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Quality of Life in patients treated with Taxane monotherapy.

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Abstract:
Context: *Taxane (Paclitaxel and docetaxel) are microtubule inhibitors, extensively used for breast carcinoma. Chemotherapy induced peripheral neuropathy not only leads to discomfort but the severity of neuropathy leads to disability resulting in significant loss of body functions, compromising the Quality of life (QOL) of patients.*
Objective: *The aim of the study is to evaluate the severity of symptomatic TIPN and corroborating it with patients QOL.*
Material and Methods: *31 newly diagnosed cancer patients were selected scheduled to be treated with taxane monotherapy with 3 weekly regimens for 6 cycles with standard dosage (175-200mg/m2). Evaluation was done in 3 phases, i.e., before, after 3rd cycle and after 6th cycle of taxane chemotherapy as per Total neuropathy score(TNS). Patient's QOL was assessed by another highly sensitive scoring system Visual Analogue Scale (VAS).*
Results: *Peripheral neuropathy developed in almost 96% of cases at the end of 3rd cycle and 100% of cases at the end of 6th cycle. The mean TNS was significantly higher in phase III as compared to phase II and phase I, indicating significant increase of TIPN with cumulative dosage. Symptom score was calculated as per TNS which highly corroborates statistically with the quality of life of patients.*
Conclusion: *Single item VAS has proved itself as a sensitive tool to reflect subjective notion towards QOL by placing the subject in a graded scale and it has nicely corroborated with the severity of neuropathy.*
Key words: *Taxane, Peripheral neuropathy, Quality of Life, Total neuropathy score.*

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I. Introduction

Cancer is a global threat as it continues to remain one of the major killer disease worldwide. According to WHO, death due to cancer, all over the world, has been estimated to be 9.6 million in the year 2018 [1]. With the increasing incidence of cancer globally, use of antineoplastic agents presumably has increased enormously. Since the initial licensing of Taxols in the field of cancer chemotherapy in Europe, Paclitaxel and Docetaxel have emerged as a fundamental drug in the treatment of breast malignancy [2]. They actually became a significant component in both early and advanced stages of this cancer [3,4]. However due to incremental advantage of their efficacy relative to previously standard therapy and thence wide use of microtubule inhibitory based chemotherapy [5], some other disabling side-effect has emerged, one of the most important, even, dose limiting side effect being Chemotherapy induced peripheral neuropathy (CIPN) [6,7]. This not only leads to discomfort but the severe disability results in significant loss of body functions, compromising the Quality of life (QOL) [8,9].

Hence, it poses an immense challenge for both patient and the practitioner in balancing the goal of cure by continuing the schedule of taxane based antineoplastic regimen and maintaining patients' quality of life.

Thus the objectives of our study are – To corroborate the severity of TIPN with patients QOL using a simple but sensitive rating scale and to assess the course of development of symptoms, in different phases of taxane chemotherapy with standard dosage (175 – 200 mg/m2).

II. Materials And Methods

The study was carried out in the Dept of Physiology, in collaboration with the Department of Radiotherapy in Institute of Post Graduate Medical Education & Research Kolkata, West Bengal It was a hospital based, observational and cross sectional study. After getting ethical clearance from institutional ethical committee the study was conducted for a period of 1 year 7 months. Patients with histologically proven, locally advanced or metastatic cancer, for whom Paclitaxel as monotherapy was a therapeutic option, were the cases for this study. The subset of 31 subjects that were investigated in this present study was selected randomly. All subjects were evaluated in three phases. Phase I - Patients before start of taxane chemotherapy. Phase II - Patients after 3rd cycle of taxane chemotherapy and Phase III - Patients after 6th cycle of taxane chemotherapy.

Subjects were selected as per the following inclusion criterias – Patients selected for Taxane monotherapy for treatment of breast carcinoma. Age >30years and <60 years. Subjects were not included if they fulfill any of the following exclusion criteria. Subjects suffering from any potential cause of peripheral neuropathy like: Diabetes mellitus, nutritional deficiency, alcohol consumption, autoimmune diseases like SLE, RA, etc. Hereditary peripheral neuropathies, Infective diseases (AIDS, post herpetic state). Exposure to toxins like heavy metals (gold, As, Hg, Pb), organophosphorus, antibiotics (INH, chloramphenicol, colchicine e.t.c). Patients suffering from heart diseases or having inadequate hepatic or renal functions. Patients with preexisting neuropathy due to malignancy itself. 31 newly diagnosed and histologically proven breast carcinoma cases those were selected for Taxane monotherapy were included as subjects for the present study. Meticulous screening of the selected cases was done to exclude patients as per the exclusion criteria. Patients were studied face to face and in presence of a relative to cross-check their statements or elicit further information whenever necessary.

