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Study of trends and patterns of Adverse Drug Reactions (ADRs) of Cisplatin in Pulmonary Cancer patients- one year prospective study

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Abstract

Background: A cross sectional prospective observational study evaluated the trends and patterns of Adverse drug reactions of cisplatin in pulmonary cancer patients .

Methods: Pulmonary cancer patients, who received cisplatin as chemotherapy regimen, were monitored for adverse reactions. New and old diagnosed cases of pulmonary cancer patients belonging to either gender and of all ages, who were receiving cisplatin under any standard regimen, were included for the study. Any ADR due to poisoning, over dosage were excluded from the study. The ADRs were recorded in Central Drugs Standard Control Organization forms. Casuality was assessed by the WHO Casuality Assessment Scale and Naranjos Alograthim.

Results:A total number of 98 patients were reported during the study period, wherein a total number of 114 ADR cases were observed.The majority of patients were in the age group of 61-80 (n=45), followed by 41 -60 years (n=41, 41.83%) .Out of the total ADRs, most frequently reported one was vomiting 18 (15.78%) followed by anemia 16 (14.03%), nausea 13(11.40%) and hair loss 12 (10.52 %) which together constituted 51.73 % of the total ADRs. The other commonly encountered ADRs were diarrhea 8 (7.01%), thrombocytopenia 6 (5.26%), constipation 6 (5.26%) neutropenia 5(4.38) and neuropathy 5(4.38%).According to WHO-UMC scale, 37(37.75%) of reports to be certain,33(33.67%) of reports to be possible and 28(28.57%) of reports to be probable where there was no case recorded as unclassified or inaccessible.Naranjo's scale which classified 65 (66.32%) to be probable and remaining 33 (33.67%) to be possible.

Conclusion: Cisplatin has high potential for adverse effects. There is a need to improve the management of adverse effects. This study also emphasizes the need to improve pharmacovigilance awareness among physicians in order to improve the pharmacovigilance in India.

Introduction: Cancer is a leading cause of morbidity and mortality globally with an annual death rate of 12%[1,2] . India cannot be exempted as more than 1300people die every day according to National Cancer Registry Programme of Indian council of Medical research. Between 2012- 2014 the estimated mortality rate due to cancer increased 6% approximately[3].Among all cancers, lung cancer is the most commonly diagnosed cancer. It is a leading cause of death in the world. Non small cell lung cancer (NSCLC) comprises the most common form of the lung cancer[4,].ADR occurs commonly in anticancer drug therapies

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because of their cytotoxic property as they can damage the normally dividing cells along in addition to the cancerous cells. Multidrug therapy in these patients also makes them more vulnerable to ADRs[5,6] Antineoplastic agents, a common class of drugs in cancer patients are responsible for a total of 21.8% of the reported ADRs. These events can beminimized by decreasing the intensity of the dose of a drug or by delaying the doses, but it carries risk of directly affecting their efficacy[7].Platinum based regimens have been used in the standard first line chemotherapy in NSCLC patients[8,9].

They also lead to diverse side effects and toxicities and the general toxicity profile differs between three platinum drugs[10] Cisplatin has a high potential for producing serious toxicities such as nephrotoxicity, ototoxicity and peripheral neuropathy. Carboplatin cause renal damage, ototoxicity, peripheral neuropathy, nausea and vomiting where as Oxaliplatin produces unique cold-induced neuropathies and peripheral neuropathies[11,12,13]. As the studies available on ADRs of platinum drugs in lung cancer patients are very less, therefore, the present study is conceived to evaluate the problem of ADR in lung cancer with platinum compounds.

Aims and objectives: To study trends and patterns of Adverse Drug Reactions (ADRs) of Cisplatin in Pulmonary cancer patients.

Materials and Methods: This one year prospective one point observational study was conducted w.e.f. November 1, 2017 to October 2018 in the ADRM centre established in Department of Pharmacology using the suspected Adverse Drug Reaction reporting form of pharmacovigilance programme of India (PvPI) in collaboration with Radiation Oncology Department, Government Medical College, Jammu, after Institute Ethics Committee (IEC) and Institutional review board of Government Medical College, Jammu permission.

METHODOLOGY

The clinical profile and the important information related to ADR in the form of patients brief history, clinical presentation, date of reaction, date of recovery, date of presentation were also recorded in ADR reporting form made available under pharmacovigilance. Patient information about suspected ADR, suspected medication was recorded. Under suspected medication, the name of the drug, brand name of manufacturer/ generic name of manufacturer (if known), expiry date, dose used, route, severity, frequency and therapy dates as well as reason for prescribing suspected drugs were also recorded and analysed.

OBSERVATIONS

The present one - year observational, prospective cross-sectional study was conducted from Ist November2017 to October 2018 with the objective to identify the lung cancer patients with Adverse Drug Reactions (ADRs) from Radiotherapy Department using suspected drug reactions monitoring data collection form.

