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Toxicity profile of weekly regimen of paclitaxel in patients with non-metastatic breast cancer-a real world experience

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SUMMARY

Introduction: Taxanes especially paclitaxel is a key chemotherapeutic agent in the management of non-metastatic breast cancer. Different schedules are utilized in management with weekly paclitaxel being one of the common regimes. The weekly regimen has a distinctive toxicity profile. Methods: This retrospective study was done to study the adverse effect profile of weekly paclitaxel used in the treatment of non-metastatic breast cancer. Data were collected from case records of patients who received or were started on weekly paclitaxel single agent or in combination with trastuzumab between May and July 2019. Results: Eighty-eight patient case records were analyzed. The median age was 46.5 yrs (Range 30-67 yrs). The majority of patients received paclitaxel as an adjuvant (N=80, 91%). Sixty-one patients (69%) received single-agent paclitaxel while the remaining received it in combination with trastuzumab. Seventy-five percent (N=66) of patients did not have any modification of dosages in their regimen. Among those patients who required dose modification 19% (N=17) of patients required it from cycle 7 or beyond. Planned 12 cycles of weekly paclitaxel were completed in 81% (N=71) patients. The median duration for completion of 12 cycles from the start of chemotherapy was 80 days (Range 53-103). Major Grade 3/4 toxicities observed included peripheral neuropathy (12%) anemia (10%) and Neutropenia(4%). Conclusion: We observed a higher incidence of acute toxicities related to weekly paclitaxel though the majority of patients were able to complete their planned schedule of paclitaxel.

Key words: weekly paclitaxel, toxicities, breast cancer, peripheral neuropathy

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INTRODUCTION

Taxanes are an important class of anticancer agents with activity against a broad range of cancers. Paclitaxel was the first taxane discovered and to be used in clinical trials [1]. Paclitaxel is active against a broad range of common cancers like non-small cell lung cancer, breast cancer, ovarian cancer, etc. Paclitaxel exerts cytotoxicity by promoting the polymerization of tubulin [1]. Any new therapy in cancer is initially tried in metastatic cancers that have failed standard available regimens. Similarly, paclitaxel was first approved in ovarian cancer when it showed impressive responses in heavily pretreated patients. Subsequently, it showed activity in other cancers including breast cancer [1]. The impressive activity of paclitaxel in metastatic breast cancer prompted investigators to use it in the adjuvant treatment of breast cancer. Adjuvant taxanes on the backbone of anthracycline-based regimen have shown survival benefits in Non-metastatic breast cancer [2,3]. In the study by Sparano et al. it was shown that 12 cycles of weekly paclitaxel after standard adjuvant chemotherapy with doxorubicin and cyclophosphamide improved disease-free and overall survival in women with breast cancer [4]. Hence currently one of the standard adjuvant regimens in breast cancer is four cycles of Doxorubicin and cyclophosphamide every 3 weeks followed by 12 cycles of weekly paclitaxel. In the case of HER2 overexpressing tumors, trastuzumab has been combined with weekly paclitaxel or other cytotoxic drugs in a neoadjuvant setting to yield improved pathological response rates and survival benefits [5,6]. Achievement of pathological complete response is significantly associated with better event-free survival and overall survival [7]. Hence neoadjuvant weekly paclitaxel with trastuzumab is one of the preferred regimens in HER2 overexpressing locally advanced breast cancer.

Cytotoxic chemotherapy is not without its own share of toxicities. In a meta-analysis, it was observed that weekly paclitaxel had a significantly lower risk of neutropenia and a trend towards a lower risk of sensory neuropathy. This meta-analysis included studies using various schedules of paclitaxel in metastatic setting [8]. In the study by Sparano et al. it was observed that the incidence of neutropenia, myalgia, and arthralgia was higher with 3 weekly paclitaxel arm while the incidence of Grade 3 or 4 neuropathy was higher with weekly paclitaxel arm. However, overall grade 3/4 toxicities did not differ significantly between the two arms [4]. In a study from India, the significant problems observed among patients who received paclitaxel were moderate paraesthesia and cardiac

