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Treatment of taxane acute pain syndrome (TAPS) in cancer patients received taxane-based chemotherapy. A prospective randomized study done at State Cancer Institute J&K.

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Abstract
Objectives: *The main aims of this study is to describe the incidence and for both prevention and treatment of TAPS.*
Methods: *The Study was a prospective one in which we included Eligible patients scheduled to receive paclitaxel, nab paclitaxel or docetaxel either weekly or 3weekly alone or combination with other chemotherapy. Patient-reported outcome for acute pain were collected and evaluated. Outcome measures of interest included the type of treatment for TAPS, as well as the response of myalgias, arthralgias, pain, and quality of life using Mc Gill Quality of life questionnaires. All those Patients who developed pain, were analyzed for response corticosteroid, gabapantine or duloxitine.*
Results: *A total of 80 patients were available for the analysis, of which 32 patients (40%) received paclitaxel and carboplatin, while as 30 patients (37.5%) received paclitaxel alone, 10 patients (12.5%) received nab paclitaxel and 8 patients (10%) received docetaxel. Among them 54 developed TAPS, comparing with corticosteroid, 30 Patients (55.5%) responded taxene induced pain by corticosteroid, 7 patients (12 percent) responded to gabapantin and 17 patients (31%) responded to duloxitine.*
Conclusion: *The present study has expanded the use of taxanes to numerous cancers. A larger number of patients are, at risk of taxane-induced pain syndrome. Possible strategies to decrease the incidence of pain syndrome include by addition of the medications, have been evaluated to reduce the incidence of TAPS. However, no therapy has been consistently successful; conventional analgesics are also inconclusive.*
More studies should be performed to identify these characteristics as well as patients at risk for the development of taxane-induced myalgia and arthralgia, thereby allowing a risk-adapted strategy of medical prevention.

Introduction

Paclitaxel is used in solid tumors like carcinomas of esophagus, ovary, lung, breast, head and neck[1]. The duration of treatment, particularly the duration of drug exposure, appears to be the most important factor influencing cytotoxicity[2]. Taxane-based chemotherapeutic agents, such as docetaxel, paclitaxel, nab-paclitaxel, and cabazitaxel, are commonly used in the treatment of many malignancies[3]. Taxanes have been associated with taxane acute pain syndrome (TAPS), also known as paclitaxel-associated acute

pain (P-APS) and taxane-induced pain. Paclitaxel is associated with a peculiar syndrome of subacute aches and pains, which has been referred to as paclitaxel-induced arthralgias and myalgias[4,5]. This pain syndrome, described in up to 58% of patients, usually develops within 1 to 3 days of paclitaxel administration symptoms largely resolve within a week.

T-APS is characterized by its early onset (occurs within 1–3 days after drug administration) and short lasting period (usually resolving within 7 days)[6].

Paclitaxel induces a peripheral neuropathy that is typified by a glove-and-stocking distribution of sensory symptoms such as numbness and paresthesia and symmetric distal loss of sensation carried by both large (proprioception, vibration) and small (pin prick, temperature) fiber [7,8]. TAPS is clinically significant as it not only affects physical function and quality of life but can also lead to chemotherapy dose delays, reductions, and discontinuation.

Nonopioid and opioid analgesics are often used for symptomatic management of P-APS. Few studies, mostly case series, have investigated the role of other medications for both prevention and treatment. Studies using Shakuyaku-Kanzo-To (a Japanese herb),[9] antihistamines[10], corticosteroids[11], and opioid analgesics[12], have not yielded enough evidence to establish a standard practice. The lone published placebo controlled, double-blinded, prevention study showed no superiority of glutamine versus placebo[13].

Duloxetine hydrochloride is a reuptake inhibitor of 5-hydroxytryptamine and nor epinephrine used to treat depression, generalized anxiety disorder, neuropathic pain. The efficacy of duloxetine in the management of peripheral nuropathy and fibromyalgia as duloxetine had not been included in the most recent systematic reviews, including one of antidepressants. Duloxetine in peripheral neuropathy alone has been the subject of a recent post hoc analysis[18].