A total number of 98 patients were reported during the study period, wherein a total number of 114 ADR cases were observed.

The majority of patients were in the age group of 61-80 (n=45), followed by 41 -60 years (n=41, 41.83%) **(Table1).Table 1: Age Distribution of ADR cases**

Age group (years)	No.	Percentage

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1-20	**0**	**0**
21-40	**10**	**10.20**
41-60	**41**	**41.83**
61-80	**45**	**45.91**
>80	**2**	**2.04**
Total	**98**	**98(100.00)**

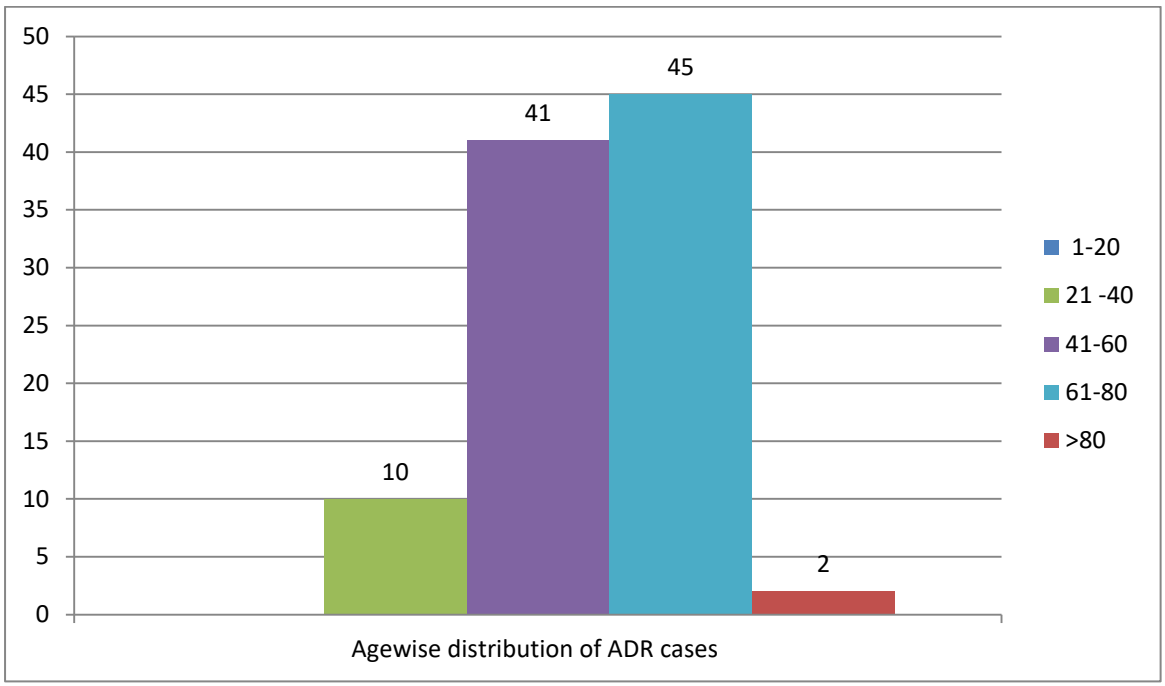

Fig. 1: Bar chart depicting Age Distribution of ADR cases

Table 2: Distribution of ADR cases According to personal habits of subjects

Personal habits	**No.(%)**

Table 2: Distribution of ADR cases According to personal habits of subjects

Personal habits	**No.(%)**
Smokers or Alcoholics	**56 (57.14)**
Non-Smokers/Non-Alcoholics	**42 (42.85)**
Total	**98 (100.00)**

