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A Study of Paclitaxel Induced Acute Pain Syndrome: A Prospective Study done at State Cancer Institute J&K

Authors
Dar Abdul Waheed, Wani Shahid Bashir, Shah Saqib Ahmad, Najmi Arshad Manzoor, Fir Afroz, Gull Mohamad

Abstract
Objectives: *To describe the incidence and characteristics of paclitaxel induced acute pain syndrome and asses the change in pain related to paclitaxel dose and number of cycle.*
Methods: *The Study was prospective in which we included the eligible patients scheduled to receive paclitaxel weekly or 3 weekly; alone or in combination with another chemotherapeutic agent Carboplatin. Details regarding acute Pain were collected and evaluated.*
Results: *Majority of patient who developed P-APS, received combination of chemotherapy as compared to patients who received chemoradiation or paclitaxel alone. The P-APS was measured on the basis of scoring provided by LANSS pain scale, majority of patients had pain score of less than 12. As far as nature of pain was concerned, we found that the commonest complaints were pinpricking (34.29%) and dull (22.8%) rather than burning (14%), numbness experienced in the knees(44%) followed by in lower limbs (24%), hand (15%), feet(8%), and 4% in ankle.*
Conclusion: *The incidence and characteristics of pain is related to paclitaxel dose and number of cycles. Subsequent cycles of paclitaxel are having no effect on intensity of pain syndrome. Duration of pain increases if patients receive combination of Paclitaxel and carboplatin. Addition of radiation is having neither synergistic nor protective effect in our study.*

Introduction

Paclitaxel is used in solid tumours like carcinomas of oesophagus, ovary, lung, breast, head and neck[1]. Paclitaxel in cancer will focus on defining their roles in earlier or advanced stages and ultimately, in adjuvant therapy after local treatment of early stage disease.

Paclitaxel is generally administered at a dose of 150-175 mg/m2 over 3 h or 135–175 mg/m2 over 24 h every three weeks and 45-50 mg /m2 over 3hr every weekly. The use of paclitaxel is optimal dosing and scheduling. The duration of treatment, particularly the duration of drug exposure appears to be the most important factor influencing cytotoxicity[2].

It has been known since 1993 that treatment of paclitaxel can immediately induce pain symptom in patients. More recently such pain has been defined as Paclitaxel induced acute pain syndrome (P-APS) [3,4] . P-APS is characterized by its early onset (occurs within 1–3 days after drug administration) and short lasting period (usually resolving within 7 days) [5,6].

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].

Clinical use of paclitaxel has led to pain, usually in trunk/upper leg/hip distribution and this has been demonstrated to be dependent upon the dose administered, the duration of the infusion, and the schedule of administration [7,8].

Severity may range from loss of sensory function and mild paresthesia to neuropathic pain, severe ataxia and weakness leading to pronounced disability. Involvement of autonomic nerve fibers with orthostatic hypotension, impotence and incontinence may further reduce the quality of life. The primary site of pathogenesis of the peripheral pain associated with paclitaxel therapy is not clear.

Carboplatin is also classified as neurotoxic agents but that it does not cause as much neurotoxicity as do other platinum drugs. Paclitaxel based Chemotherapy is being Increasingly utilized With Carboplatin And Radiation, as Concurrent Chemo-radiation in most Of The Solid Malignancies Like Lung, Esophagus, GE Junction, Ovary Carcinomas[10,11]. It is likely that the increased intensity of the P-APS is related to the paclitaxel dose, as opposed to the concurrent administration of carboplatin. This is because carboplatin is not generally known to be associated with acute aches and pains

Methods

The study was conducted over a period starting from August 2015 to June 2017. The Study was a prospective one in which we included Eligible patients scheduled to receive paclitaxel weekly and 3 weekly. Patient-reported outcome for acute pain were collected and evaluated. Eligible patients for the present study were scheduled to receive Paclitaxel either at a dose of 45- 50mg/m2 over 2hr infusion at weekly interval or 150-170 mg/m2 over 3hr infusion at 3week intervals, either alone or in combination with another chemotherapeutic agent Carboplatin

Participants for the study were all the patients who received paclitaxel 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 Paclitaxel induced acute pain syndrome is by history with specific attention to pain questionnaire. These questions were derived and adapted from LANSS PAIN SCALE. To assess pain, patient were asked to rate any ache/pain that were new since their last dose of paclitaxel and that they might think be related to their chemotherapy treatment cycle one or the sub sequent cycle.

