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RESEARCH ARTICLE

A COMPARATIVE PROSPECTIVE STUDY OF PACLITAXEL INDUCED ACUTE PAIN SYNDROME, SINGLE AGENT PACLITAXEL COMPARED TO COMBINATION OF PACLITAXEL AND CARBOPLATIN

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ABSTRACT

Objectives: To describe the incidence and characteristics of Paclitaxel induced acute pain syndrome. To assess the change in pain (i.e., P-APS) related to paclitaxel alone or combination of carboplatin.
Methods: The Study was a prospective one 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 paclitaxel alone. Majority of patients (59.2%) developed onset of PAPS on day 2nd either received paclitaxel alone or combination of chemotherapy, however majority of patients received combination of chemotherapy remained symptomatic for more than 4days.The P-APS was measurement 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 (37%) and dull (18.6%) rather than burning (14%), numbness (7%). Majority of patient experienced pain in the knees (37%) followed by in lower limbs (22.2%), hand (20%), feet (11%), and 5% in ankle.
Conclusion: The incidence and characteristics of pain is related to paclitaxel dose. Subsequent cycles of paclitaxel are having no effect on intensity of pain syndrome. Duration of pain increased by combination of Paclitaxel and carboplatin. Addition of carboplatin contributed chronicity of pain.

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INTRODUCTION

Paclitaxel is used in solid tumours like carcinomas of oesophagus, ovary, lung, breast, head and neck (Bissery *et al.,* 1995). 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 duration of treatment, particularly the duration of drug exposure, appears to be the most important factor influencing cytotoxicity (Kearns *et al.,* 1995). Paclitaxel is associated with a peculiar syndrome of subacute aches and pains, which has been referred to as paclitaxel-induced arthralgias and myalgias (Rowinsky *et al.,* 1993; Garrison *et al.,* 2003). 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. 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) (Rowinsky *et al.,* 1993; Garrison *et al.,* 2003).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) (Reeves *et al.,* 2002; Loprinzi *et al.,* 2011). 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 (Rowinsky *et al.,* 1993; Chaudhry *et al.,* 1994). 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 (Rowinsky *et al.,* 1993; Chaudhry *et al.,* 1994). A randomized study comparing the efficacy of short versus extended infusion of paclitaxel in metastatic breast cancer demonstrated a 25% incidence of acute pain problems in the 3-hour infusion group versus a 2% incidence in the 96-hour infusion group. It usually occurs at cumulative doses in excess of 1,400 mg/m2 or with lower doses of paclitaxel (40-60

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mg/m2) weekly regimens (Moulder *et al.,* 2010). 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, Oesophagus, GE Junction, Ovary Carcinomas (Slater *et al.,* 2011; Choy *et al.,* 1988). 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 a prospective one in which we included Eligible patients scheduled to receive paclitaxel either weekly or 3weekly alone or combination with carboplatin. Patient-reported outcome for acute pain were collected and evaluated. Eligible patients for the present study were scheduled to receive Paclitaxel at a dose of 150-170 mg/m2 over 3hr infusion at 3week intervals and 45-50mg/m2 over 2hr infusion weekly 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 3 weekly paclitaxel alone or combination of carboplatin. 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 to describe the incidence and characteristics of Paclitaxel induced acute pain syndrome. To assess the change in pain (i.e., P-APS) related to paclitaxel alone or combination of carboplatin.

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 44 received paclitaxel and carboplatin, while 36 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 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 (55%) received paclitaxel and carboplatin based Chemotherapy and 36 patients (45%) received paclitaxel alone.

Table 1A. Distribution of Study Subjects According To Demographic Profile

Age(Years)	N = 80	percentage
≤20	01	0.1
21 – 30	06	7.1
31 – 40	10	12.5
41 – 50	30	37.5
51 – 60	20	25
61+	13	16.25
Mean ± SD	**45 ± 18**	
Gender		
Male	13	16.25
Female	67	83.75

Table 1B. Case Distribution According To Site of Primary Malignancy

Site	N	%
Breast	30	37.5
Gastroesophagus Junction	04	05
Lung	07	8.7
Nasopharynx	02	02
Ovary	37	46.2
Total	**80**	**100.0**

PAPS

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 80 patients, 36 patients who received paclitaxel alone, 22 patients (61.1%) developed PAPS, while as 44 patients who received paclitaxel and carboplatin, 32 patients (72.7%) developed PAPS and it was statistically significant (p=0.0131). All the 54 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 paclitaxel alone or combination of paclitaxel and carboplatin, however it was statistically significant (p=0.0131). Out of 54 patients who developed PAPS, 44 patients were on 3weekly protocol and 10

patients were on weekly protocol. Six patients (60%) among 10 received paclitaxel alone and 28 patients (65%) among 44 patients received paclitaxel and carboplatin. it was statistically significant (p=0.001).