Methods

The Study was a prospective one in which we included Eligible patients scheduled to receive paclitaxel, nab paclitaxel or docetaxel either weekly or 3weekly alone or combination with other chemothearpy. Patient-reported outcome for acute pain were collected and evaluated.

Participants for the study were all the patients who received taxene as their primary chemotherapeutic agent. Patients were asked comprehensive history about their symptoms and timing of symptom, after each cycle of chemotherapy received. The most sensitive and reliable method of detecting taxene induced acute pain syndrome is by history with specific attention to pain questionnaire. These questions were derived and adapted from LANSS PAIN SCALE. Outcome measures of interest included the type of treatment for TAPS, as well as the response of myalgias, arthralgias, pain, and quality of life using Mc Gill Quality of life questionnaires. All those Patients who developed pain, were analyzed for response either corticosteriod, gabapantine or duloxitine.

Patients on this study must have been at least 18 years**,** Patients with documented cases of malignancy, Patients who received taxene alone or combination of other chemotherapy. Patient able to provide written and informed consent, Patients with life expectancy of more than 6 months. Patients excluded with previously diagnosed peripheral pain syndrome, diabetic neuropathy or neuropathy due to other drugs.

Statistical Analysis

The data was analyzed statistically with the statistical software version 20. All the continuous variables of the study were represented by descriptive statistics and the entire categorical variable in terms of frequency and percentage. Depending on the variable of interest, mean (SD), median (range) and frequency (percentage) were used to summarize data in a descriptive manner. Nonparametric Wilcoxon rank-sum tests, two-sample t-tests and chi-square tests (or Fisher's exact tests) were used to compare differences in

scores by pain groups defined in the first cycle. Also the appropriate statistical charts were used to represent the data.

The main aims of this study was to describe the incidence and for both prevention and treatment of TAPS.

Results

A total of 84 untreated cancer patients were enrolled in the study. Out of these, 4 patients were excluded because they did not complete their treatment for various reasons. Therefore, a total of 80 patients were available for the analysis, of which 32 patients (40%) received paclitaxel and carboplatin, while as 30 patients (37.5%) received paclitaxel alone, 10 patients (12.5%) received nab paclitaxel and 8 patients (10%) received docetaxel. Among them 54 developed TAPS, all the Patients were received first corticosteroid, those who didn't responded were received gabapentin and those who did not respond either of two received duloxitin All the patients were compared with respect to their age sex, ECOG performance, dose of chemotherapy and type of chemotherapy received.

Table 1(A) Distribution of Study Subjects According To Demographic Profile

Age(Years)	N = 80	percentage
≤20	1	0.1
21 – 30	6	7.1
31 – 40	10	12.5
41 – 50	30	37.5
51 – 60	20	25
61+	13	16.25
Mean ± SD	**47.6 ± 11.77**	
Gender		
Male	13	16.25
Female	67	83.75

Table 1A,1B illustrates patients characteristics Most commonly observed age group was in between 41-50 years(37.5%) closely followed by age group of 51-60 years (25%) and >61 years (16.25%). Males constituted 16.25% while as females were 83.75%. Most of the patients were having ovary cancer (46.2%) as their primary site of malignancy followed by breast cancer (37.5%) and lung cancer (8.7%) patients. In this study, most of the patients (46.2%) were having serous carcinoma histology followed by invasive ductal cell carcinoma (37.5%) patients. Most patients were having ECOG performance score 1 (75%), followed by 20% patients had ECOG performance score 0. Most of the patients (40%) received paclitaxel and carboplatin based Chemotherapy followed by 36 patients (37.5%) received paclitaxel alone, 10 patients (12.5%) received nab paclitaxel and 8 patients (10%) received docetaxel.

