(43.5%) had involvement of their left breast. The patients were in different stages of the disease with 5 (5.4%), 33 (35.9%), 33 (35.9%) and 21 (22.8%) patients in stage 1, stage 2, stage 3 and stage 4 respectively. 52 (56.5%) patients were ER+,

Table 1: *Demographics*

	Demographics	Count	Percentage (%)
	Total Participants	n=92	100
Gender	Female	92	100
Breast Involvement	Right	52	56.5
	Left	40	43.5
Stage of the Disease	Stage 1	5	5.4
	Stage 2	33	35.9
	Stage 3	33	35.9
	Stage 4	21	22.8
ER/PR/HER 2neu	ER+	52	56.5
	PR+	47	51.1
	HER2neu+	41	44.6
Treatment Setting	Adjuvant	38	41.3
	Neo-Adjuvant	33	35.9
	Palliative	21	22.8
Age (years)	Mean Age = 48.78 ± 11.69 SD (range=70-25)		
Height (cm)	Mean Height = 154.36 ± 5.89 SD (range=169-140)		
Weight (kg)	Mean Weight = 70.17 ± 11 SD (range=96-45)		
Comorbid Conditions	Total Patients with comorbid conditions	42/92 (45.65%)	100%
	Hypertension	27	42.9%
	Diabetes	25	39.7%
	Asthma	3	4.8%
	Hepatitis C	3	4.8%
	Arthritis	3	4.8%
	Photosensitivity	1	1.6%
	Hypothyroidism	1	1.6%
	Chronic Liver Disease	1	1.6%

47 (51.1%) patients were PR+ and 41 (44.6%) patients were HER2neu+. 47(51.1%). The type of treatment was Adjuvant for 38 (41.3%) patients, Neo-Adjuvant for 33 (35.9%) and Palliative for 21 (22.8%) patients as shown in **(Table-1).**

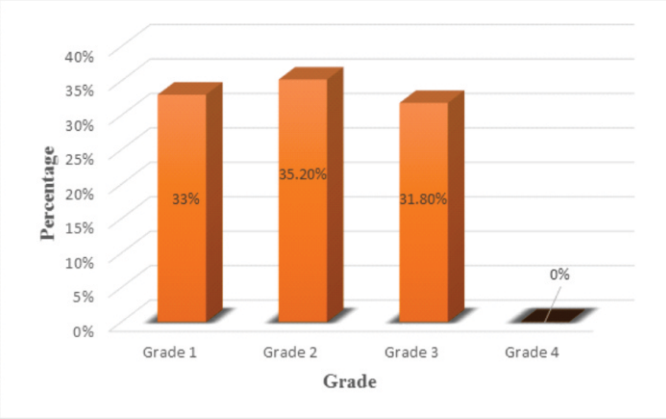
42 (45.65%) patients had co-existing comorbid conditions with Hypertension (64.3%) and Diabetes (59.5%) being the most common among the cases.

Peripheral neuropathy was present in 88 (95.7%) patients. Among these 88 cases, according to NCI-CTCAE guidelines, 29 (33%) had Grade 1 neuropathy, 31 (35.2%) had Grade 2 neuropathy and the remaining 28 (31.8%)

Table 2: *Peripheral Neuropathy/Grade of Neuropathy/ FACT-Taxane QOL*

		Count	Percentage (%)
	Total Participants	**n=92**	**100**
Peripheral Neuropathy	Present	88	95.7
	Absent	4	4.3
Grade of Neuropathy	Grade 1	29/88	33
	Grade 2	31/88	35.2
	Grade 3	28/88	31.8
	Grade 4	0/88	0
Quality of Life	0-100	47	51.1
	101-172	45	48.9

had Grade 3 neuropathy. No patient (0%) had Grade 4 neuropathy as shown in **(Table-2)**. According to FACT-TAXANE, quality of life was low (1-100 score) in 47(51.1%) patients whereas 45(48.9%) patients had high (101-172 score) quality of life.