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

Pain	Total	%	Location	Total	%
Aching	03	05	Ankle	03	05
Burning	08	14.8	Face	02	3.7
Dull	10	18.6	Feet	06	11
Hot	06	11	Hand	11	20.3
Numbness	07	12	Knee	20	37
Pinpricking	20	37	Lower Limbs	12	22.22
Total	54	100.00	Total	54	100.00

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 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. Severity of pain score were calculated by LANSS PAIN SCALE. Among the 54 patients who developed PAPS, 20 patients (37.7%) had LANSS PAIN SCORE 11-13, followed by 17 patients (31%) who had 14+ pain score. Among the 20 patients who developed PAPS had LANSS Pain score 11-13, in them majority of patients (65%) received paclitaxel and carboplatin, 35 % received paclitaxel alone. Similarly, 17 patients had LANSS Pain score >14, in them majority of patients (94.1%) received paclitaxel and carboplatin, 5.9% received paclitaxel alone. Among 54 patients, 20 patients (37%) remained symptomatic for a period of 5 days, followed by 11 patients (20%) who were having pain for duration of 6 days. Among 22 patients who received paclitaxel alone, 10 patients (45%) remained symptomatic for period of ≤ 3 days and 12 patients (37.2%) remained symptomatic for period of ≥ 4 days. Similarly, 32 patients who received paclitaxel and carboplatin, 20 patients (62.5%) remained symptomatic for period of ≥ 4 days and 12 patients remained symptomatic for period of ≤ 3 days. However, it was statistically insignificant (P=0.562). 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 (p=0.562).

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. 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 (Loprinzi *et al.,* 2011). 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 P-APS were female. This was in close agreement with the study done by *Brandi n. and reeves, M.D,* (Reeves *et al.,* 2002). Out of 80 patients who received chemotherapy, 54 patients (67.5%) developed PAPS, whereas out of 36 patients who received paclitaxel alone chemotherapy, only 22 patients (61.1%) developed PAPS, and 44 patients who received combination of paclitaxel and carboplatin, only 32 patients(72.7%) developed PAPS. This was statistically significant (p value=0.001). It was evident from our study that combination of paclitaxel and carboplatin were increase incidence of development of acute pain syndrome**.** In our study, we observed that majority of patients noted pain on day 2 and 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. 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.

In this study we found that majority of patients (81.2%) of patient who developed PAPS received either paclitaxel alone or combination of paclitaxel and carboplatin chemotherapy 3 weekly based protocol, it reveals that it is paclitaxel dose which increase the incidence and intensity of PAPS. In this study it was observed that most of the patients had a pain score between 11-13 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. However our results were different 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 (Reeves *et al.,* 2012). In the present study there were 17 patients (31.4%) who developed PAPS, had LANSS pain score 14, and all the patients received combination of carboplatin and paclitaxel 3weekly based protocol, it reveal combination of chemotherapy increase duration of PAPS which is contradicted with study conducted by *Brandi n. and Reeves, M.D.* All the 17 patients had LANNS pain score >14, this suggested 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 (Bennett *et al.,* 2001). 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 11-13 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 (37%) and dull (18.6%) rather than burning (14%), numbness (7%). Moreover, the pain was experienced in the knees (37%) followed by in lower limbs (22.2%), hand (20%), feet (11%), and 5% 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. The 4 month follow up of the study 17 patients was symptomatic for pain, however it was found that all the patients had received combination of chemotherapy with LANSS pain scale was >14, it reveals that again it is combination of carboplatin which increase the duration of pain and likely contributed neuropathic mechanism of pain and contributed chronicity of pain. This study further suggests that the LANSS PAIN SCALE can distinguish patients with neuropathic pain from those with nociceptive pain with similar accuracy. As per Michal Bennet, revealed that neuropathic mechanisms are likely to contribute patients pain who have pain score more than 12 (Bennett *et al.,* 2001).

Conclusion

Clearly the conclusions were drawn from 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. Subsequent cycles of paclitaxel are having no effect on intensity of pain syndrome. Duration of pain increased by combination of Paclitaxel and carboplatin. Addition of carboplatin contributed chronicity of pain.

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