problems [9]. In another study from India which used single agent weekly paclitaxel for locally advanced breast cancer in neoadjuvant setting observed incidence of Grade 3/4 neuropathy and neutropenia were very low. No cases of febrile neutropenia were observed in this study [10]. In the cohort of patients who had received short course adjuvant trastuzumab in breast cancer at our center previously, the major observed Grade 3/4 toxicities included peripheral neuropathy, neutropenia, hyponatremia, hepatotoxicity, and febrile neutropenia requiring hospitalization [11]. Another adverse effect observed with paclitaxel is a hypersensitivity reaction. It has been shown to be histamine-mediated and is thought to be due to polyoxyethylated castor oil vehicle (Cremophor El) [1]. Antihistamines and corticosteroid premedications have helped in reducing hypersensitivity reactions to paclitaxel [1]. Limited real-world data exists looking at toxicity of weekly paclitaxel regimen in non-metastatic breast cancer. Hence, we undertook a retrospective study to evaluate the toxicity profile of weekly paclitaxel regimen administered in adjuvant or neoadjuvant settings among breast cancer patients.

MATERIALS AND METHODS

This is a retrospective study done at a tertiary cancer center in South India. At our center, all high-risk node-negative and node-positive breast cancer patients receive adjuvant Doxorubicin with Cyclophosphamide (AC) for four cycles followed by 12 cycles weekly Paclitaxel. Adjuvant weekly for 9 doses or 3 weekly trastuzumab for 17 doses is offered to patients with HER2 positivity based on their choices and affordability. Trastuzumab is started along with the weekly paclitaxel regimen. Those patients with locally advanced breast cancer undergo neoadjuvant chemotherapy with weekly paclitaxel for 12 cycles along with 9 weeks of trastuzumab if their tumor is HER2 positive while those with other subtypes undergo 4 cycles of neoadjuvant AC followed by surgery and then 12 cycles weekly paclitaxel. Paclitaxel was administered in a dose of 80 mg/m^2 weekly for 12 cycles over 1 hour. Premedications were given included Ranitidine 50 mg IV, Pheniramine 50 mg IV, and Dexamethasone 10 mg IV. The aim of this study was to evaluate the toxicity profile of a weekly regimen of Paclitaxel in patients with non-metastatic carcinoma breast. This study was done among patients with non-metastatic breast cancer who received or were started on weekly paclitaxel single agent or in combination with trastuzumab between 01/05/2019 to 31/07/2019 at our hospital. The hospital ID of these patients was obtained from the register maintained at daycare. Case records of these patients were accessed for the collection of data for this study. Approval was obtained from the Institutional Review Board before the start of the study. Waiver of consent was obtained since this was a retrospective study involving a collection of data from patient case records. Those patients on weekly paclitaxel in combination with Carboplatin or Cisplatin, patients with a history of exposure to paclitaxel previously, and those with concurrent malignancy other than breast cancer were excluded from this study. Toxicity assessments were done using CTCAE Version 4.03.

STATISTICAL ANALYSIS

The data were tabulated electronically in Microsoft Excel and analyzed by using the software IBM SPSS 20.0 version (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The demographic details of the participants were expressed in frequency and percentage.

RESULTS

In our study cohort data of 88 patients who received weekly

Tab. 1. Demographic Characteristics

Variable	Number (%)
Median Age	46.5 yrs (Range 30-67 yrs)
Weekly Paclitaxel	
Adjuvant	80 (91)
Neoadjuvant	08 (9)
Comorbidities	
Diabetes Mellitus	08 (9)
Hypertension	08 (9)
Hypothyrodism	05 (6)
Both Diabetes & Hypertension	05 (6)
Hypercholesterolemia	01 (1)
Psychiatric Illness	01 (1)
Psychiatric Illness with Diabetes	01 (1)
Regimen	
Weekly Paclitaxel alone	61 (69)
Weekly Paclitaxel with Trastuzumab	27 (31)
Total Cycles received	
8	1(1)
9	4 (4)
10	5 (6)
11	7 (8)
12	7 (81)

