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ORIGINAL RESEARCH

Estimation Of The Point Prevalence Of Adverse Drug Reactions Of Platinum Compounds In Lung Cancer Patients And To Establish Cause Effect Relationship Of Each Adverse Drug Reaction Using Appropriate Scales

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Abstract

Background: The aim of the present study was to monitor the prevalence of Adverse Drug Reactions to commonly used platinum compounds in lung cancer patients and also to establish cause effect relationship of each adverse drug reaction using appropriate scales. It was a prospective observational study.

Methods:A observational study conducted in the ADRM centre established in Department of Pharmacology using the suspected ADR reporting form in collaboration with Radiation Oncology Department, Government Medical College, Jammu after IEC permission.New and old diagnosed cases of lung cancer patients belonging to either gender and of all ages, who were receiving platinum under any standard regimen, were included for the study.Patients other than lung cancer receiving platinum therapy, receiving concomitant chemo-radiotherapy,any ADR due to medication error, overdosage, poisoning were excluded. The suspected ADRs were classified in term of casuality using WHO-UMC scale. The cause and effect relationship of each ADR was assessed by using Naranjos Probability scale.

Results: There were a total of 98 patients with adverse drug reactions reported from the study.The majority of patients were smokers and/or alcoholics and in the age group of 61-80.The largest number of reports was associated with cisplatin 48 (48.97%) followed by carboplatin 38 (38.77 %) and oxaliplatin 12 (12.24%) . Most frequently reported ADR was vomitingfollowed by anemia .The frequency of deranged LFT's was 4 (3.50%) and elevation in creatinine was 4 (3.50%). It was observed that gastrointestinal system accounted for 51 (44.73%) ADR cases, followed by hematological system 28 (24.56%) and dermatological system 12 (10.52%). Validation of the causality assessment severity was done by Naranjo's scale which classified 65 (66.32%) to be probable and remaining 33 (33.67%) to be possible.Regarding management of ADRs I,ntervention was done in 48(48.97%) of the patients. The current study depicted 47(47.95%) ADR cases as fully recovered, 22(22.44%) cases as recovering.

Conclusion: Platinum compounds have a high potential to cause various adverse effects in lung cancer patients. As most of the ADRs were preventable, hence warranting urgent attention and remedial intervention.

Introduction: Cancer is characterized by uncontrolled cell division having the ability to invade locally other tissues by invasion or by distant metastasis[1] . Lung cancer prevalence is very common. In 2012, worldwide lung cancer occurred in 1.8 million people and resulted in 1.6 million deaths[2].The most common symptoms of lung carcinoma are cough (including coughing up blood)weight loss, shortness of breath and chest pain[3]. The 85% of cases of lung cancer are due to long term tobacco smoking. However 10 – 15% of the cancer occurs in people who have never smoked[4]These are often caused by a combination of genetic factors and exposure to asbestos, radon gas, other forms of air pollution, or second- hand smoke[5]. Platinum based chemotherapy is commonly given in Lung cancer patients.Unpredictable and occasional serious side effects,especially hematological toxicity, continues to be an intractable problem. Severity of toxicities and the incidence vary greatly between individuals [6]. Many of the platinum compounds induce damage to tumors through induction of apoptosis and is responsible for the haematological toxicity, gastrointestinal toxicity and most other toxicities. Molecules related to apoptosis are potential predictive markers for survival and toxicity in platinum based treatment. An apoptosis related gene i.ecaspase -3(CASP3) was reported to be associated with a risk of severe haematologic toxicity[7].Among platinum compounds cisplatin, carboplatin and oxaliplatin are some of the most widely prescribed and approved anti cancer drugs in the world[8]

As the studies available on ADRs of platinum drugs in lung cancer patients are very less, therefore, the present study is conceived to give estimation of point prevalence of ADR in lung cancer with platinum compounds and to establish cause effect relationship of each adverse drug reaction.

Aims and objectives:

1. To estimate the point prevalence of Adverse Drug Reactions (ADRs) of Platinum compounds in Lung Cancer patients.
2. To establish cause effect relationship of each adverse drug reaction using appropriate scales.

