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Original Research Article

Taxanes induced hypersensitivity reactions in cancer chemotherapy patients reported at adverse drug reaction monitoring centre at a tertiary care hospital

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ABSTRACT

Background: Cancer chemotherapy involves highly complex regimens using antineoplastic agents like taxanes (paclitaxel, docetaxel) etc. Taxanes cause hypersensitivity reactions (HSRs) like redness, rashes, dyspnoea, severe anaphylaxis and death. In this study, adverse drug reactions (ADRs) associated with taxanes are described & analysed on their severity and preventability. The present study aims to analyse and determine the prevalence of ADRs, especially HSRs in patients treated with taxanes.
Methods: After getting IEC approval, the present study is done retrospectively by assessing the HSRs in suspected ADR reporting forms from December 2019 to February 2022 in ADR monitoring centre (AMC) in the Department of Pharmacology at Kurnool Medical College, Kurnool. Descriptive statistics used to analyse patient demography, frequency, various carcinomas under treatment & organ involved, causality assessment using WHO-UMC Scale and Naranjo's Algorithm, severity assessment using modified Hartwig & Siegel's scale and preventability by modified Schumock & Thornton scale.
Results: A total of 258 ADRs were recorded, of which 30 cases reported HSRs with taxanes-paclitaxel (22) and docetaxel (8). The most commonly occurred HSR is shortness of breath. Naranjo's algorithm showed 52.5% possible (score 1-4) HSRs. WHO-UMC causality assessment scale showed 56.4% as probable HSRs. Modified Hartwig & Siegel severity scale showed 46.6% moderate (level 3). Modified Schumock and Thornton scale showed 76.9% as not preventable.
Conclusions: Chemotherapy-related ADRs among cancer patients urges the oncologists to be actively involved in ADR reporting, in the need of the hour in order to mitigate, avoid their occurrence and reducing morbidity and mortality, when practiced with diligence.

Keywords: Taxanes**,** Cancer chemotherapy, Hypersensitivity reactions

INTRODUCTION

An adverse drug reaction (ADR) is defined as 'any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy' (The Uppsala monitoring centre, 2002).[1] ADR is one of the leading cause of morbidity and mortality in which the drug toxicity stands as a major limitation in providing healthcare to patients at a global level.[2] Cancer chemotherapy involves highly complex regimens using natural antineoplastic agents like vinca alkaloids, taxanes (paclitaxel, docetaxel etc.,). The latter being an important

cause of hypersensitivity reactions (HSRs) in cancer patients.[3] These reactions maybe either immediate or delayed type. These HSRs present clinically as face redness, skin rashes, cough, flushing, wheezing, anxiety, urticaria, bronchospasm, dyspnoea, chest pain/tightness, severe anaphylaxis and death.[4]

In India, there are only a few studies reported on taxanes (microtubule-damaging antineoplastic drugs) induced hypersensitivity reactions. Paclitaxel is a commonly utilized anticancer agent for the treatment of various tumours like breast, ovarian, peritoneal, gastric, and non-small-cell lung cancer for cancer chemotherapy patients. Currently weekly paclitaxel infusions are given in low doses. Paclitaxel had earned a black box warning by the Food and Drug Administration (the drug approval and regulation body in the USA) due to the occurrence of complicated HSRs after administration. The cause of the HSR is not fully understood even after the postulation of IgE-mediated response, direct interaction of drug with mast cells and basophils, sensory nerve peptide interaction and polyoxyethylated castor oil (vehicle) induced histamine release. There are less studies even on the administration of premedications for weekly paclitaxel infusion.[4] The management of HSRs requires a process of reporting, monitoring, preventing, and managing the symptoms by filling the suspected ADR reporting forms.[5] Now-a-days, commercially available paclitaxel solutions are being used immediately after dilution with 5% dextrose or 0.9% sodium chloride injection showing higher safety outcome.

Docetaxel binds to microtubules, induces cell cycle arrest & apoptosis. It was first approved in the USA in 1995 for anthracycline-refractory metastatic breast cancer, locally advanced breast cancer, non-small cell lung cancer, and androgen-independent prostate cancer.

Docetaxel is now being used in single or combination chemotherapy widely.[2] In this study, HSRs associated with taxanes are described and analysed on their severity and preventability.