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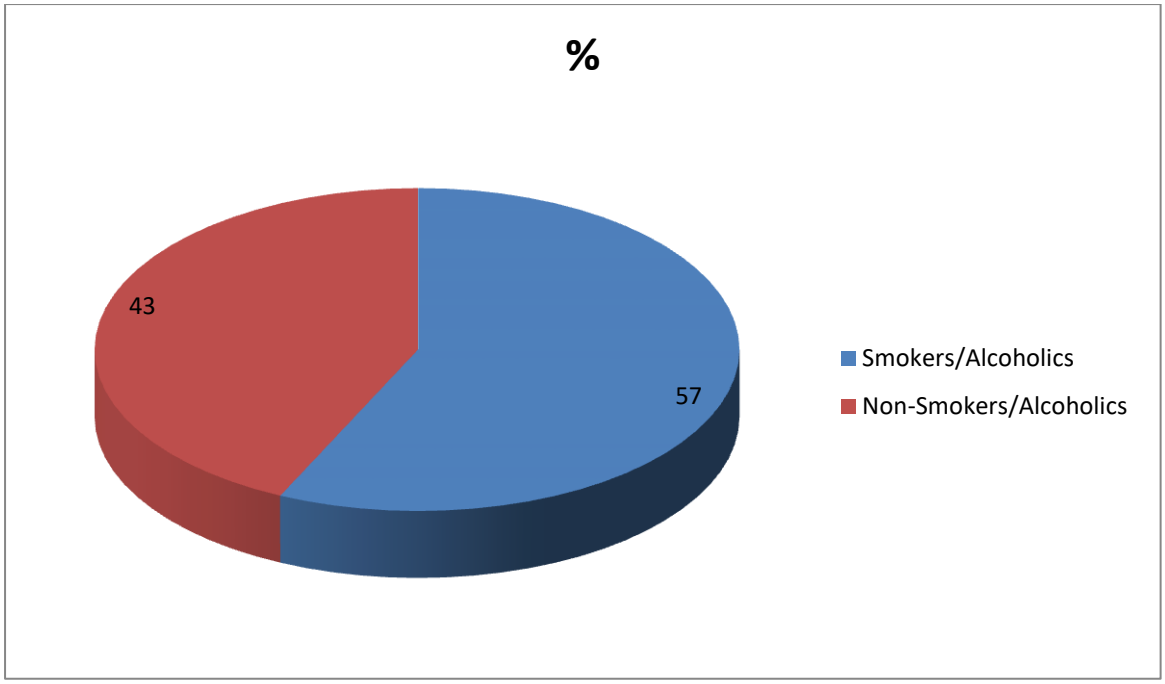

Fig. 2: Pie chart Depicting Distribution of ADR cases According to personal habits of subjects

Table 3: Drugs resulting into ADR (n=98)

Name of drug	No.	%
Cisplatin	**54**	**47.36**
Carboplatin	**43**	**37.71**
Oxaliplatin	**17**	**14.91**
Total	**114**	**100.00**

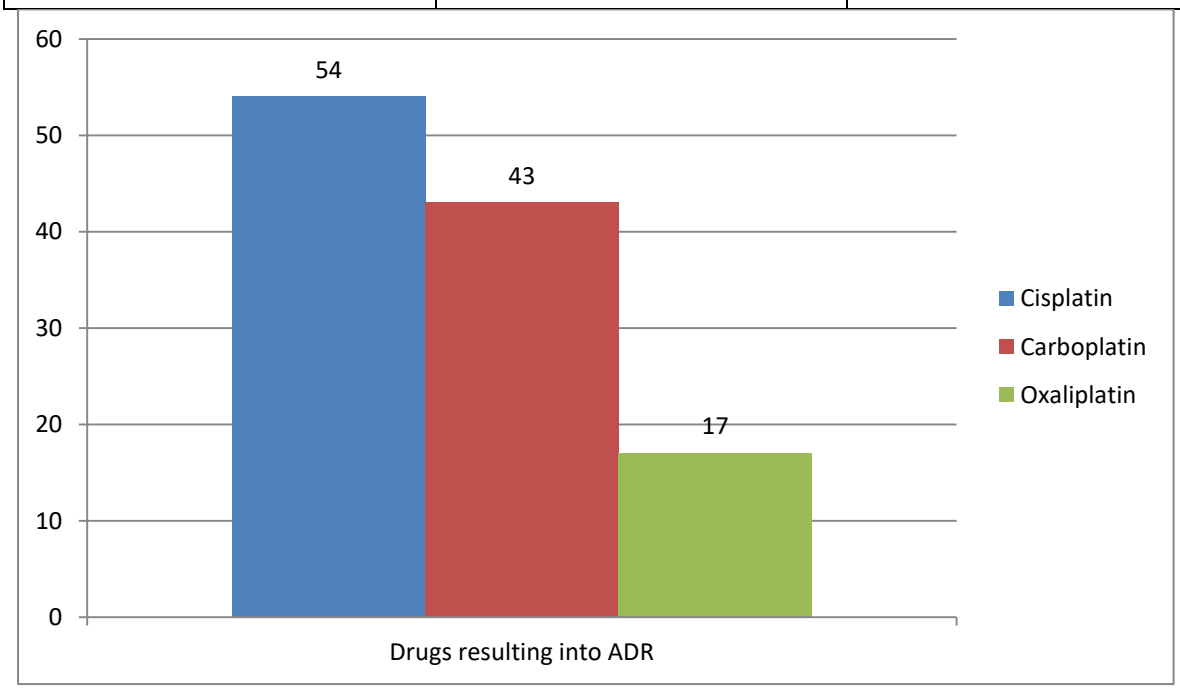

Fig 3: Bar chart depicting Platinum analogs resulting into ADR

The largest number of reports was associated with cisplatin 48 (48.97%) followed by carboplatin 38 (38.77 %) and oxaliplatin 12 (12.24%) (Table 3).