There is no gold standard for QOL assessment. In this study we have chosen Visual Analogue scale (VAS) for quality of life assessment in cancer patients. A VAS is a line, measuring 10 cm, with descriptors at each end (Very low to Very high). We have selected single-item VASs for QOL estimation as it has been suggested to best represent individual QOL because they do not constrain responses to the domains determined by health care providers [10].

Each and every patient was asked single question 'Please rate your overall Quality of life for last 7 days? Patients were asked to place a mark 'X' in a box indicating their subjective experience with anchors "lowest quality to highest quality."The score was measured as the distance of the mark from one end of the line. The line does not have markings, words, or numbers along it. VASs have been described as simple, highly sensitive, and reliable rating scales for subjective experiences[11]. The main advantage of a VAS is that respondents may indicate any place along the line rather than be restricted by categories or numbers. VASs have been used to assess cancer QOL since 1976[12].

How would you rate your overall Quality of Life for last 7 days?

Detailed history was taken and special emphasis was given to evaluate presence or absence of peripheral neuropathy. The symptoms were scored as per Total Neuropathy composite scoring system. The results were expressed as mean ± SD. $p < 0.05$ were considered significant. Statistical analysis was done by using the software Graphpad Prism.

III. Results

The neurological symptom was evaluated in 3 phases of taxane monotherapy. In Phase I most of the patients neither complained of sensory nor motor symptoms except for generalized myalgia in 9 cases (30%), which may be due to disease process itself. In Phase II i.e. after 3rd cycle of chemotherapy 7 patients (22%) had a complain of paresthesia/tingling; 5 cases (16%) complained of numbness and generalized myalgia by 19 patients (61%). But, the incidence of neuropathic pain was significantly increased in the form of burning sensation and aching which was complained by 21 (68%) patients. In Phase III, i.e. after 6th cycle of chemotherapy 9 cases out of 31 (29%) complained of paresthesia/tingling, 8 cases (25%) complained of numbness and 24 patients (77%) complained of generalized myalgia. But, interestingly neuropathic pain as predicted was the most common symptom complained by 29 cases, with statistically significant ($p < 0.05$). There was appearance of motor symptoms in the form of hand dexterity in 5 cases (16%), difficulty in walking in 3 cases (9%) and difficulty in combing hair in 8% of cases. None of the patients had difficulty in climbing steps.

According to the symptoms the Symptom score was calculated (as per TNS) and are depicted in Table 1 and Table 2. Important statistical parameters Of Quality Of Life (QOL) in three phases of taxane monotherapy are shown in Table 3. Table 4 delineates intergroup statistical significance of QOL Score. Interestingly QOL has progressively deteriorated with the progression of chemotherapy which highly corroborates with the expected results. Graphical representation of progressive changes in QOL in different phases of Taxane chemotherapy is given in figure 1.

IV. Discussion

The study aims to assess the abnormalities in three phases of taxane chemotherapy and corroborate the severity of TIPN with patients QOL. In this study TNS was selected to grade the severity of TIPN. Several scoring system that are commonly used in oncology for grading TIPN are NCI-CTC Ver. 3 (2006), ECOG, Anjani Score, WHO rating and TNS. Most of these scales contain 4 or 5 point rating system where 0 = no neuropathy 4/5 = paralysis / debilitating paresthesia. The use of broad categories within these measures and their ordinal constrains limit the ability to detect incremental changes in impairment. Moreover the highest score cannot discriminate between the most severe cases of peripheral neurotoxicity due to the ceiling effect. Total Neuropathy Score (TNS) on the other hand has a much larger range of values (0-32) and it is thus conceivable

that TNS would be a more appropriate, reliable and accurate scoring system to grade CIPN. Hence, in our present study we adapted TNS composite score to evaluate symptomatic TIPN.

The alteration of sensory symptoms as graded by TNS Composite score in three phases of taxane therapy is depicted in Table 2. In phase I none of the patients complained of sensory symptoms except for generalized myalgia in 9 patients (30%) which may be due to the disease process itself. Velasco et al. are of the opinion that this type of myalgia commonly occurring in cancer patients should not be included in the clinical spectrum of neuropathy[13]. In phase II and Phase III however the symptoms increased significantly ($p < 0.05$) along with the increase in incidence up to 60%.