Aim and objectives

The present study aims to analyse and determine the prevalence of HSRs in patients treated with taxanes and to look for unexpected hypersensitivity reactions. Objectives of the present study are to assess the patient demography, types of cancers to chemotherapeutic agents related HSRs, different grades of reactions, severity, de-challenge, re-challenge & preventability of the HSRs occurred.

METHODS

Study design, location and duration

The present study was done retrospectively by assessing the HSRs in the suspected ADR reporting forms at AMC in the Department of Pharmacology at Kurnool Medical College, Kurnool, received from Government General Hospital, Kurnool, that were reported from December 2019 to February 2022 in cancer chemotherapy patients.

Data collection

All of the suspected cases of ADRs that were reported to the ADR Monitoring Centre were entered in Vigiflow to the National Coordination Center (NCC) by filling the suspected ADR reporting forms of Indian Pharmacopoeia Commission (IPC). A total of 258 chemotherapy ADRs were reported out of which 30 cases showed hypersensitivity reactions to taxanes, of which 22 were due to paclitaxel and 8 due to docetaxel.

Data analysis

Data analysis is done by assessing different grades of hypersensitivity reactions according to Common Terminology Criteria for Adverse Events (CTCAE) & European journal of allergy and clinical immunology.[6,7] The pattern of HSRs due to paclitaxel and docetaxel are identified and their causal associations were analysed by using the Naranjo's algorithm and WHO-UMC causality assessment scale. The severity of HSRs were analysed by using the modified Hartwig & Siegel scale. The preventability of HSRs were assessed by modified Schumock and Thornton scale.

RESULTS

A total of 258 ADRs were recorded, out of which 30 cases reported HSRs occurred due to taxanes-paclitaxel (22) and docetaxel (8) (Table 1). The major HSRs are shortness of breath (70%), utricaria (23.3%), face redness (10%) and chills, rashes (3.3% each) (Figure 4). ADRs related with taxanes are seen as 50% in breast carcinomas, 36.6% in lung carcinomas and 6.6% in both ovarian & large cell neuro-endocrine carcinomas (Table 3) (Figure 3). Naranjo's algorithm showed 47.4% probable (score 5-8) & 52.5% possible (score 1-4) HSRs (Table 4).

WHO-UMC causality assessment scale showed 39.7% as certain, 56.4% as probable HSRs (Table 5). Modified Hartwig and Siegel's severity scale showed 20% mild (level 2), 46.6% moderate (level 3) & 33.3% moderate (level 4) (Figure 5). Modified Schumock and Thornton scale showed 76.9% as not preventable and 16.6% as definitely preventable HSRs (Table 6).

Table 1: Patients gender distribution in relation to hypersensitivity reactions.

Gender	Males	Females
Paclitaxel	9	13
Docetaxel	4	4
Total	13 (43.3)	17 (56.6)

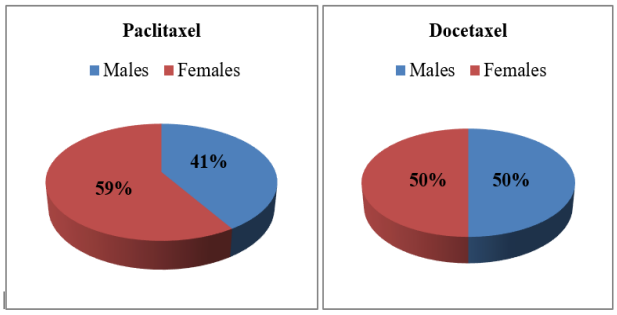

Figure 1: Patients gender distribution in relation to hypersensitivity reactions.

Table 2: Patients age distribution in relation to hypersensitivity reactions.

Age	31-40 years	41-50 years	51-60 years	>60 years
Paclitaxel	3	9	7	3
Docetaxel	3	4	1	0
Total (%)	6 (20)	13 (43.3)	8 (26.6)	3 (10)

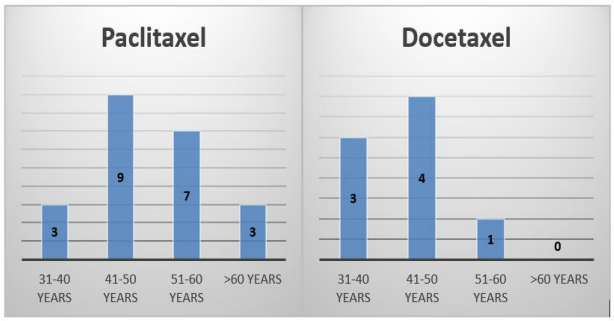

Figure 2: Patients age distribution in relation to hypersensitivity reactions.