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Table 4: Frequency of distribution of various ADRs (n=98)

S.No.	ADR name	Frequency	Percentage
1	Vomiting	18	15.78
2	Anemia	16	14.03
3	Nausea	13	11.40
4	Hair loss	12	10.52
5	Diarrhea	8	7.01
6	Constipation	6	5.26
7	Thrombocytopenia	6	5.26
8	Neutropenia	5	4.38
9	Neuropathy	5	4.38
10	Elevation in creatinine	4	3.50
11	Deranged LFT's	4	3.50
12	Loss of appetite	4	3.50
13	Increase in uric acid	3	2.63
14	Musculoskeletal pain	3	2.63
15	Altered taste	2	1.75
16	Dizziness	1	0.87
17	Headache	1	0.87
18	Fatigue	1	0.87
19	Fever	1	0.87
20	Dryness of mouth	1	0.87
	Total	114	100.00

The total number of ADRs developed by the patients was found to be 114. Out of the total ADRs, most frequently reported one was vomiting 18 (15.78%) followed by anemia 16 (14.03%), nausea 13(11.40%) and hair loss 12 (10.52 %) which together constituted 51.73 % of the total ADRs. The other commonly encountered ADRs were diarrhea 8 (7.01%), thrombocytopenia 6 (5.26%), constipation 6 (5.26%) neutropenia 5(4.38) and neuropathy 5(4.38) depicted in (Table 4).

The frequency of deranged LFT's was 4 (3.50%) and elevation in creatinine was 4 (3.50%). The other ADR cases were loss of appetite 4(3.50%), increase in uric acid 3 (2.63%), followed by musculoskeletal pain 3 (2.63%) and altered taste 2 (1.75%). ADRs like dizziness, headache, fatigue, fever and dryness of mouth were rare with a frequency of 1(0.87%) each (Table 4).

Table 5: Analysis of Severity of ADR According to WHO- UMC scale (n=98)

Severity of ADR	No. (%)
Certain	37 (37.75)
Probable	28 (28.57)
Possible	33 (33.67)
Unlikely	0
Conditional	0
Unclassifiable	0

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Total	**98 (100.00)**

'Table 6: Analysis of ADR in Reference to Causality Assessment Severity Naranjo's Scale (n=98)

Causality Assessment	**No. (%)**
Definite (_>9)	0
Probable (5-8)	65 (66.32)
Possible (1-4)	33 (33.67)
Doubtful	0
Total	98 (100.00)

DISCUSSION:ADRs significantly affect the quality of life and strongly suggests that they are the leading cause of morbidity, mortality and economical burden worldwide[14,15,16]**.**They are a matter of concern not only for the patients whose suffering gets worsened but also for the treating physicians and other health care providers and the treating health centre. ADRs are now considered a significant public health problem, warranting urgent attention and remedial intervention.The occurrence of ADRs in patients with cancer chemotherapy is found to be grave concern, the elimination of side effects, and possible toxicities have become a major problem during chemotherapy, especially with Platinum agents. Platinum based chemotherapy has been applied in Lung cancer treatment for a long time. As Lung cancer is the most common malignant tumor globally. As yet, only limited studiesin the field, particularly in relation to cancer chemotherapy, are available[17,18].

The demographic profile of present study shows that more number of males accounted for ADRs, with male to female ratio as 2.76:1. It is generally held that cancer predominantly occur in males, perhaps on account of certain factors such as smoking and alcohol consumption[19]. This is comparable to study conducted in a tertiary care hospital[20,21,22,23] where majority of the patients were males. In a similar study[24]observed highest tumor incidence in males and most frequent tumor was lung tumor with a male/female 4:1 ratio.

Other common ADRs encountered in our study were constipation, thrombocytopenia, neutropenia and neuropathy. In series[25] constipation turned out to be the most common ADR from cancer chemotherapy. However, constipation was seen in only a small proportion of cases in the series [26]. Reduced dietary intake due to anorexia in cancer may be an important factor in causing constipation. Intestinal denudation by chemotherapy, especially alkylating agents, could well be the contributing factor in development of constipation[27]**.** Thrombocytopenia requires oprelvekin or platelet transfusion. Neutropenia can be managed by sargramostin, filgrastin.

CONCLUSION: The benefits of ADR monitoring are well known. In the past, poor awareness and non availability of a central coordinating body resulted in lack of ADR monitoring in India. The National Pharmacovigilance Programme was recently initiated in the country, encouraging ADR monitoring in selected centres, including our own centre. Ours

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is the first study of its kind at GMC and Associated Hospital, Jammu providing an insight into the burden and pattern of ADRs in patients on cisplatin chemotherapy. More such studies with improved facilities need to be conducted periodically to generate robust data in this field.

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