Graph-1: *Grade of Neuropathy after 6 cycles*

The grade of peripheral neuropathy had a significant impact on the Quality-of-Life scores ($p<0.05$). Higher grades of neuropathy were associated with poor quality of life and vice versa. Additionally, co-morbid conditions like diabetes, hypertension and high BMI had significant association with both the grade of peripheral neuropathy as well as the Quality-of-Life as shown in table-3 and **(Table-4).**

There was no significant association of Quality-of-Life scores with the age groups of the patients. Similarly,

Table 3: *Correlation of variables with the QOL Groups*

		LOW QOL (0-100)	HIGH QOL (101-172)	p-value
Grade of Peripheral Neuropathy	Grade 1	4	25	0.00
	Grade 2	16	15	
	Grade 3	27	1	
	Grade 4	0	0	
BMI	<25	3	12	0.008
	>=25	44	33	
Diabetes	Present	20	5	0.001
	Absent	27	40	
Hypertension	Present	19	8	0.017
	Absent	28	37	

Table 4: *Correlation of variables with Grades of neuropathy*

		Grade 1	Grade 2	Grade 3	Grade 4	p-value
BMI	<25	9	3	1	0	0.009
	>=25	20	28	27	0	
Diabetes	Present	3	8	14	0	0.004
	Absent	26	23	14	0	
Hypertension	Present	4	9	13	0	0.026
	Absent	25	22	15	0	

the stage of the disease, treatment setting and the ER, PR & HER2neu status had no significant association with either the grade of peripheral neuropathy or the Quality-of-Life.

Discussion

Among Asian countries, Pakistan has one of the highest breast cancer rates with most cases presenting late in the course of the disease.[11] Paclitaxel, being the mainstay of treatment for breast cancer, is widely used in Pakistan as well. Taxanes, including paclitaxel, are well-known for causing neurotoxicity in the patients.[12] This neurotoxicity has direct impact on the treatment delivery and can lead to dose reductions.[13]

The results of our study indicated that the majority of the patients developed peripheral neuropathy after 6 cycles of chemotherapy which is in line with the available data. A previous study by Hershman et al showed similar results where 81% of patients also developed some form of neurological symptoms following chemotherapy.[14]

In our study, patients were almost equally distributed among grade 1, 2 and 3 of peripheral neuropathy. The grade of neuropathy was significantly associated with FACT-Taxane QOL scores with higher grade resulting in poorer quality of life. Similar findings were seen in some other studies where related scales like FACT/GOG-Ntx and CIPN15 were used as a measure of quality-of-life in patients receiving neurotoxic chemotherapy.[15,16]

This chemotherapy induced peripheral neuropathy can lead to long term quality of life decline due to increased falls, gait problems and disability.[4,17]

In our study, co-morbid conditions including diabetes, hypertension and a high BMI were associated with higher grades of neuropathy and thus, poor quality-of-life. A previous study by de la Morena Barrio et al has reported an increased severity of neuropathy and delayed recovery among diabetic patients who received paclitaxel- findings similar to our study.[20] Some other studies have also reported 'high BMI' as a risk factor for paclitaxel induced neuropathy.[18,21]

In our study, no significant impact of other risk factors (age, stage, treatment setting and ER / PR / HER2neu status) on the grade of neuropathy or on the quality of life was seen. This is contrary to the findings by Ghoreishi Z. et al[18] where they found a significant association of age and PR+ status of the patient with the severity of paclitaxel induced neuropathy. This may be due to the fact that a different measure called reduced Total Neuropathy Score (r-TNS)[19] was used to assess the severity of peripheral neuropathy. A similar study by Mizrahi D. et al[21] has also reported 'age' as a risk factor for paclitaxel- and oxaliplatin-induced neuropathy.

There are certain limitations of this study. Firstly, due to smaller sample size, there were only 5 patients with stage 1 breast cancer taking part in the study. This can be resolved by involving a larger study population. Secondly, the participants were chosen from a single tertiary care hospital. A larger multi-centered study will be preferred. Thirdly, 25 (27%) patients had co-existing diabetes mellitus which itself is a well-known risk factor for peripheral neuropathy.

Conflict of Interest

None

Conclusion

Paclitaxel-induced neuropathy can lead to poor quality of life. Its potential adverse effects may outweigh the benefits in some patients. Moreover, further research is needed to highlight this relationship and find a preventive measure/ cure for chemotherapy induced peripheral neuropathy.

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AA, AZ: Conceptualization of Project
AA, HS: Data Collection
AA, AL: Literature Search
HS, AL, AK: Statistical Analysis
AL, AZ, AK: Drafting, Revision
AL, AZ, AK: Writing of Manuscript