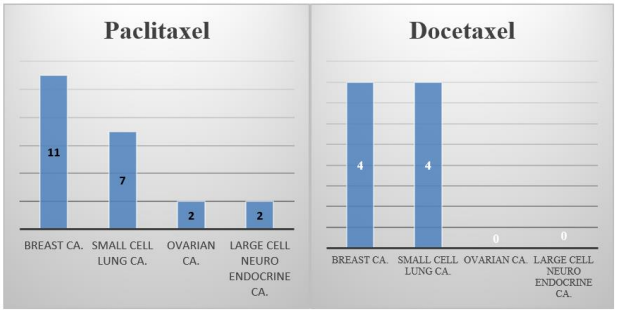

Figure 3: Analysis of types of cancer to chemotherapeutic agents related HSRs.

Different grades of HSRs with taxane chemotherapy

The different types of reactions consistent of signs and symptoms were of Grade-II and Grade-III according to the grading available from the National cancer institute's common terminology criteria for adverse events (CTCAE) version 3.0 and European journal of allergy & clinical immunology.[6,7] According to European journal of allergy & clinical immunology different grades were; grade-I: local reaction, grade-II: mild to moderate systemic reaction without CVS/respiratory system, grade-III: severe systemic reaction with CVS/respiratory system (anaphylaxis).

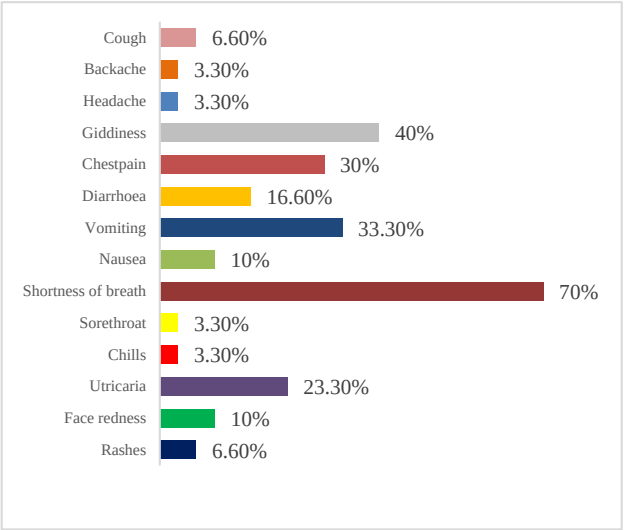

Figure 4: Pattern of HSRs.

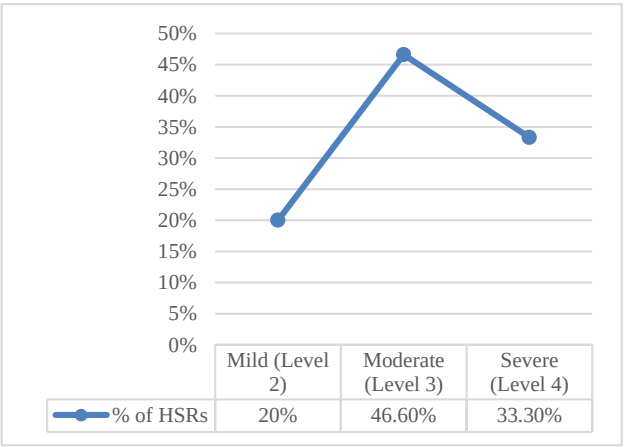

Figure 5: Modified Hartwig & Siegel's scale: severity assessment.

Table 3: Analysis of types of cancer to chemotherapeutic agents related HSRs.

Type of cancers	Breast cancer	Lung cancer	Ovarian cancer	Large cell neuro endocrine cancer
Paclitaxel	11	7	2	2
Docetaxel	4	4	0	0
Total N (%)	15 (50)	11(36.6)	2 (6.6)	2 (6.6)

Table 4: Naranjo's algorithm-causality assessment.