Patients on this study must have been at least 18 years**,** Patients with documented cases of malignancy, Patients who received weekly or 3 weekly paclitaxel, 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. Also the categorical variables were analyzed with the help of chi-square test and Fisher exact test. All the results were discussed at 5 percent level of significance, i.e. $p<0.05$ was considered significant. Also the appropriate statistical charts were used to represent the data.

The primary goal for this study was to describe the incidence and characteristics, to assess the change in pain (i.e., P-APS) related to paclitaxel dose and number of cycles.

Results

A total of 200 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 196 patients were available for the analysis, of which 150 received paclitaxel and carboplatin, while 46 received paclitaxel alone. Patients who developed acute pain symptoms were compared with respect to their age sex, ECOG performance, dose of chemotherapy and type of chemotherapy received.

Table 1(A). Patient characteristics

Age(Years)	N = 196	Percentage
≤20	1	0.5
21 – 30	6	3.1
31 – 40	28	14.3
41 – 50	46	23.5
51 – 60	57	29.1
61+	58	29.6
Mean ± SD	**54.17±12.46**	
Gender		
Male	87	44.4
Female	109	55.6
ECOG Performance score		
0	**16**	**8.2**
1	178	90.8
2	2	1.0

Table 1A, 1B illustrates patients characteristics. Most commonly observed age group was ≥ 61years closely followed by age group of 51-60 years (29.1%) and 41-50 years (23.5%). Males constituted 44.4% while as females were 55.6%. Most of the patients were having esophageal cancer (42.3%) as their primary site of malignancy followed by breast cancer (24.5%) and lung cancer (19.4%) patients. In this study, most of the patients (61.7%) were having squamous cell histology followed by invasive ductal cell carcinoma (24.4%) patients. Most patients were having ECOG performance score 1(90.8%), followed by 8.2% patients had ECOG performance score 0 Most of the patients (76.5%) received paclitaxel and carboplatin based Chemotherapy and 46 patients (23.5%) received paclitaxel alone. 61.2% patients received chemotherapy weekly and 38.7% patients Received chemotherapy after interval of 3 Weeks.

Table 1B Case Distribution According To Site of Primary Malignancy

Site	N	%
Breast	48	24.5
Esophagus	83	42.3
Ge Junction	6	3.1
Lung	38	19.4
Nasopharynx	2	1.0
Ovary	17	8.7
Stomach	2	1.0
Total	**196**	**100.0**

Most common site of malignancy is esophagus followed by breast.

Paclitaxel induced acute pain syndrome

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 PAPS 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 196 patients, 70 patients (35.71%) developed PAP, among them, 27 patients(38%) received paclitaxel alone and 43 patients (61%) received combination of paclitaxel and carboplatin based chemotherapy it was stastisticaly significant (0.002). Sixty patients were on 3weekly protocol and 10 patients were on weekly protocolit was stastiticaly significant (<.001). Out of 131 patients who received chemotherapy alone, 60 patients (45%) developed PAPS, whereas out of 65 patients who received chemo radiation, only 10 patients (15.38%) developed PAPS, this was statistically significant (p=0.005).

All the seventy patients noted pain on first cycle of chemotherapy. Thirty-seven patients (52.85%) started with PAPS on Day two, 21 patients (30%) started on day one and 12 patients (17.14%) started on third day of chemotherapy. Majority of patients developed onset of PAPS on day 2nd either received paclitaxel alone or combination of paclitaxel and carboplatin, however it was statistically insignificant (0.49). Table 2 illustrates the nature of the P-APS, 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 lower extremities and was most often described as being aching. Among 70 patients 24 patient (34.29%) experienced pinpricking sensation, followed by 16 patients (22.86%) experienced dull type pain. Most common site was knee observed in 44.29% patients, followed by lower limbs 24.29% patients[5,6].

Table1 2 Distribution of Cases Who Developed PAPS with Respect to Pain Characteristics and Location

Pain	Total	%	Location	Total	%
Aching	7	10.00	Ankle	3	4.29
Burning	10	14.29	Face	2	2.86
Dull	16	22.86	Feet	6	8.57
Hot	6	8.57	Hand	11	15.71
Numbness	7	10.00	Knee	31	44.29
Pinpricking	24	34.29	Lower Limbs	17	24.29
Total	**70**	**100.00**	**Total**	**70**	**100.00**

Most common pain characteristics are pinpricking and location was in knee.