Table 2 Case Distribution According To Site of Primary Malignancy

Site	N	%
Breast	30	37.5
prostrate	4	05
Lung	7	8.7
Nasopharynx	2	02
Ovary	37	46.2
Total	**80**	**100.0**

TAPS

To assess pain, patients were asked "rate any aches/pains that are new since your each subsequent dose of paclitaxel, and that you think might be related to your chemotherapy treatment by best describes onset of aches/pains, intensity of TAPS with subsequent cycle of chemotherapy and its duration of pain. Patients were asked pain questionioriers according to LANNS PAIN SCALE. From the data it has been found that, among 80 patients, 32 patients (40%) who received paclitaxel and carboplatin, 21 patients (26%) developed PAPS, while as 30 patients who received paclitaxel alone 23 patients (28%) developed PAPS. Ten patients who received nab paclitaxel 6 patients (7.5%) developed PAPS and 8 patients who received docetaxel, 4 (5%) patients developed PAPS, however it was statistically insignificant (p= 0.487), as shown in table 2.

Table 2: Taxane induced pain symptoms.

Chemotherapy Scheduled	N	Patient Developed TAPS	Percentage	P Value
Paclitaxel Alone	30	23	28.5	0.487
Paclitaxel And Carboplatin	32	21	26	
Nap paclitaxel	10	6	7.5	
docetaxel	8	4	05	
Total	**80**	**54**	**67**	

All the 54 patients among 80 (67. %) noted pain on first cycle of chemotherapy, Thirty two patients (59.2%) started with PAPS on Day two, 12 patients (22%) started on day third and 10 patients (18%) started on day first of chemotherapy. Majority of patients developed onset of PAPS on day 2nd either received taxene alone or combination of carboplatin, however it was statistically insignificant (p=0.487).

The character and location of pain as experienced by patients, following their first paclitaxel infusion, was assessed by questionnaire. The pain was most prominent in the knee and was most often described as being pinpricking sensation. Among 54 patients 20 patient (37%) experienced pinpricking sensation, followed by 10 patients (18.6%) experienced dull type pain. Most common site was knee observed in 37% patients, followed by lower limbs 22% patients.

Treatment of TAPS

Fifty four patients had TAPS during the course of treatment, and therefore they were analyzed for response, all the 54 patients first received corticosteroids started from 2nd cycle of chemotherapy over a period of five days after convention or high dose of chemotherapy, Evaluations of toxicities were done after each cycle and classified according to LANSS PAIN SCALE. Among them, 24 patients undergoing conventional or high dose with TIP-based chemotherapy there were not statistically significant difference of response of myalgias between patients treated with corticosteroid. Among 24 patients, 10 patients, who received paclitaxel alone, 8 patients received combination treatment, and 4 patients who received docetaxel and 2 patients received nab paclitaxel. The difference in response was statically insignificant (.p=0.487).

Among 54 patients, 24 patients (44.4%) had TAPS during the course of treatment, not responded to corticosteroid and had to receive gabapentin after convention or high dose of chemotherapy. However among them 17 patients was not significant response to gabapantin. Among them 4 patients received docetaxel alone , 7 patients received combination paclitaxel and carboplatin and 4 patients who received paclitaxel and 2 patients received nab paclitaxel. Among 24 patients, 17 patients (70%) had TAPS during the course of treatment, not responded to gabapentin and had to receive duloxitine after subsequent cycle of chemotherapy. The different response to various medication reveals statically significant (p= <0.001) Table 3 mentioned administration route and dose of medication used in TAPS.