Tab. 2. Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	30 (34%)	37 (42%)	09 (10%)	0
Neutropenia	17 (19%)	06 (7%)	02 (2%)	02 (2%)
Peripheral Neuropathy	34 (39%)	13 (15%)	11 (12%)	0
Vomiting	05 (06%)	01 (1%)	01 (1%)	0
Diarrhea	03 (4%)	01 (1%)	0	0
Mucositis	06 (7%)	01 (1%)	02 (2%)	0
Transaminases elevation	10 (11%)	05 (6%)	0	0
Fatigue	10 (11%)	09 (10%)	01 (1%)	0
Myalgia	14 (16%)	04 (5%)	0	0
Peripheral Limb Edema	80 (91%)	08 (9%)	0	0

paclitaxel and hence a total of 1023 infusion cycles were administered to these patients during this period. The median age was 46.5 yrs (Range 30-67 yrs). The majority of patients received paclitaxel as an adjuvant (N=80, 91%). Most of the patients had no comorbidities (n=59, 67%). Only single-agent weekly paclitaxel was received by 61 (69%) while the remaining received it in combination with trastuzumab (Table 1).

Seventy-five percent (N=66) of patients did not have any modification of dosages in their regimen. Among those patients who had required dose modification 19% (N=17) of patients required it from cycle 7 or beyond. Around 7% (N=6) required it from Cycle 7 while 6% (N=5) required it from Cycle 10. Dose modifications were done in view of various toxicities. Planned 12 cycles of weekly paclitaxel were completed in 81% (N=71) patients. The median duration for completion of 12 cycles from the start of chemotherapy was 80 days (Range 53-103).

Anemia was observed in 77 (86%) patients. A large majority (N=68, 78%) of these patients had either grade 1 or grade 2 anemia. Data was missing in 2 patients. The weekly paclitaxel-based regimen was well tolerated as Grade 3/4 neutropenia was observed in 4 (5%) patients only. Data was missing in 2 patients. Peripheral neuropathy of some grades was observed in 58 (66%) patients. It was Grade 3/4 in 11 (12%) patients. Out of 58 patients who had reported some grades of peripheral neuropathy 34 (59%) neuropathy was observed from cycle 9 or beyond. Grade 2 peripheral edema was seen in 8 (9%) patients while the remaining had grade 1 edema. Grade 2 myalgia was observed in 4 (5%) patients and Grade 1 in 14 (6%). More than half of the patients (N=10, 56%) who had complained of myalgia reported after completion of 6 cycles. Among 20 (22%) patients who reported fatigue while on weekly paclitaxel chemotherapy, 10 (11%) had grade 1 fatigue, 9 (10%) had Grade 2 while one (1%) had grade 3 fatigue. Among those who complained of fatigue 11 (55%) had complained of fatigue after completion of at least 6 cycles of weekly paclitaxel. Two patients complained of arthralgias, one each grade 1 and 2 respectively. Some degree of vomiting was reported by 7 (8%) patients. It was Grade 1 in 5 patients (6%) and one each (1%) had grade 2 and grade 3 respectively. Diarrhea was reported by 4 patients (4%) and it was Grade 1 in 3 patients (3%) while Grade 2 in one patient (1%). Mucositis was reported by 9 patients (10%) and it was grade 1 in 6 (7%), Grade 2 in 1 (1%), and Grade 3 in 2 patients (2%). Liver enzymes – Aspartate Aminotransferase (AST) and/or Alanine Aminotransferase (ALT) elevations were noted in 15 (17%) patients and it was grade 1 in 10 (11%) and grade 2 in 5 (6%). Grade 1 hypersensitivity reaction to paclitaxel was observed in one patient and it did not recur in subsequent cycles. Hence, the incidence of hypersensitivity reaction observed was 0.09%. Table 2 gives detailed data on toxicity in our study.