Severity of pain score were calculated by LANSS PAIN SCALE. Among the 70 patients who developed PAPS, 40 patients (57.14%) had LANSS PAIN SCORE 8-10, followed by 17 patients (25%) who had 14+ pain score. Among the 40 patients who developed PAPS had LANSS Pain score 8-10, in them majority of patients (57.5%) received paclitaxel and carboplatin, 42.5 % received paclitaxel alone. Similarly, 17 patients had LANSS Pain score >14, in them majority of patients (58.8%) received paclitaxel and carboplatin, 41.1% received paclitaxel alone. However the intensity of pain or pain score remained same with subsequent cycle of chemotherapy. From the data it has been found that majority of patients were having pain for a period of > 4 days. While compared with type of chemotherapy, patients who received combination of chemotherapy paclitaxel and carboplatin remained symptomatic for >4 days as compared to paclitaxel alone group but it was statically insignificant (0.49).

Discussion

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

A total of 196 patients were included in our study, among them, majority of patients n=150 (76.5%) received two drugs paclitaxel and carboplatin, and 46 patients (24.5%) received paclitaxel alone.. Majority of patients in our study were in the age group above 61 year of age (29.6%), females (55.6%) were predominant. Carcinoma oesophagus N=83 (42.3%), carcinoma breast N=48 (24.8%) and carcinoma lung N=38 (19.4%), were most common type of malignancy. Wani et al. (2014) conducted a study regarding the Cancer

trends in Kashmir; common types, site incidence and demographic profiles and they concluded that Cancers of oesophagus, stomach and lungs have a high incidence both in men and women in Kashmir[12]. Seventy patients out of 196 (35.7%), developed paclitaxel induced acute pain syndrome (P-APS) who received paclitaxel or paclitaxel and carboplatin based chemotherapy. Since in the Paclitaxel and carboplatin group most of the patients were age group ≥61 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 P-APS were female N=43 (61.4%). This was in close agreement with the study done by *Brandi n. and reeves, M.D*[5].

Out of 131 patients who received chemotherapy alone, 60 patients (45%) developed PAPS, whereas out of 65 patients who received chemo radiation, only 10 patients (15.38%) developed PAPS, this was statistically significant (p=0.005). This suggests that radiation per se has no role in the causation of pain syndrome and is solely due to chemotherapeutic agent received. It further seems that radiation has neither synergistic nor additive effect in the causation of symptoms in these patients and there are no randomized trials to suggest that radiation causes PAPS. However further studies and research in this regard is warranted.

A study conducted by *Brandi N. Reeves revealed that* Transient myalgia, usually noted 2–5 days after paclitaxel infusion is also common and a myopathy may occur with high doses of paclitaxel combined with carboplatin[4].These results of our study were comparable to the results of the study done by Brandi N Reeves. We observed that the intensity of pain experienced with the first paclitaxel infusion remained same when compared with subsequent infusions of chemotherapy. However, a study conducted by *Charles L. Loprinzi* regarding P-APS, reported that patients had minimal acute pain with initial infusions but had more intense pain with subsequent infusions[6].

In the study, out of 46 patients who received paclitaxel alone, 27 patients (58%) developed P-APS, while as 150 patients who received paclitaxel and carboplatin, 43 patients (28.66%) developed P-APS. This was statistically significant (p value=0.002). It was evident from our study that paclitaxel alone was responsible for the symptoms and addition of carboplatin played no role in the development of acute pain syndrome as Paclitaxel only group had higher incidence of symptoms. Our results were consistent with the study conducted by *Brandi n. and Reeves, M.D.* which showed that the increased intensity of the P-APS was related to the paclitaxel dose, as opposed to the concurrent administration of carboplatin. This is because carboplatin is not generally known to be associated with acute aches and pains[5].

In this study it was observed that most of the patients had a pain score between 8-10 whether they received paclitaxel alone or combination with carboplatin, however it was noted that those who had received combination of both drugs, suffered from pain for a longer time, which was ≥4 days in our study. Regarding longer duration of symptoms in paclitaxel and carboplatin group, two questions need to be answered, whether it was the dose of paclitaxel that increase duration or it was the addition of carboplatin that increase duration. In this regard, more studies are needed to be done.