In our study pain and burning sensation was more severe than tingling and numbness, which occurred in 29 patients (more than 93%) in phase III. This is in corroboration with several studies who reported that about 20-60% of patients receiving standard doses and merely all patients receiving high dose of taxane therapy developed neurotoxicity[14,15]; mostly in the form of neuropathic pain syndrome which often begins simultaneously in hands and feet[16,17,18]. Symptoms were more severe 48-72 hrs after the therapy and continued to decrease and subsequently became almost normal before the next cycle. This observation was also reported by Argyriou in 2008[19]. Multiple pathophysiological factors have been implicated in the development of painful neuropathy. Firstly, it has been reported, taxane interfere with mitochondrial energetic, resulting in an energy deficiency that leads to dysfunction of N+/K+ ATPase pump. As a result normal Resting Membrane Potential (RMP) is lower and axons depolarise to the threshold quickly, necessary for spontaneous discharge[20].

In the present study motor symptoms were minimal as depicted in Table 2. Total Motor score was 0 for hand dexterity (buttoning), walking, climbing steps and combing hair, even after the 3rd cycle of taxane chemotherapy. After 6th cycle some abnormalities in buttoning, walking and combing hair was observed in 9 cases out of 31 (less than 29%). However climbing steps were still normal. These finding are very similar to that reported by Kouri et al[21]. in 2004 who described that among the motor symptoms inability to button up or write or mild instability in gait may occur after repeated cycles of taxane chemotherapy.

We found overall TN Score was significantly higher following 6th cycle of chemotherapy. As the cumulative dose of taxane increases it accounts for most of the neuropathy in Phase III [22]. After 6 cycle of chemotherapy there is significant alteration in Symptom score resulting in a very high TNS in 14 cases (45%) and a high TNS in 17 cases (55 %). These findings were corroborated in several studies[23,24]. Several experiments done in animal models has shown that with cumulative dose of taxane chemotherapy there is progressive demyelinating axonopathy resulting in worsening of the scoring system[20].

In our present study we have selected single item Visual analogue scale (VAS) for evaluating Quality of life in cancer patients in three phases of taxane monotherapy. The results are shown in table 3, 4 and Figure 1. Several single-item VASs for QOL have been validated in Oncology. The single item global question that we have selected to score the quality of life of each patient was-How would you rate your overall Quality of Life for last 7 days ?

The reason behind choosing the single item VAS is that it is stable QOL in cancer patients in hospice care[25] and correlated well with cognitive, physical and spiritual well-being and social activity. In our present study a low QOL score indicates healthy wellbeing whereas a high score indicates poor quality of life. In Phase I, 21 patients had a score of 0, 6 cases had a score of 1 and 4 out of 31 patients had score 2 before start of chemotherapy. The value increases minimally in phase II, the QOL scores in this phase was 5 for 2 cases, 3 for 7 cases and 2 for 22cases respectively. In phase III there was progressive change of QOL score with 26 patients had a score of 8, 3 patients had a score of 9 and 2 cases were estimated to have QOL score of 7. The interphase comparison was also highly statistically significant with a p value < 0.001.

The assessment of QOL by purely subjective Visual Analogue Scale reveals that in Phase II where most of the patients were asymptomatic QOL corroborates by showing a minimal alteration (score being 2-5) but in Phase III where there is symptomatic neuropathy with gross alteration in electrophysiological study QOL also deteriorates correspondingly showing the obvious clinical neuropathy due to taxane chemotherapy.

This study finds the corroboration of TNS with QOL assessment. TNS is an objective assessment system whereas QOL assessment by single item VAS is purely subjective. It is interesting to note that in Phase II when QOL by VAS varied from 2-5, mean TNS was as high as 14.42 and this again point towards the fact that TNS is much more sensitive and objective assessment tool to detect subclinical neuropathy which is not still reflected to compromise patients QOL. This is a unique corroborative finding of our study and shows the reliability of TNS composite scoring system in grading severity of both symptomatic and subclinical neuropathy.

V. Conclusion

Taxane induced peripheral neuropathy develops after repetitive cycle of taxane monotherapy and cumulative dose has a definite role. The symptoms do not always corroborate with the findings and this

bringing us to the conclusion that subclinical neuropathy starts well ahead of clinical neuropathy and can be detected only by a sensitive and objective scoring system like TNS which includes the electrophysiological parameters too. Single item VAS in our study has proved itself as a enough sensitive tool to reflect subjective notion towards QOL by placing the subject in a graded scale and it has nicely corroborated with the severity of neuropathy.

But still because of limited number of cases we cannot comment freely on the incidence of TIPN, its natural course and development of subclinical neuropathy. A comparative study by assessing QOL by FACT-Taxane and single item VAS would have completed our work more perfectly if both are seen to grade the QOL comparatively.