DISCUSSION

This was a single-center retrospective study done to see toxicity profile with weekly paclitaxel received as a single agent or along with trastuzumab in patients with non-metastatic breast cancer as their adjuvant or neoadjuvant. We observed that most of the patients in our study had hematological or peripheral neuropathy as major toxicities. This is similar to those which have been observed in major adjuvant clinical trials in breast cancer and in a meta-analysis [4,8]. We observed that grade 3 anemia incidence was 10% while Grade 3/4 neutropenia was 4%. This is higher than what has been observed in the adjuvant breast cancer trial by Sparano et al. [4]. In the trial by Sparano et al. only Grade 4 anemia was reported as an adverse effect and it was observed in less than 0.5% of the trial population [4]. The higher incidence of hematological toxicities seen in our study could be due to multiple reasons. One reason could be because our study includes patients from the real world who may have other concurrent morbidities. This may contribute to the development of hematological problems like anemia. Studies have shown that there is a higher prevalence of anemia in cancer patients especially iron deficiency anemia among Indian patients [12]. The majority of our patients received weekly paclitaxel in the adjuvant setting after they had received doxorubicin with cyclophosphamide and this also could have contributed to higher grades of anemia observed during weekly paclitaxel. The study by Gupta et al. reported hematological complications were lower compared to our study. The possible explanations include lower numbers in their study, lower cumulative paclitaxel received by patients in that study and all patients having received paclitaxel as upfront neoadjuvant therapy [10]. Peripheral neuropathy of any grades was seen in 66% of our study population and Grade 3/4 peripheral neuropathy was seen in 12% of our patients. This is higher than what has been reported in a trial by Sparano et al. where grade 3 neuropathy was seen in only 8% [4]. The incidence of grade 2,3 and 4 peripheral neuropathy seen in the study by Sparano et al. and our study was similar [4]. Similarly, we observed a higher incidence of grade 3 myalgia and fatigue among our patients

compared to other studies. Incidence of neuropathy, fatigue, and myalgia also was lower in a study by Gupta et al [10]. In a meta-analysis, the incidence of clinically significant neutropenia and neuropathy was more likely with increasing dose density and hence lower risk with weekly paclitaxel regimes [8]. However, we observed a higher incidence of hematological toxicity and neuropathy with a weekly paclitaxel regimen. The meta-analysis included studies using various schedules of paclitaxel in various metastatic cancers. Hence this population was heterogeneous. Also, multiple studies used varying doses [8]. Only one patient in our study (0.09%) had a grade 1 hypersensitivity reaction and it did not recur on rechallenging paclitaxel. Almost similar incidence of hypersensitivity reactions has been observed in other studies using weekly paclitaxel in breast cancer [13]. It is to be noted that real-world data are important on three counts as it helps in gathering information about chronic toxicity, toxicity profile in special patient population (such as older individuals or patients with concurrent comorbidities), or drug interactions that are often incomplete or not available from clinical trial data. Since clinical trial includes patients with good performance status and those with well-controlled comorbidities as a result of very restrictive eligibility criteria, risk of overall toxicities will be lower than that seen in the real world [14]. This could be another potential reason for an observed higher incidence of hematological toxicities and peripheral neuropathy in our study.

This is one of the few real-world studies which have looked specifically into weekly paclitaxel used in the management of non-metastatic breast cancer both in adjuvant and neoadjuvant settings. This study has the limitations of being a single-center retrospective study with short follow-up. Due to short follow up delayed toxicities will be missed. Subjective symptoms are also likely to be missed out in such retrospective studies.

CONCLUSIONS

We observed a higher incidence of acute toxicities related to weekly paclitaxel though the majority of patients were able to complete their planned schedule of paclitaxel. Real-world data on commonly used regimens help in a better description of treatment tolerability. Knowledge of adverse events occurring within a more heterogeneous population base adds to the body of evidence to guide day-to-day practice.

CONFLICTS OF INTEREST

All the authors declare there is no conflicts of interest.

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