In the present study there were 17 patients (24.28%) who developed PAPS, had LANSS pain score 14, it seems that neuropathic mechanisms are likely contributing in patients' pain. A study conducted by Michal Bennet, revealed that neuropathic mechanisms are likely to contribute patients pain who have pain score more than 12[13]. This study further suggests that the LANSS PAIN SCALE can distinguish patients with neuropathic pain from those with nociceptive pain with similar accuracy. In our study majority of patients had pain score of less than 12, which in the light of the study conducted by Bennet seems to be not neuropathic in nature, which may primarily be nociceptive. Interestingly majority of the patients in our study had pain symptoms score in the range

of 8-10 and did not have any significant effect on their daily lives till these results were reported.

In our study, we found that the commonest complaints were pinpricking (34.29%) and dull (22.8%) rather than burning (14%), numbness (10%). Moreover, the pain was experienced in the knees (44%) followed by in lower limbs (24%), hand (15%), feet (8%), and 4% in ankle. The study conducted by *Brandi n*; reported that the commonest characteristic of pain experienced numbness, tingling and burning in fingers, hand and feet[5].

Conclusion

This current prospective study adds to the understanding of the PAPS in patients treated with chemotherapy, which is quite bothersome side effect and can often lead to stop or discontinuation of potentially curative chemotherapy in cancer patients.

To sum up, the following conclusions were drawn from the present study:

The incidence and characteristics of pain is related to paclitaxel dose and number of cycles. A subsequent cycle of paclitaxel is having no effect on intensity of pain syndrome. Duration of pain increases if patients receive combination of Paclitaxel and carboplatin. Addition of radiation is having neither synergistic nor protective effect in our study.

References

1. Bissery M-C, Nohynek G, Sanderlink G-J, Lavelle F. 1995. Docetaxel (Taxotereâ): a review of preclinical and clinical experience. Part Preclinical experience. *Anti- Cancer Drugs 6:339–55.*
2. Kearns CM, Gianni L, Egorin MJ. 1995.Paclitaxel pharmacokinetics and pharmacodynamics. *Sem. Oncol.* 22(Suppl. 6):16–23.
3. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol. 1993;20:1–15.
4. Garrison JA, McCune JS, Livingston RB, Linden HM, Gralow JR, Ellis GK, et al. Myalgias and arthralgias associated with paclitaxel. Oncology (Willisto Park). 2003;17:271–7. Discussion 281–272, 286–278.
5. Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, Kamal A, et al. Further data supporting that paclitaxel-associated acute pain syndrome is associated with development of peripheral neuropathy: North Central Cancer Treatment Group trial N08C1 Cancer.2012;118:5171–8.
6. Loprinzi CL, Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, et al. Natura history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. J Clin Oncol. 2011;29:1472–8.
7. Rowinsky EK, ChaudhryV, Cornblath DR, Donehower RC. 1993. The neurotoxicty oftaxol. *Monogr. Natl Cancer Inst. 15:107–* 15.
8. Chaudhry V, Rowinsky EK, Sartorius SE, et al. 1994. Peripheral neuropathy from taxol and cisplatin combination chemotherapy: clinical and electrophysio-logical studies. *Ann. Neurol. 35:490–97.*
9. Moulder SL, Holmes FA, Tolcher AW, et al: A randomized phase 2 trial comparing 3-hour versus 96-hour infusion schedules of paclitaxel for the treatment of metastatic breast cancer. Cancer 116: 814-821, 2010.
10. Slater M S, Holland J, Faigel D O, Sheppard B C, Deveney CW. Does neo-adjuvant chemoradiation downstage esophageal carcinoma? Am J Surg 2001; 181: 440–4.
11. Choy H, Akerley W, Safran H *et al.* Multi institutional phase II trial of paclitaxel, carboplatin, and concurrent radiation therapy for locally advanced non-small-cell lung cancer. J Clin Oncol1998; 16: 3316–22.

12. MA Wani, FA Jan, NA Khan. Cancer trends in Kashmir; common types, site incidence and demographic profiles: National Cancer Registry 2000-2012. Indian J Cancer [serial online] 2014 [cited 2016 Jun 21];51:133-7.
13. Bennett M, The LANSS Pain Scale: The leed Assessment o neuropathic symptoms and sign Pain 2001;92: 147-157.