Table 1: Total Neuropathy Score

Parameter	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to finger and toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbow or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/ assistance	Paralysis
Autonomic symptoms	0	1	2	3	4 to 5
Pin sensitivity	Normal	Reduced in fingers and toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensitivity	Normal	Reduced in fingers and toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild (MRC:4)	Moderate weakness (MRC 3)	Severe weakness (MRC 2)	Paralysis (MRC 0-1)
Deep tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Vibration sensation (QST % ULN)	Normal to 125%ULN	126%-150% ULN	151%-200% ULN	201%-300% ULN	> 300% ULN
Sensory Nerve SNAP; % LLN	Normal/ reduced to < 5%LLN	76%-95% of LLN	51%-75% of LLN	26%-50% of LLN	0%-25% of LLN
Peroneal nerve CMAP; %LLN	Normal/ reduced to < 5%LLN	76%-95% of LLN	51%-75% of LLN	26%-50% of LLN	0%-25% of LLN

Adapted from Cavaletti et al15. QST: Quantitative sensory test; ULN: Upper limit of normal; LLN: Lower limit of normal; SNAP: Sensory nerve action potential; CMAP: Amplitude of the compound muscle potential; MRC: Medical Research Council.

Table – 2: Severity of neurologic symptoms in different phases of taxane chemotherapy according to Total neuropathy score

SYMPTOMS		SS* In Phase-I (Mean)	SS* In Phase-II (Mean)	SS* In Phase-III (Mean)
SENSORY	Paresthesias (tingling)	0	0-1	1-2
	Numbness	0	0-1	1-2
	Neuropathic pain (aching, burning)	0	1-2	2-3✱
	Myalgias or cramps	Generalized myalgia	Generalized myalgia	Generalized myalgia
MOTOR	Hand dexterity (buttoning)	0	0	0-1
	Foot (walking)	0	0	0-1
	Legs (climbing steps)	0	0	0
	Arms (combing hair)	0	0	0-1

SS – Symptom Score (as per TNS) ✱ - $p < 0.05$

Phase I = Before taxane chemotherapy, Phase II = After 3rd cycle of taxane chemotherapy Phase III =After 6th cycle of taxane chemotherapy

Table – 3: Statistical significance of the outcome of Quality of Life (QOL) in three phases of taxane chemotherapy

Statistical Parameters	QOL in Phase I	QOL in Phase II	QOL in Phase III
Number of cases	31	31	31
Mean	1.41	2.58	8.09
Std. Deviation	0.56	0.81	0.78
Median	1.00	2.00	8.00
25% Percentile	1.00	2.00	7.00
75% Percentile	2.00	3.00	9.00
Minimum	0.00	2.00	7.00
Maximum	2.00	5.00	9.00
Lower 95% CI	1.21	2.28	7.81
Upper 95% CI	1.62	2.87	8.38

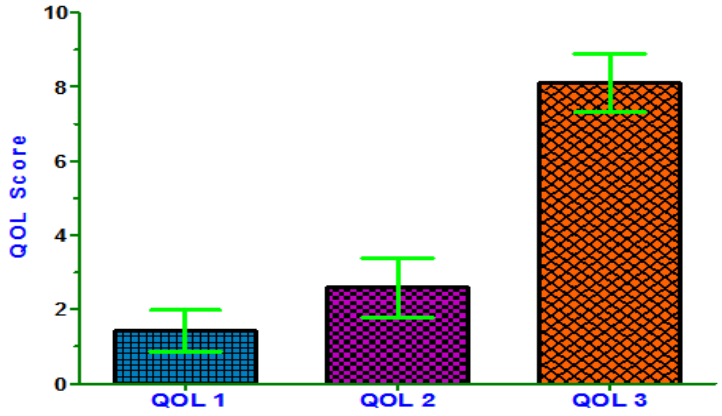
Statistical analysis by 1 way ANOVA (Repeated measures)

Table-4: Interphase statistical significance of Quality of Life Score

Comparison Group	Mean Difference	P value	95% Confidence Interval of difference
QOL in Phase I vs. QOL in Phase II	-1.16	<0.05	-1.60 to -0.71
QOL in Phase II vs. QOL in Phase III	-5.51	<0.01	-5.95 to -5.07
QOL in Phase I vs. QOL in Phase III	-6.67	<0.01	-7.12 to -6.23

Tukey's Multiple Comparison Test (Post ANOVA)

Figure – 1: Graphical representation of progressive changes in Quality of Life score in different phases of chemotherapy



QOL 1 = Quality of Life before start of taxane chemotherapy.
QOL 2 = Quality of Life after 3rd cycle of taxane chemotherapy
QOL 3 = Quality of Life after 6th cycle of taxane chemotherapy

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