Materials and Methods: This was a one point , prospective, observational study conducted in the ADRM centreestablished in Department of Pharmacology using the suspected Adverse Drug Reaction reporting form in collaboration with Radiation Oncology Department, Government Medical College, Jammu, after Institute Ethics Committee (IEC) and Institutional review board of Government Medical College, Jammu conducted w.e.f. November 1, 2017 to October 2018. The patients were enrolled for the study after taking their written informed consent. In case of children, their parent's consent was taken.The patients were eligible for the study as per the following inclusion and exclusion criteria:

INCLUSION CRITERIA

1. New and old diagnosed cases of Lung cancer patients receiving platinum based chemotherapy admitted in the wards or attending OPDs in the department of Radiation Oncology.
2. Patients of Lung cancer receiving platinum based chemotherapy reporting to ADR monitoring centre, in Department of Pharmacology.3. Any ADR report from OPD/Indoor patients of any severity (Mild, Moderate, Severe), any type- Serious/ Nonserious of reaction and any duration were recorded.
3. AGE: All age groups.
4. SEX: either.

EXCLUSION CRITERIA

1. Patients other than Lung cancer receiving platinum based chemotherapy.
2. Patients receiving concomitant chemo- radiotherapy.
3. Any ADR due to poisoning, medication error, overdosage, non compliance, natural product or alternate medicines and unidentified drugs were excluded.

METHODOLOGY

The number and event of ADRs experienced by the Lung cancer patients receiving platinum based chemotherapy admitted in Radiation Oncology department were recorded. The "Suspected Adverse Drug Event Reporting Form" available with the ADRM centre, operating from the Department of Pharmacology, GMC Jammu was used.

Patient information about suspected ADR, suspected medication was recorded. Undersuspected 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. The information about dechallenge and the rechallenge, concomitant medical treatment record, the relevant laboratory investigation and other relevant histories including preexisting medicalconditions e.g., smoking, allergy, pregnancy and alcohol use and any organ dysfunction was recorded. Important information like platinum chemotherapy related factors, most common systems involved, ADR risk factors as well as documentation of ADR whenever applicable was carried out. The severity and serious of reaction, the outcome of reaction and onset time was recorded for every suspected ADR.

The ADR were defined and categorized as per the definition of Edwards &Arsonson, 2000[9]**.** The suspected ADRs were classified in term of casuality using WHO-UMC scale and were categorized as:-

Certain

Probable / Likely

Possible

Unlikely

Conditional/ Unclassified

Unassessable / Unclassifiable

The cause and effect relationship of each ADR was assessed by using Naranjo's Probability scale [10]Scores were given accordingly and the drug reaction can be classified as:-

Highly probable: 9Probable: 5 - 8

Possible or: 1 - 4
Doubtful: 0

The severity of the ADR was also assessed by using the Modified Hartwig and Siegel scale[11] which classifies severity of ADR as:-
A= Mild (bothersome but requires no change in therapy);B=Moderate (requires change in therapy, additional treatment, hospitalization);
C=Severe (disabling or life- threatening)

The types of ADR was classified as A, B, C, & D as per RAWLIN & THOMPSON classification[12].
Detailed evaluation of the case sheets was done. The patient information, Drug related suspected ADR, medicine relatedinformation was analyzed; the identity of reporter was kept confidential as per recommended SOP (Standard Operating Procedure) of PvPi.

OBSERVATIONS

There were a total of 98 patients reported for the study from November 2017 to October 2018, wherein a total number of 114 aalction form.
The majority of patients were in the age group of 61-80 (n=45), followed by 41 -60 years (n=41, 41.83%). Regarding personal habits of the subjects presenting with ADR, 56 (57.14%) were smokers and/or alcoholics, whereas 42 (42.85%) were non-smokers as well as non-alcoholics.
The largest number of reports was associated with cisplatin 48 (48.97%) followed by carboplatin 38 (38.77 %) and oxaliplatin 12 (12.24%) 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).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 1: Most common organ system involved (n=98)

Organ System	No.	Percentage
Gastrointestinal	51	44.73
Hematological	28	24.56
Dermatological	12	10.52
Neurological	5	4.38
Renal	4	3.50
Others	5	4.38
Hepatobiliary	4	3.50