HSRs	Doubtful	Possible	Probable	Definite	Total
Shortness of breath	-	10	11	-	21
Rashes	-	2	-	-	2
Face redness	-	3	-	-	3
Utricaria	-	4	3	-	7
Chills	-	1	-	-	1
Sorethroat	-	1	-	-	1
Cough	-	2	-	-	2
Nausea	-	3	-	-	3
Vomiting	-	6	4	-	10
Diarrhoea	-	1	4	-	5
Chest pain	-	1	8	-	9
Giddiness	-	5	7	-	12
Headache	-	1	-	-	1
Backache	-	1	-	-	1
Total N (%)	-	41 (52.5)	37 (47.4)	-	78

Table 5: WHO-UMC Causality assessment scale.

HSRs	Certain	Probable	Possible	Unlikely	Total
Shortness of breath	9	12	-	-	21
Rashes	-	2	-	-	2
Face redness	-	3	-	-	3
Utricaria	4	3	-	-	7
Chills	1	-	-	-	1
Sorethroat	1	-	-	-	1
Cough	-	2	-	-	2
Nausea	2	1	-	-	3
Vomiting	5	5	-	-	10
Diarrhoea	1	4	-	-	5
Chest pain	3	5	1	-	9
Giddiness	4	7	1	-	12
Headache	-	-	1	-	1
Backache	1	-	-	-	1
Total N (%)	31 (39.7)	44 (56.4)	3 (3.8)	-	78

Table 6: Modified Schumock and Thornton scale: Preventability assessment.

Definitely preventable	Probably preventable	Not preventable
Nausea, vomiting	Diarrhoea	Shortness of breath, face redness, chest pain, utricaria, giddiness, cough. Rashes, chills, sorethroat, headache, backache.
16.6	6.4	76.9

DISCUSSION

There is slight increase in occurrence of HSRs with paclitaxel than docetaxel HSRs in the patients undergoing cancer chemotherapy involved in this study. Most of the HSRs were of moderate severity & not preventable due to the poor predictability of the HSRs and poor mechanisms to explain their cause of occurrence. According to European journal of allergy and clinical immunology, grade-III HSRs have occurred majorly that are severe.

However according to the research by the European organization for research and treatment of cancer-early clinical trials group, there is no recommended optimal premedication regimen for the prevention of hypersensitivity to paclitaxel & docetaxel.[2] Similar studies can be used as audit tools for iatrogenic adverse events and assessment of prevention of expected adverse drug reactions. In Chopra, et al adverse drug reactions in oncology patients study it was described that the causality assessment revealed that most of the ADRs were possible followed by probable category.

The majority of the ADRs reported in this study were mild (86.97%) and (51%) of the ADRs were classified as not preventable, which is in concordance with findings of other authors.[3] In Lal et al study of retrospective evaluation of weekly paclitaxel infusions, the hypersensitivity reactions were reported in electronic medical record system. Occurrence of more number of reactions with existing hypertension were seen as there was recording of blood pressure during pre-paclitaxel and post-paclitaxel infusions.[4]

In Wahlang et al study the ADRs for causality assessment were analysed by using Naranjo scale in which 13.2% were probable and 86.7% were possible. The assessment of the severity of adverse drug reactions was done by using the Hartwig & Siegel scale, showed that 77.4% were mild (level 1), 18.9% were moderate (level 3-4) and 3.8% were severe (level 5). Preventability was assessed by using the Modified Schumock and Thornton scale which showed that 45.3% of reactions as mostly preventable, while 54.7% were not preventable.[10]

CONCLUSION

Chemotherapy-related HSRs among cancer patients urges the oncologist to pay attention, in order to mitigate & avoid their occurrence. This study showed that most of the cancer patients recovered from HSRs that are preventable with effective ADR monitoring. Medical oncologists should be actively involved in ADR reporting, the need of the hour, which would be of immense value in reducing morbidity and mortality, when practiced with diligence. Successful inter-professional teamwork and communication assure that all patients receive their appropriate dose and regimen based on FDA guidelines or hospital protocol. Oncologists should thoroughly evaluate the patient and select an appropriate treatment regimen based on guidelines and patient-specific factors. Nurses should also be made aware of the signs and symptoms of hypersensitivity reactions to paclitaxel. The fatal outcome of the paclitaxel & docetaxel associated HSRs in the patient warns the need of suggestion of IV premedication guidelines before the drugs administration by the concerned authorities.

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