Table 3: Medications for Taxane-induced pain syndrome

Medication	**Administration route and dose**	**total**	respond	Not responded	P VALUE
Corticosteroid	Oral, 20 mg starting day first of the chemotherapy and For a total of 5 days.	54	30	24	
Gabapentin	Oral, 900 mg/day 2 days before and for 5 days after taxane infusion	24	7	17	
Duloxitine	Oral 60mg single daily dose continuing.	17	17	0	<0.001
Total		54			

Discussion

This report provides a detailed prospective evaluation of T-APS in a cohort of patients treated with this drug alone or combination of carboplatin. Taxane is associated with a peculiar syndrome of subacute aches and pains, which has been referred to as *taxene -induced arthralgias and myalgias*. The nature and temporal profile of the T-APS distinguishes it as a separate entity from chemotherapy-induced peripheral neuropathy; however, it is not known if those patients who develop the taxane induced acute

pain syndrome(T-APS) are more likely to develop peripheral neuropathy[6]. While it would be nice to have supporting evidence from objective neuro-diagnostic physiologic testing and imaging, it should be noted that there is no physiologic testing or imaging to support that the P-APS is from muscle or joint pathology.

Paclitaxel and carboplatin group most of the patients were age group 51 to 60 years, it is more likely that they would developed pain syndrome in view of old age. Majority of the patients in our study who developed T-APS were female. This was in close agreement with the study done by *Brandi n. and reeves, M.D,* [5].

Corticosteroid has been wildly used in taxane induced myalgia and has been proven role of taxane induced myalgia. In present study among 80 patients 54 had TAPS during the course of treatment , all of them had received predinilisone over a period of five days after subsequent cycle of chemotherapy started from day first, among them 30 patients(55.4%) experienced substantial relief of symptoms., No significant toxicities were noted in any patient receiving prednisone. While as 24 patient not responding to predinosilone after convention or high dose chemotherapy. Our study was similar to a study conducted by Markman and colleagues[15,16] according to study ,low-dose oral prednisone regimen may result in a substantial improvement in the majority of patients expe-riencing significant paclitaxel-associated arthralgia/myalgia.

Gabapentin is a second-line antiepileptic that has been widely used in the treatment of neuropathic and myofascial pain syndromes and has been proven role in treatment of taxane induced nuropathy. In our study among 54 patients 24 had TAPS during the course of treatment, and therefore they were not responding to corticosteroid, all of them patients received gabapentin over a period two day before and five days after subsequent cycle of chemotherapy. Among them only 8 patients (14%) responded well, however there was no significant toxicities were noted. Our study was similar to a study conducted by Nguyen and Lawrence[17], gaba-pentin (300 mg three times daily) was taken 2 days prior to and for 5 days following taxane infusion, and it has been found that gabapentin reduced or prevented myalgias and arthralgias with subsequent exposure to paclitaxel or docetaxel.

Duloxetine hydrochloride is a serotonin-norepinephrine reuptake inhibitor used to treat depression, generalized anxiety disorder, neuropathic pain, and stress incontinence in women. We investigated the efficacy of duloxetine in the management of TAPS and myalgia as duloxetine had not been included in the most recent systematic reviews, including one of antidepressants. Duloxetine in TAPS alone has been the subject of a recent post hoc analysis.

In our study 17 patients (31%) among to 54 had TAPS during the course of treatment neither response to corticosteroid nor gabapentin, but significantly relief by duloxitine of taxene induced symptoms. Our study was similar to study conducted by Asquad Sultan*, Helen Gaskell[18], that Duloxetine is equally effective for the treatment of peripheral diabetic nuropathy and fibromyalgia Comparing duloxetine with antidepressants for pain relief in peripheral diabetic neuropathy(PDN) shows inadequacies in the evidence for efficacy of antidepressants, which are currently recommended in PDN care pathways.

Conclusion

The present study have expanded the use of taxanes to numerous cancers. A larger number of patients are, at risk of taxane-induced pain syndrome. Possible strategies to decrease the incidence of pain syndrome include by addition of the medications, have been evaluated to reduce the incidence of TAPS. However, no therapy has been consistently successful; conventional analgesics, are also inconclusive. The small number of patients in these clinical trials does not permit definitive conclusions to be drawn regarding patient characteristics that may predict

response to these drugs. More studies should be performed to identify these characteristics as well as patients at risk for the development of taxane-induced myalgia and arthralgia, thereby allowing a risk-adapted strategy of medical prevention.

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