Metabolic	3	2.63
CNS	1	0.87
Immunological	1	0.87
Total	114	100.00

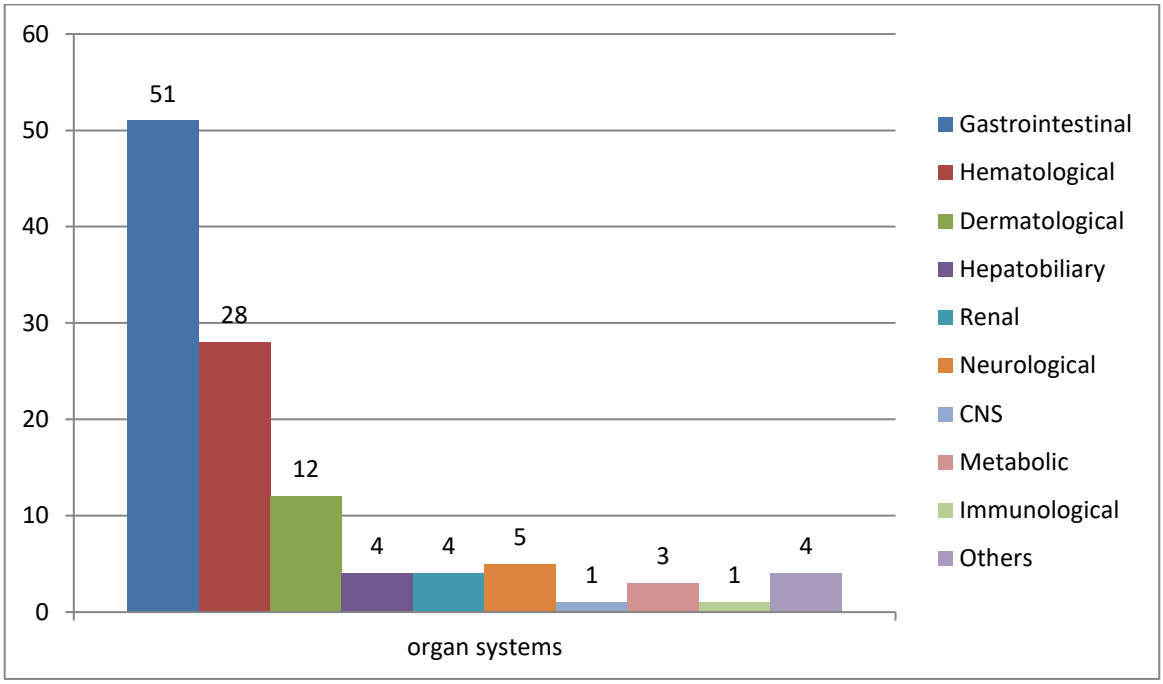

Fig. 1: Bar chart depicting most common organ systems involved

While evaluating the common organ systems in the present study, it was observed that gastrointestinal system accounted for 51 (44.73%) ADR cases, followed by hematological system 28 (24.56%) and dermatological system 12 (10.52%). The other systems which were affected include neurological 5 (4.38%) hepatobiliary system 4 (3.50%), renal 4 (3.50%), metabolic 3 (2.63%), CNS 1 (0.87%), immunological 1 (0.87%) and others 5 (4.38%) **(Table 1)**.

ADRs experienced by the patients with lung cancer who were administered platinum compounds were predominantly of latent onset 62(63.26%) followed by those of subacute onset 25(25.51%) and acute onset 11(11.22%).

Table 2: Analysis of ADR According to Severity (n=98)

Severity	**No. (%)**
Mild	55 (56.12)
Moderate	43 (43.87)
Severe	0
Total	98 (100.00)

In the present study, majority of ADRs were of mild severity 55 (56.12%) and 43 (43.87%) were of moderate severity **(Table 2)**. No case of fatality was reported.

Table 3: 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
Total	98 (100.00)

The present study while evaluating the severity of ADR according to WHO-UMC scale, reported 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 **(Table 3)**.

Table 4: 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)

Further, validation of the causality assessment severity was done by Naranjo's scale which classified 65 (66.32%) to be probable and remaining 33 (33.67%) to be possible **(Table 4).**

Table 5: Management of ADR (n=98)

Intervention done	No.(%)
No intervention	29 (29.59)
Therapeutic	48 (48.97)
Unknown	21 (21.42)
Total	98 (100.00)

In the current study, intervention was done in 48(48.97%) of the patients, while in 29(29.59%) cases no intervention was done and in 21(21.42%) ADR cases intervention was unknown **(Table 5).**

Table 6: Outcome of ADR (n=98)

Outcome of ADR	No. (%)
Recovered	47 (47.95)
Recovering	22 (22.44)
Continuing	8 (8.16)

Unknown	21 (21.42)
Fatal	0
Total	98 (100.00)

The current study depicted 47(47.95%) ADR cases as fully recovered, 22(22.44%) cases as recovering, whereas rest 21(21.42%) was unknown at the time of collection of data and 8(8.16%) ADR cases were continuing **(Table 6).**

DISCUSSION: The present study was done to evaluate the prevalence of various adverse drug reactions with platinum compounds, their severity, preventability as well as their causality assessment. Age is generally believed to be an independent risk factor for ADRs [13]**.** In the current study patients aged 61-80 years encountered majority of the ADRs followed by 41 – 60 years. In general the incidence of ADRs is higher in elderly patients as found in other studies [14,15]. According to **Cancer Research UK, 2012,** cancer is primarily a disease of older people, with incidence rates increasing with age for most cancers. Regarding the personal habits of subjects, among total population reported for ADRs in the current study, 57.14% were either smokers oralcoholics. This observation is supported [16] where majority of the patients were smokers (56.6%) and (43.4%) were non-smokers.

In the current study, the most common platinum analogue resulting into ADR remained cisplatin (47.36%), followed by carboplatin (37.71%) and oxaliplatin (14.91%). Similar study was observed [17,18] in which the mostcommon platinum analogue used in the study population was cisplatin followed by carboplatin and oxaliplatin.

In the present study the most frequent adverse reaction was vomiting followed by anemia, nausea, hair loss. This is complementary to the finding[19] which revealed the frequency of vomiting (41%) higher in a study done**.** ADRs[20]similar to our study in which vomiting was the most reported ADR. This was contrary to the findings[21] which showed fatigue as the major ADR followed by vomiting, dysphagia, insomnia.

Cancer chemotherapy is known for its high emetogenic potential by both a central action on the CTZ and a peripheral action on the gastrointestinal tract. The dominant receptors in the CTZ located in the floor of fourth ventricle are serotonin type 3(5-HT3) and dopamine type 2[22]. As serotonin receptors in the brain are involved in the mechanism of acute onset vomiting, ondansetron has a definite role in its prevention[23]

With this backdrop, all patients in our series had received an appropriate premedication (like ondansetron, ranitidine or dexamethasone) as a safeguard against nausea and vomiting. It seems that administration of premedication not only reduced the incidence but also the severity of nausea and vomiting. However, it could not offer an absolute prevention for these common adverse effects. Perhaps, more work is needed for improved modalities for prevention of nausea and vomiting as adverse effects of cancer chemotherapy.In most cases in whom nausea and vomiting occurred despite use of a premedication, these could be controlled with the use of appropriate antiemetic drugs (like ondansetron, metaclopromide or domperidone) which were given during the course of the chemotherapy, as and when needed. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting[24]are of value in this context. Anemia is a well known ADR after vomiting in our study. Some of our

cases with significant haematological pathology had to be given blood transfusion and erythropoietin.

The commonest cutaneous ADR in our series was alopecia which was seen in 10.52% cases. It occurs because of the cytotoxic effect of the chemotherapeutic drugs even to the normal cells of the body, especially the fast growing cells as those of hair, besides the cancercells. The actual mechanism of interference with the DNA integrity and function, thereby inducing cell death in rapidly proliferating tissues, remain unclear[25].

Next common adverse effect was diarrhea. Diarrhea can occur due to mucosal cell toxicity. Animal studies have demonstrated the effect of cisplatin causing specific mitochondrial oxidative DNA damage in gastrointestinal mucosal cells and increased gastrointestinal permeability, an indicator of toxicity[26].Causality assessment is used to determine the likelihood that a drug caused a suspected ADR. There are a number of different methods used to judge causation, including the Naranjo algorithm, WHO causality term assessment criteria [27].

Assessment of causality by WHO Causality Assessment Scale indicated that 37 (37.75%) reactions belong to the category "certain," followed by the category "possible" with frequency of 33 (33.67%) and 28 (28.57%) were "probable". This was contrary to the findings[28]in which there were no certain reactions.

As per Naranjo'sAlogrithm 65 (66.32%) ADRs were categorized as "probable" with score ranging from 5 - 8 and 33 (33.67%) of the ADRs were categorized as "possible" with score ranging from 1-4[29]also showed causality assessment similar to our study i.e. 62% of the ADRs were categorized as "probable" and 38% of the ADRs were categorized as "possible".

Regarding the management of ADRs in the present study, 29.59 % required no change in the treatment, 48.97 % required intervention whereas management of 21.42% of the patients was unknown at the time of study. Regarding the outcome 47.95% of patients recovered from ADR at the time of reporting, while in 22.44% ADRs, patients were recovering whereas 8.16% of patients were continuing with treatment for ADR at the time of reporting and outcome of 21.42% ADRs was unknown at the time of reporting, nor any fatality was observed in the present study.

CONCLUSION

Platinum compounds have a high potential to cause various adverse effects in lung cancer patients. Most common adverse effect was vomiting followed by anaemia and nausea, which can be preventable, so there is a need to improve the management of vomiting, since the rates of prevention of these adverse effects were poor. Anaemia can be managed by erythropoietin, hematinics and blood transfusion. Thrombocytopenia requireoprelvekin or platelet transfusion. Neutropenia can be managed by sargramostim, filgrastim. As most of the ADRs were preventable, hence warranting urgent attention and remedial intervention.

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